Review

Biomolecular Basis of Life

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Abstract: Life is considered a characteristic of the biological system that preserves, furthers, or reinforces its existence in a given environment. It is defined descriptively by the capacity for metabolism, homeostasis, self-organization, growth, adaptation, information metabolism, and reproduction. All these are achieved by a set of self-organizing and self-sustaining processes, among which energy and information metabolism play a dominant role. The energy metabolism of the human body is based firstly on glucose metabolism, supplemented by lipid metabolism. All energy-dependent life processes are controlled by phosphate and calcium signaling. To maintain the optimal levels of energy metabolism cells, tissues, and the brain communicate mutually, and as a result of this signaling metabolism, emerges self-awareness which allows for conscience social interactions which are the most significant determinants of human life. Consequently, the brain representation of our body and the egocentric representation of the environment are built. The last determinant of life optimization is limited life/death cycle which exhibits the same pattern at cellular and social levels. This narrative review is my first attempt to systemize our knowledge of life phenomena. Due to the magnitude of this challenge, in the current article, I tried to present knowledge about fundamental life processes, i.e. energy and information metabolism, and thus initiate a broader discussion about the life and future of our species.

Keywords: life; energy metabolism; information metabolism; cellular turnover; senescence; death

1. Phenomenon of Life

Life is considered a characteristic of the biological system that preserves, furthers, or reinforces its existence in a given environment. It is defined descriptively by the capacity for metabolism, homeostasis, self-organization, growth, adaptation, response to stimuli, and reproduction. A living organism forms a thermodynamic open system with an organized molecular structure that can evolve and reproduce. To survive in a changing environment, the body must maintain homeostasis i.e., a stable internal environment despite changes in the environment. It ensures optimal body functioning based on several physicochemical conditions, such as constant body temperature and fluid balance, cytoplasmic pH, sodium, potassium, and calcium ion concentrations, and blood sugar levels, which must be maintained within narrow limits, despite changes in diet or activity level. From a thermodynamics perspective, living organisms must maintain thermal, mechanical, and chemical equilibria to ensure the proper course of biochemical reactions essential to life.

Life is, first of all, a complex form of energy exchange, thus energy metabolism must be considered as the foundation of life. The body's energy balance is achieved by the interaction of several vital processes such as respiration, the acquisition and distribution of energy metabolites, and removing of the waste product. The uninterrupted respiratory and circulatory activity provides the living organism with oxygen, glucose, and fatty acids which are essential for life at the cellular level [1,2]. Consequently, monitoring and control of these metabolites in the blood is a source of life signaling for all tissues, particularly for the brain. The brain, based on these signals, coordinates internal interorgan interactions and also controls organismal behavior. This behavioral control concerns predominantly all aspects and forms of motor activity, including locomotion, physical work, respiration, and heartbeat which are the main energy-consuming contributors of energy consumption. In addition, the digestive processes dependent on smooth muscle activity impacts

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significantly energy balance. Importantly, all these motor activities relying on muscular activities are performed under the control of calcium-phosphate metabolisms [3].

Life depends on an organism's ability to stabilize internal bodily mechanisms independently of environmental variations such as food accessibility, changes in their composition and energy value, as well as physical-chemical parameters of our environment, etc. This physiological mechanism of regulation, called allostasis, allows an organism to anticipate and adjust its energy use according to environmental demands. Allostasis depends on several organismal capabilities such as the accumulation of energy and metabolic resources as well as their optimal use and recovery when possible. Toward these aims human body accumulates heat and energy substrates such as glucose and fat. Moreover, the kinetics of all metabolic processes are finely adjusted to internal and external environmental conditions.

Life is characterized by cyclicality dictated mainly by the energy harvesting necessary for the realization of basic metabolic processes. Due to limited energy resources, the implementation of processes with high energy consumption is spread over time in the circadian cycle. Alternating states of wakefulness and sleep allow for the temporal separation of energy-consuming processes requiring conscious nervous control (such as motor activity, work, food consumption, etc.) from regenerative, developmental, and repair processes that also require high energy expenditure, but can be carried out without the participation of consciousness.

1.1. Algorithm of Life

Energy metabolism is the foundation of life therefore the understanding of the mechanisms of its regulation is the basis of understanding life phenomena. In the living cell, all bioenergetic processes are coupled with each other via adenosine nucleotides [4,5]. The most important regulatory elements involved in the coupling of catabolic and anabolic reactions are ATP, ADP, and AMP. The adenosine nucleotides are not only tied to the metabolic pathways involved in the cell's energetic system but also act as allosteric control of numerous regulatory enzymes allowing changes in ATP, ADP, and AMP levels can practically regulate the functional activity of the overall multienzymatic network of cell. The heart and diaphragm are the main sources of ATP entering the bloodstream in the resting phase [6,7]. Mitochondria in cardiomyocytes constitute approximately one-third of the cell volume and produce more than 95% of the ATP in the myocardium [7]. To maintain the optimal life-sustaining level of ATP production, the heart permanently consumes large quantities of energy and fatty acids seem the preferred substrate, accounting for 60–90% of the myocardium's energy supply [8]. In the heart, mitochondrial fatty acid oxidation leads to substrate production for the tricarboxylic acid cycle in the form of acetyl CoA and provides adenosine triphosphate for the skeletal muscles [2]. It has been estimated that cells within the human body depend upon the hydrolysis of 100 to 150 moles of ATP per day to ensure proper functioning and life [9].

In energy metabolism, the ATP is the primary life signaling molecule that coordinates all life processes at cellular, tissue, and systemic levels. In resting conditions, i.e., without the activity of the neuromuscular system, the heart and diaphragm are the main sources of ATP circulating in the blood. The ATP/ADP ratio in the blood determines KATP channel activity thus cellular activity in all cells in the body. KATP channels are widely distributed in plasma membranes and some may be found on subcellular membranes. An ATP-sensitive potassium channel uses intracellular nucleotides, ATP, and ADP gates. Mg-nucleotides are required for the activation of KATP channels and, in particular, magnesium adenosine triphosphate (MgATP) and adenosine diphosphate (MgADP) are indispensable for inducing KATP channel activity [10]. At rest, heart-derived ATP released to the circulation is spontaneously hydrolyzed, while the kinetic of this process is regulated by magnesium ions. The ATP entering the circulation, if not combined with magnesium ions is unstable and prone to irreversible hydrolysis thus increasing the concentration of inorganic phosphate [11]. This ATP life signaling is significantly modulated by main energy metabolites, including oxygen, glucose, and fatty acid levels. During motor behavior, e.g., during locomotion, skeletal muscles become additional providers of the circulating ATP that allows for adjustment of the energy metabolism to the active state.

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The ATP-dependent potassium channels (KATP) play a vital role in energy metabolism adjustment in all insulin target tissues including the brain, heart, liver, kidneys, and skeletal muscles [10,12]. The KATP channels regulate physiological processes, including hormone secretion, vascular tone, learning and memory, and cardiac and neuronal protection against ischemic insults [12]. Vascular KATP channels contribute also to energy metabolism control and are critical to sustaining normal vascular tone. They are responsible for the endothelial cells and pericytes' functioning and interaction. In particular, endothelial cells regulate exchanges between the bloodstream and the surrounding tissues. Pericytes, in turn, help in the maintenance of homeostatic and hemostatic functions of the central nervous system. In the brain, pericytes regulate capillary blood flow and the clearance and phagocytosis of cellular debris. Pericytes in the skeletal striated muscle are of two distinct populations. The first subtype can differentiate into fat cells while the other into muscle cells. In the pancreas, KATP channels are primarily responsible for maintaining the β-cell membrane potential and are involved in depolarization-mediated insulin release [10]. The membrane depolarization triggers the action potential that activates voltage-gated calcium channels, and the influx of Ca^{2+} results in insulin release [10].

The ATP/ADP ratio determines KATP channel activity. In the heart, glucose metabolism and oxidative phosphorylation set the resting ratio of ATP to ADP which controls the activity of the KATP channel in all tissues [10]. In fat tissue, the inhibition of KATP channels promotes fatty acid synthesis and lipolysis [10]. Free fatty acids even at low concentrations can activate the KATP channels [10]. In peripheral tissues, the activation of KATP channels decreases membrane glucose receptor expression and glucose transport [10]. At the cellular level, hypoxia activates numerous major signaling pathways, resulting in changes in gene expression, which influence the cellular ability to survive or die. This mechanism depends on changes in the NAD/NADH ratio and activation of phosphatidylinositol (PI) 3-kinase and extracellular signal-regulated kinases (ERKs) seem to be crucial for the cytoprotective effect of mild hypoxia [13].

The brain is the main controller of life thus its homeostasis is the main determinant of organismal integrity. The brain monitors oxygen and glucose circulating levels, which are foundations of brain energy metabolism and its functioning [14,15,16]. Hepatic glucose production through glycogenolysis, gluconeogenesis, and glycolysis is the brain's major energy source [15,17,18]. The liver maintains euglycemia between meals by releasing into the blood postprandially stored glucose [14]. The decline in liver-produced and released glucose levels is signaled in the brain as stress. Blood glucose and oxygen levels are the main factors that control the motivational/emotional status of the organism by the release of catecholamines.

Catecholamines, particularly norepinephrine, are the primary activators of stress-induced lipolysis. Also, other hormones including cortisol, glucagon, growth hormone, and adrenocorticotropic hormone have similar effects. During intense physical work, systemic glucose decline activates hormonal signaling inducing compensatory lipolysis by stimulating hormone-sensitive lipase activity in the adipose tissue [19]. Consequently, lipids become an important participant in energy metabolism in case of stressful or conflict situations, the resolution of which requires additional energy. In the case of defensive reflexes, the body limits behavior to simple fight-or-fly responses, hormonally controlled mainly by catecholamines.

Catecholamines are the primary activators of lipolysis. During fasting states lipolysis in the adipose tissue is initiated by hormone-sensitive lipases, and adipocytes release fatty acids and glycerol to supply energy fuel to non-adipose tissues [19,20]. Dysfunctional lipolysis in non-adipose tissues impairs their normal function, leading to excessive triglyceride accumulation and lipid storage disease [21]. Especially, the failure to package free fatty acids into lipid droplets causes their chronic elevation in circulation. Consequently, it leads to progressive, chronic inflammation, mitochondrial dysfunctions, and cell death [21,22].

The liver glycogen content decreases by 65% after 24 hours of fasting [14]. During fasting, the compensatory transition from glucose to fatty acid metabolism takes typically 2–5 days [23]. The biochemical profile associated with a fat-based metabolism includes elevated ketone bodies, adenosine, orexin, AMP-activated protein kinase (AMPK), and homeostatic responses to

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mitochondrial reactive oxygen species, including uncoupling proteins [23]. In the liver, the metabolic switch occurs typically 12 hours after the last meal and when glycogen stores are depleted [24]. The switch aims for survival by protecting brain and muscle functioning [24].

Blood glucose level is a sensitive indicator of energy balance used by the brain to control the circadian cycle. It is responsible for the sleep/wake transition based on the catecholamines-dependent release of calcium and phosphate ions from the bones. Importantly, energy balance recovery is inextricably linked to the motor activity of both skeletal and smooth muscles and their activity is strictly dependent on calcium signaling. Therefore the catecholamine-dependent calcium release from the bone constitutes a metabolic trigger allowing the body to switch from resting to active state. Calcium entering the neural and muscle cells through voltage-gated calcium channels serves as the second messenger of electrical signaling, initiating multiple cellular events [25]. In the myocardium, activation of calcium channels initiates contraction directly by increasing cytosolic Ca^{2+} concentration and indirectly by activating calcium-dependent calcium release by ryanodine-sensitive Ca^{2+} channels. In skeletal muscle cells, voltage-gated Ca^{2+} channels in the transverse tubule membranes interact directly with ryanodine-sensitive Ca^{2+} release channels and activate them to initiate muscle contractions enabling locomotory movements [25]. In motoneurons, voltage-gated calcium channels initiate transmission at the neuromuscular junction by the release of acetylcholine neurotransmitters [25].

2. Energy Metabolism as a Basis of Life

Foods consumed by humans contain several energy components, of which glucose and fatty acids constitute the basis of the body's energy metabolism [1]. In response to the postprandial rise of blood glucose levels, the pancreas-released insulin initiates glycogenesis in skeletal muscles, liver, and adipose tissue. In humans, the majority of glycogen is stored in skeletal muscles (up to 500 grams) and the liver (100 grams) [14]. In humans, almost 80% of the glycogen is stored in skeletal muscles, which are the tissue that transforms chemical energy into mechanical work and therefore uses most of the glucose-derived energy during motor activity. In contrast to muscular stores, the liver glycogen complements blood glucose levels, to maintain the energy supply to the brain and other glucose-consuming tissues. Maintenance of blood glucose concentration in a narrow range is a major physiological priority [17,18]. Four grams of glucose circulate in the blood of an average individual [17]. The brain consumes about 60% of the blood glucose used in the sedentary, fasted person [17]. The liver releases glucose into the blood at rates equal to the uptake of blood glucose.

Resting and action-related energy metabolisms shape the energy balance of all living organisms. The first one is characterized by lower energy consumption while focusing on maintaining the homeostasis necessary for the optimal functioning of all body organs. In the resting state, even the continuously acting muscles including the heart and diaphragm secondary respiratory muscles, work with a slower rhythm thus with a lower energy consumption. Simultaneously, the skeletal muscles in the resting state, despite their large mass, do not use significant amounts of energy, and their activity is limited to the storage of glucose fuel and maintaining cellular homeostasis. The crucial and energy-consuming element of homeostasis is the clearance of waste products generated during a state of activity. Focusing on energy metabolism one can claim that the brain's motivational system depending on the energetic status of the entire organism reluates the rest/activity rhythm. The active state is characterized by the elevated activity of the neuromuscular system. Although the transformation of biochemical energy into mechanical work consists of the supreme load for the neuromusculoskeletal system it usually requires the synchronized activity of several organs such as the liver, kidney, and the circular and respiratory systems.

The circadian cycle allows the most energy-consuming processes to spread over time. During the day, processes related to motor activity dominate, and their implementation requires conscious nervous control. Energy used by muscles is undoubtedly the most important contributor to the body's energy balance. In the neuromuscular system, the largest energy expenditures are primarily related to processing biochemical energy into muscle work. However, large amounts of energy are allocated to the production and metabolism of acetylcholine, the main neurotransmitter in neuromuscular

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transmission. In addition, motor activity is controlled by the brain, which, based on sensory stimuli from the internal and external environment of the body, decides to implement an adequate motor response and additionally adjusts it on an ongoing basis to the current environmental conditions.

2.1. Metabolites of Life

The purinergic signaling system is composed of mononucleosides, mononucleoside polyphosphates, and dinucleoside polyphosphates as agonists, as well as the respective purinergic receptors [26]. Purinergic receptors are present in many cells in the liver [27]. Consequently, purinergic signaling has a role in many normal hepatic functions such as glycogenolysis, gluconeogenesis, and glycolysis [27]. Glycogenolysis is controlled by glucagon, additionally modulated by noradrenaline, and ATP released from the splanchnic nervous system contributes [27]. Extracellular ATP arises not only from the splanchnic nervous system but also from hepatocytes and activated platelets. The extracellular ATP mediates glycogenolysis predominately through stimulation. The mechanism of regulation appears to be via modulation of glycogen phosphorylase. Glycogen phosphorylase catalyzes the rate-limiting step in glycogenolysis and is directly activated in human hepatocytes, by activation of P2YX receptors. The mechanism of activation relies on the increase of intracellular calcium and additionally the activation of phospholipase D [27].

The energy metabolism network in which the bones, kidneys, intestines, and liver form an allostatic team controlling mineral metabolism necessary for the coordination of energy distribution between respiratory, circulatory, and muscular systems [28]. In the living cell, all energy-dependent processes are coupled with each other via adenosine nucleotides [4,5]. ATP is used for biosynthetic pathways, maintenance of transmembrane gradients, movement, and cell division [5]. The extracellular ATP is rapidly hydrolyzed and used as a short-term neurotransmitter in neuromodulation and neurotransmission. ATP combined with magnesium plays a role as a long-term signaling molecule in cell differentiation, proliferation, and death [29,30]. The circadian regulation of hematopoietic stem cells release into circulation is coordinated by the extracellular ATP-dependent pathway [31,32]. Importantly, processes such as glycogenolysis, gluconeogenesis, and intracellular glycolysis are all ATP-dependent [27]. Similarly to glycogenolysis, this effect appears to be mediated through an increase in intracellular calcium [27].

The ATP entering the bloodstream acts as a trophic signaling molecule and as a transmitter or a co-transmitter in the peripheral and central nervous systems. The extracellular ATP, however, can be rapidly hydrolyzed as a short-term neurotransmitter in neuromodulation, secretion, and neurotransmission, and plays a role as a long-term signaling molecule in cell differentiation, proliferation, and death [30]. Thus the activation of purinergic receptors contributes mostly to stem cell differentiation and neuronal function [29]. Importantly, the circadian regulation of hematopoietic stem/progenitor cells release into peripheral blood is coordinated by the extracellular ATP-associated pathway [31,32].

ATP acts as a signaling molecule with potent long-term trophic roles in cellular homeostasis as well as in cell proliferation, growth, and development [33]. ATP is involved in signal transduction by serving as a substrate for kinases, enzymes that transfer phosphate groups. Adenylate kinase (phosphotransferase with a phosphate group as an acceptor) is considered a key enzyme in energy metabolism for all organisms [5]. The concentration ratio of ATP to ADP is known as the "energy charge" of the cell. The uptake of cytosolic ATP into the endoplasmic reticulum lumen is critical for the proper functioning of chaperone proteins that assist the conformational folding or unfolding of large proteins or macromolecular protein complexes [34]. The endoplasmic reticulum uses energy from ATP hydrolysis for protein folding and trafficking [35]. Under physiological conditions, increases in cytosolic Ca^{2+} inhibit ATP import into the endoplasmic reticulum lumen. The endoplasmic reticulum ATP level is readily depleted by inhibition of oxidative phosphorylation leading to protein misfolding [35].

Maintenance of serum phosphate levels within a relatively narrow range is crucial for several important cellular processes, including energy metabolism and signal transduction, or as a constituent of phospholipids and nucleic acids [36]. Fibroblast growth factor-23 (FGF23) is

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produced in osteoblasts in response to increases in serum phosphate. The phosphate levels are stabilized by FGF23-dependent phosphate excretion by the kidney and suppression of phosphate reabsorption in renal proximal tubules [37]. To exert its physiologic effects FGF23 requires the presence of a cofactor, Klotho, which is produced in the kidney and activates FGF receptor.

2.2. Role of Insulin and Insulin-Like Growth Factor in Energy Metabolism

Evolutionary changes have adapted living organisms to their natural environment. Human food preferences have been shaped by the content of metabolites necessary for life in various foods. The sense of taste plays a special role, in establishing food preferences necessary for maintaining life. Feeding preferences are the basic mechanism that adapts food habits to the needs of the organism. In particular, foods containing energy fuels in the form of glucose and fatty acids are preferred. The sweet taste receptor is involved in nutrient sensing, monitoring changes in energy storage, and triggering metabolic and behavioral responses to maintain the energy balance [38,39]. Secreted by the liver, fibroblast growth factor 21 (FGF21) regulating mainly monosaccharides intake and preferences for sweet foods, impacts also bone remodeling by increasing the differentiation of osteoclasts [40].

Sugar preference and intake are controlled at least on three levels: gustation, gut-brain axis, and brain-glucose sensing [38]. The brain can sense glucose via oral and visceral sensations. Nutrient sensing initially occurs in the gastrointestinal tract. The gut sends signals to the rest of the body, including the brain, about current nutritional status by secreting hormones, such as ghrelin, gastric inhibitory peptide, peptide YY, cholecystokinin, glucagon-like peptide-1, and serotonin that are important regulators of glucose and energy homeostasis [41].

The glucose/lipid metabolic synergy is based largely on mutual reciprocal inhibition, in which the fundamental role is played by their different kinematics of chemical processes. Firstly, the half-life and the time of staying in the circulation of insulin and free fatty acids significantly impact this. In young healthy individuals, insulin secretion is tightly controlled to maintain steady plasma glucose levels despite its continuous use by all tissues. The glucose control is based on uninterrupted insulin and glucagon secretion patterns complemented by markedly increased prandial insulin secretion [42,43]. The estimated biological half-life of insulin in the bloodstream lies between 3 and 10 minutes. Insulin activity in the liver is highly downregulated by free fatty acids, reaching even the threshold of insulin resistance.

The insulin-like growth factor (IGF-1) is a protein with high sequence similarity to insulin. It mediates anabolic biological processes, including the increase in glucose metabolism, glycogenesis, lipid and protein synthesis, and the inhibition of gluconeogenesis, lipolysis, and protein degradation. Its action is mainly dedicated to energy metabolism in body development. Insulin and IGF-1 share the same tyrosine kinase receptor, therefore IGF-1 complements the function of insulin [44]. However, they differ substantially with a half-life and the IGF-1 is a relatively stable protein produced during sleep by the liver in response to growth hormone release.

IGF-1 exerts anabolic action on the skeleton by modulating the effects of parathyroid hormone and through crosstalk with mechanosensory pathways. IGF-1 responsiveness in osteocytes and osteoblasts is increased after mechanical load whereas the parathyroid hormone promotes the proliferation and maturation of osteoblast precursors and exerts anti-apoptotic activity on osteoblasts [44]. IGF-1 is also known to induce muscle cell proliferation and hypertrophy through the activation of the PI3K-Akt-mTOR signaling pathway [44]. In the brain, IGF-1 regulates neural development, neurogenesis, myelination, dendritic branching, and synaptogenesis [44]. Receptors for IGF-1 are found in vascular smooth muscle, while receptors for insulin are not present there.

The systemic production of growth hormone and IGF-1 declines, steadily reaching very low levels in humans aged 60 years [44,45]. In adults, alterations in the activity of the growth hormone and IGF-1 have been documented in aging, stress, hormonal changes, motor activity, nutrition level, disease state, and circadian rhythm [44].

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2.3. Oxidative Phosphorylation

Cellular respiration is a set of metabolic reactions and processes that convert the chemical energy of glucose and oxygen to drive the bulk production of NADH and adenosine triphosphate. At the cellular level, glycolysis, which occurs both in aerobic and anaerobic conditions, is the basic source of energy, the effect of which is the production of 32 ATP molecules [1]. NAD is an essential pyridine nucleotide that serves as a rate-limiting cofactor and substrate for critical cellular processes involved in oxidative phosphorylation [46]. It plays decisive roles in ATP production, DNA repair, epigenetically modulated gene expression, intracellular calcium signaling, and immunological functions [47,48,49]. ATP acts as a fast excitatory neurotransmitter and has potent long-term trophic roles in cell proliferation, growth, and development [33]. In the reduced form (NADH) it serves as a hydride donor to ATP synthesis in mitochondria [46]. Some NAD is also converted into the coenzyme nicotinamide adenine dinucleotide phosphate (NADP) which plays an essential role in antioxidant defense and regulates cellular signaling via NADPH oxidases.

NAD is continually turned over by three classes of NAD-consuming enzymes: the NADases, the protein deacetylase family of sirtuins, and PARPs, which have various important cellular functions impacting metabolism, genomic stability, gene expression, inflammation, circadian rhythm, and stress resistance [46,48,49,50]. Sirtuins (SIRT) regulate energy homeostasis by controlling the acetylation status and activity of several enzymes and transcriptional regulators. SIRT3 is the major mitochondrial deacetylase that serves as an important regulator of energy metabolism and is highly expressed in metabolically active tissues such as the brain, skeletal muscle, liver, kidney, heart, and adipose tissue [51].

In young, healthy individuals, high NAD levels ensure the proper conduct of all biochemical processes necessary for cell life. NAD deficiency due to increasing demands for NAD-consuming enzymes, as occurs in aging causes the mitochondria to become less efficient and produce less ATP [52]. Sirtuin activity in older adults might be compromised due to the systemic decline in NAD [53]. Cellular NAD levels decline steadily to reach 100% of the brain's physiological needs by the age of 45 [54]. In old age, the NAD deficit can reach up to 20% of physiological needs, leading to massive death of neurons and disintegration of their neuronal networks. The decline in SIRT1 activity down-regulates mitochondrial biogenesis, oxidative metabolism, and antioxidant defense pathways, leading to damage to complex I of the electron transport chain. Oxidative stress increases the amount of incorrectly formed proteins that cannot be fixed due to a decrease in the synthesis of NAD-dependent enzymes. As a consequence, the cellular energy deficit and metabolic crisis are rapidly escalating. When the energy deficit exceeds a critical level, oxidative phosphorylation arrests cellular respiration and initiates the process of programmed death. Activation of the nuclear enzyme, poly(ADP-ribose) polymerase-1 (PARP-1) plays a critical role in various cellular responses to injuries mainly as a death messenger [52].

Cellular energy metabolism is a highly organized, evolutionarily conserved series of metabolic reactions that sense substrate availability and derive sufficient ATP to feed its cellular needs, including cell function, survival, proliferation, and turnover [55]. In cellular energy metabolism, the phosphorylation of glucose plays a rate-limiting role. It controls the quantity of sugar entering glycolysis. The aerobic pathway allows for the transformation of pyruvate to acetyl-CoA, and the production of high ATP amounts through oxidative phosphorylation. Depending on the plasma oxygen level, both aerobic and anaerobic pathways are activated [56]. Cells utilize different metabolic pathways to fulfill maximally their energy needs. The anaerobic glycolysis reduces pyruvate to lactate by the enzyme lactate dehydrogenase to regenerate nicotinamide adenine dinucleotide (NAD) [56]. The metabolism of glucose is essential for cell proliferation [57]. In particular, aerobic glycolysis seems necessary to maintain increased levels of glycolytic intermediates to support anabolic reactions during cellular turnover.

Glycation is the attachment of sugar to a protein, lipid, or nucleic acid molecule that alters its functions. In particular, high glucose levels may induce oxidative stress which results in intensive glycation directing stem cells into apoptosis [58]. In conditions of chronic hyperglycemia, the process of protein glycation exceeds the physiological level escalating aging. Excessive glucose can attach to

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hemoglobin raising the level of the glycated hemoglobin [59]. It results in the stiffening of the collagen in the blood vessels, resulting in high blood pressure and an aneurysm which may cause strokes in the brain [59]. Glycated proteins and lipids are implicated in aging and the development of several pathologies, such as diabetes, atherosclerosis, chronic kidney disease, and dementia [59]. Sarcopenia is also associated with glycation end products in myocytes [59,60].

2.4. Beta-Oxidation

Foods consumed by humans contain several energy components, of which glucose and fatty acids constitute the basis of the body's energy metabolism [1]. The process of beta-oxidation of fatty acids occurs in parallel with glycolysis, which in physiological conditions supplements energy metabolism. For the proper functioning of cells, tissues, and the entire organism, maintaining the appropriate proportions between both energetic processes is essential. Mitochondrial beta-oxidation of fatty acids requires four steps, all of which occur in the mitochondrial matrix, to produce three energy storage molecules per round of oxidation, including one NAD, one flavin adenine dinucleotide, and one acetyl CoA [2]. Therefore from a metabolic perspective, beta-oxidation cannot fully substitute oxidative phosphorylation. The balance between glucose and fatty acid metabolism is established both by food habits and preferences, and especially the quantitative and qualitative composition of the food consumed, and also depends on the condition of the organism. In the latter case, involution processes and the aging of the organism are of significant importance.

Beta-oxidation is a significant source of metabolic energy during interprandial periods and high energy demand states [2]. The process of beta-oxidation is distributed between mitochondria, peroxisomes, and endoplasmic reticulum [2]. This metabolic pathway provides a large portion of the energy requirement of skeletal muscle, heart muscle, and kidneys [2]. Other forms of fatty acid oxidation are used to remove lipid-based cellular components, such as sphingolipids and plasma membrane constituents [2].

Glucose, fatty acids, and amino acids are the main substrates an organism can use to maintain metabolic homeostasis [61]. Fatty acids are required for the generation of energy, but also as building blocks for the biosynthesis of molecules [61]. Under physiological conditions, glucose is the preferred substrate for energy metabolism in the neuromuscular system while during fasting, fatty acids and ketone bodies may become a dominant energy source [19,61]. Fatty acid oxidation is exceptional in the heart, whose energy metabolism relies on fatty acids for a major proportion (60–90%) of its energy needs [19].

The functions of lipids in the organism include storing energy, signaling, and acting as structural components of cell membranes [62,63]. Fat is primarily stored in subcutaneous depots, which are characterized by a lower rate of lipogenesis and breakdown compared with visceral depots [64]. Excessive accumulation of fat, primarily due to an imbalance between energy intake and expenditure [64]. Frequent intake of fat-rich foods leads to the expansion and remodeling of adipose tissue leading to several metabolic diseases including hyperlipidemia, hypertension, and type 2 diabetes [63,64].

The fatty acids are the structural elements of cell and mitochondrial membranes, therefore de novo lipogenesis takes place in every cell. Fatty acids are components of the phospholipid bilayers that enclose the cell and all its organelles such as the nucleus, mitochondria, endoplasmic reticulum, and the Golgi apparatus. Cellular life strongly depends on the membrane's ability to precisely control the exchange of solutes between the internal and external compartments [65]. Choline is a nutrient essential for life needed for the structural integrity and signaling functions of cell membranes, for normal cholinergic neurotransmission, for normal muscle function, and for lipid transport from the liver [65,66]. It is also critical for cell proliferation and apoptosis. Choline and acetyl-CoA availability determines the rate of acetylcholine synthesis.

Choline obtained either by dietary consumption or by the metabolism of choline-containing lipids accounts for approximately 70% of phosphatidylcholine biosynthesis in the liver, while the phosphatidylethanolamine N-methyltransferase (PEMT) pathway plays a critical role in providing phosphatidylcholine during times of starvation [67]. Phosphatidylcholine made via PEMT plays a

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wide range of physiological roles, utilized in choline synthesis, hepatocyte membrane structure, bile secretion, and very low-density lipoprotein secretion [67]. Choline deficiency may result in muscle damage resulting in elevated serum creatine phosphokinase levels. Both, hepatocytes and myocytes when deprived of choline died by apoptosis [68].

The liver is the major organ of whole-body lipogenesis, while the adipose tissue contributes much less extent. Fetuin-A serves as a major carrier protein of free fatty acids in the circulation. This blood protein is secreted by the liver following the influx of free fatty acids, and in high concentration activates the toll-like receptor 4 (TLR4) [69,70]. However, humans fed with a carbohydrate-rich diet revealed that total fat synthesis in adipose tissue significantly exceeded hepatic de novo lipogenesis. Recent studies show that adipocytes generate adipocyte-specific fatty acids that act to improve systemic insulin sensitivity and decrease inflammation [71]. Therefore, adipocyte de novo lipogenesis is an important source of endogenous fatty acids and plays a key role in maintaining systemically metabolic homeostasis. In physiological conditions, skeletal muscle lipogenesis is not a dominant energetic process, however, the situation changes radically under conditions of high-fat diet consumption. Inhibition of de novo lipogenesis via skeletal muscle fatty acid synthase (FASN) improves systemic sensitivity to insulin without affecting obesity but reduces muscle strength [71].

Adipose tissue is the major organ for fat-derived energy storage [62.71]. It stores excess energy fuels in the form of triglycerides or fat, which can be mobilized to meet energy demand in states of fasting or physical work. Dysfunction in adipose tissue metabolism is a cardinal event in the development of insulin resistance and associated disorders [62]. Fat accumulation depends on the balance between the synthesis and breakdown of triglycerides [62]. Fatty acids stored in adipose tissue are from two distinct sources: circulating triglycerides, and de novo lipogenesis. During periods of energy deficiency adipocytes mobilize stored fat by lipolysis to fulfill the energy demands of other organs. The triglycerides are broken down into fatty acids and glycerol and the fatty acids are then oxidized in muscles or brown adipose tissues, while glycerol is used in the liver as the precursor for gluconeogenesis [62].

2.5. Glucose-Fatty Acid Interactions

The proportions between glucose and lipid metabolism are determined in part by the different contributions of metabolic processes by individual organs and cells. In organs whose energy metabolism is characterized by high-intensity changes, such as skeletal muscle and brain, energy production from glucose prevails. However, the heart muscle deserves special attention, where energy metabolism is dominated by fatty acids. In the heart and kidney, β-oxidation of fatty acids provides more than 90% of ATP with a simultaneous reduction in the NADH-to-NAD ratio [72]. During β-oxidation, the electrons enter the respiratory chain simultaneously through complexes II and III, and, to a lesser extent, through complex I. However, the mitochondria can oxidize fatty acids at the highest rate only with fully functional respiratory complex I, when pyruvate and succinate are present [72]. In these conditions, mitochondria in the heart and kidney maintain high rates of respiration and ATP production even at the maximal functional loads in these organs [72]. *They are, however, equipped with a biochemical mechanism of intrinsic inhibition of the respiratory complex II to prevent oxidative stress during decreased activity. In contrast, kidney mitochondria constantly work at a high rate but lack the inhibition of complex II. Therefore, oxidative stress is the central pathomechanism in the heart and brain while being secondary in the kidney. In that latter case, the primary mechanisms are kidney hypoxia caused by persistent hyperglycemia and hypertension [72].*

The glucose-fatty acid cycle is a biochemical mechanism that controls fuel selection and adapts substrate supply and demand in normal tissues in coordination with hormones controlling substrate concentrations in the circulation [19]. The hormones controlling lipolysis affect circulating concentrations of fatty acids, in turn, control glucose metabolism in the liver and skeletal muscles [19]. The adipose tissue lipolysis is inhibited by glucose and insulin. So far, the inhibition of glucose utilization by fatty acids has been documented in the heart, liver, and pancreas [19]. The cycle can be extended to lactate in the heart and liver, two lactate-consuming organs, within which lactate inhibits the oxidation of both glucose and fatty acids [19].

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De novo lipogenesis is another metabolic process that impairs energy metabolism. In the process, excess carbohydrates, such as glucose, are converted into fatty acids, and then into triglycerides or phospholipids [73]. In physiological conditions, de novo lipogenesis occurs mostly in the liver and adipose tissue [73]. Both, a high carbohydrate diet, and type 2 diabetes increase de novo lipogenesis in intestinal enterocytes thus intensifying pathogenic visceral fat accumulation [74].

While glucose enters directly the bloodstream, fats go to the lymphatic system first and then to the liver [74]. The left subclavian vein plays a key role in the absorption of fats and lipids. It carries lymph enriched with chylomicrons formed in the intestines from dietary fat and lipids, directing them to enter the bloodstream. Unlike digested carbohydrates and proteins, chylomicrons bypass the hepatic portal system and thus avoid first-pass metabolism [74]. The lymphatic circulation carries lymph containing chylomicrons to the lymphatic ducts, and then it enters the venous return of the systemic circulation, transporting lipids first to the myocardium and then to adipose and skeletal muscle tissue. Up there their triglyceride components are hydrolyzed by the activity of the lipoprotein lipase, allowing the released free fatty acids to be absorbed and stored by the tissues [74].

Because fatty acids have more stored energy per mole than glucose, fatty acid oxidation as a source of ATP is only relevant during states of glucose starvation [55]. However, lipids are also essential for brain functioning, participating in synaptogenesis (learning and memory) as well as repair and cellular turnover. Sphingolipids are essential constituents of all eukaryotic membranes. The sphingolipid signaling mediates processes involved in cellular turnover, inflammation, and programmed cell death [75]. Therefore the control and setting of physiological proportions between glucose and lipid metabolism are fundamental for health and life.

A high-fat diet may induce both liver inflammation and high fetuin-A production in the liver resulting in a significant increase in plasma level and reduced whole-body insulin sensitivity [70]. Fat deposition in the liver increases insulin resistance, inhibiting the process of oxidative phosphorylation [74,76]. The excessive accumulation of visceral fat leads to liver damage and inflammation [24]. Non-alcoholic fatty liver disease may exhibit initially some psychophysical symptoms such as fatigue, malaise, and pain [24]. The disease has been identified, however, as an independent risk factor for cardiovascular disease, chronic kidney disease, type 2 diabetes, and cancers [77]. Steatosis alters the liver proteic secretome with a pathogenic impact on distant organs, especially their cellular turnover [70].

Accumulation of fatty acids in the liver inhibits glucose utilization thus limiting oxidative phosphorylation in other tissues [78]. As a result, the efficiency of all metabolic processes at the cellular level rapidly decreases. Due to changes in blood vessels, pathological diffusion barriers are created for oxygen, and toxic metabolic waste products, the accumulation of which does not allow for maintaining homeostasis and proper functioning of the organism. Importantly, in highly active cells like neurons and myocytes, ionic channels coordinate and control several functions like neurotransmission, secretion, muscle contraction, growth, proliferation, and migration, as well as, the regulation of cell volume [10]. Towards this aim, ionic channels allow for the controlled transmembrane transport of Na^+, K^+, Cl^-, and calcium ions [10,65]. The extracellular fat accumulation, however, impairs the functioning of ionic channels, making their signaling dysfunctional [10].

An uncontrolled increase of some free fatty acid metabolites such as palmitoylcarnitine, and palmitoyl-coenzyme A, which are indispensable for β-oxidation, may be harmful to cells [79]. These metabolites, at low concentrations, stimulate ATP synthesis, but in higher concentrations are toxic [79]. In particular, elevated palmitoyl carnitine concentrations inhibit electron transport chain activity and simultaneously lead to the decrease of the mitochondrial inner membrane potential [79]. Thus the chronic increase in concentration of free fatty acids leads to lipotoxicity, mitochondrial dysfunction, and insulin resistance. The 40% decrease in inner membrane potential may abolish ATP synthesis completely, which opens a vicious circle of cellular senescence and death.

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3. Cellular Turnover

Cell death is a fundamental biological process essential for an organism's development, growth, and persistence. It maintains homeostasis by cellular turnover or replacing infected, damaged, and autoreactive cells [80]. Apoptosis, necroptosis, and pyroptosis are genetically programmed cell death mechanisms that eliminate obsolete, damaged, infected, and self-reactive cells [80]. Apoptosis is associated with mechanisms that minimize the immune response, whereas necroptosis and pyroptosis release proinflammatory molecules that amplify the immune response to noxious stimuli, such as infections. Adipocyte death is crucial for the turnover of adipose tissue [64]. In fat tissue, the cellular turnover was found to be between 10% and 17%, with a mean half-life of 8–14 months [64].

The cellular composition of the organism is precisely tailored to the needs of the organism, and at the same time is tuned to the availability of particular metabolites and substrates in a given ecosystem. Therefore, both the body's anthropometry and the metabolism mostly match the proper course of energy processes. The phenomenon of life is a process that depends on a fine adaptation to the environment. In the holistic approach, it is formed on symbiotic relationships with the ecosphere.

Therefore maintaining optimal endogenous synergy is a primary condition for an organism's healthy and physiological functioning. For this reason, all inefficient, damaged, or dysfunctional cells must be immediately and effectively replaced by resident progenitor cells. Cellular turnover has different dynamics and timing for particular cells [81]. As a highly energy-dependent process, it plays a decisive role in the physiology or pathophysiology of each organ. Moreover, the limited number of correct stem cell divisions impacts the effectiveness of cellular turnover and is responsible for aging and cancerogenesis.

During the postnatal period, the organism's development continues until allostasis is achieved, i.e., a balance is established between the anatomical body structure, its cellular composition, and physiology that match energy metabolism according to environmental demands. The accessibility of energy substrate at the cellular level plays a decisive role in individual and population life. Individual life depends on the availability of dietary energetic substrates and their distribution along with oxygen supply within the body. Therefore, the structure and adaptability of the circulatory system are one of the basic determinants of ontogenetic development. There is a limit to which tissue can expand without new vasculature to supply oxygen and nutrients. It has been estimated that tissue growth beyond the volume of one cubic millimeter is already in need of new vasculature. Angiogenesis is dependent on both the expression of pro-angiogenic- and anti-angiogenic factors. The renewed tissue has to produce pro-angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) [82]. Pro-angiogenic signaling increases by hypoxia, which may result from increased cell number, as well as dysfunction of blood circulation [82]. Growth factors inhibiting neovascularization include those that affect endothelial cell division and differentiation. They include insulin-like growth factor, fibroblast growth factor, hepatocyte growth factor, and platelet-derived endothelial growth factor [82].

In the optimizing and adaptive processes, an important role is played by cell death and cellular turnover, i.e. replacing inefficient cells with stem cells. Cellular turnover is an uninterrupted repair, optimizing, and adaptation process, the implementation of which is possible only if it is at a low level, spread over time, or limited to repairs caused by damage, inflammation, or disease processes. Cellular turnover processes are at their highest in tissues involved in key metabolic processes such as energy metabolism. Blood cells, intestinal linings, and liver cells are all exchanged very intensively [81]. The liver is a central organ for homeostasis with unique regenerative capacities [83]. Mature hepatocytes possess a remarkable capacity to proliferate upon injury, challenging efforts to discern the role of adult liver stem cells in this process. Throughout life, the liver is exposed to chemical, physiological, and pathological insults that require the activation and appropriate differentiation of hepatic progenitor cells [83]. To maintain liver homeostasis or restore the function of the damaged liver, the hepatic progenitor cells must differentiate into hepatocytes or cholangiocytes. In addition to resident hepatic progenitor cells, those transitional cell types as potential resident hepatic progenitor cells play important roles in liver regeneration after liver injury.

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The limited viability of cells means that in subsequent periods of life, allostasis is maintained through the cyclical exchange of inefficient cells in a process called cellular turnover [81]. Cellular turnover plays an important role in the adaptation processes [81]. In this process, cells are exchanged in individual tissues and organs, with the main goal of cellular exchange being to achieve the most efficient and balanced cellular activity. This highly energy-consuming process occurs at different rates in individual tissues, with the cells of the intestinal lining being the fastest to be replaced, and the largest population of cells being replaced are erythrocytes [81]. The cellular structure of skeletal muscles is not replaced cyclically but is mainly adapted to their mechanical activity and the availability of energy fuel in the form of glucose or fatty acids. In the human body, only three types of cells, in particular neurons, cardiomyocytes, and osteocytes, belong to the group of long-lived cells and are not subject to regular replacement [81]. Osteocytes characterized by long lifespans constitute 90–95% of all bone cells in the adult skeleton [84]. While osteoblasts and osteoclasts are viable from days to a few weeks, the osteocytes can live in the bone matrix for decades [85].

Bone metabolism requires coordinated differentiation and proliferation of bone marrow mesenchymal stem cells [58]. The osteogenic ability of bone marrow mesenchymal stem cells is inhibited under high glucose conditions, which contributes to reduced bone turnover and impaired bone quality [58]. Bones are constantly renewed through a mechanism called bone remodeling [86]. The skeleton remodeling cycle takes approximately 120 days, and 10% of the human skeleton is normally remodeled every year [55]. The process requires the differentiation of mesenchymal stem-cell-derived osteoblasts with subsequent collagen synthesis. Bone marrow-derived mesenchymal stem cells require mitochondrial biogenesis to effectively undergo osteoblastic differentiation [87]. The concomitant recruitment of hematopoietic-derived osteoclasts is necessary for bone resorption and the communication of skeletal signals to those cells from the deeply embedded osteocytes. All this translates into high energy consumption of the skeletal system [55].

Importantly, bone marrow fat impairs hematopoiesis, bone remodeling, and energy metabolism. Lipid droplets can gather in bone marrow and mesenchymal stem cells, osteocytes, as well as macrophages of the skeletal niche [55]. Droplet accumulation in osteocytes is responsible for their necrosis [55]. Deposition of bone marrow fat starts during childhood and continues throughout adulthood. Marrow adipose tissue accounts for approximately 10% of the total fat mass in healthy adult humans. By the age of 25 years, approximately 70% of the human bone marrow consists of marrow adipose tissue, with its continued gradual accumulation throughout life [55,88].

The lipid content of marrow adipose tissue is composed of triglycerides and saturated fatty acids [88]. During times of increased metabolic need, adipose tissue lipases break down triglycerides to release free fatty acids for use as an energy source to regulate osteoblasts, osteoclasts, and hematopoietic cell populations [88]. However, excessive marrow adipose tissue accumulation is associated with aging, diabetes, anorexia nervosa, estrogen, and growth hormone deficiency [88]. In the bone marrow, fatty acid metabolism is critical for hematopoietic and mesenchymal stem cell proliferation and function.

Depending on signaling molecules, bone marrow stem cells can differentiate into adipocytes and osteoblasts. Lysine, threonine, methionine, tryptophan, and isoleucine can increase osteoblast activity, proliferation, and differentiation while decreasing osteoclast activity [89]. Oxidized L-tryptophan promotes bone marrow stem cells differentiating into osteoblasts. However, kynurenine, the product of tryptophan intensifies osteoclast activity and enhances the differentiation of adipocytes from bone marrow stem cells [89].

The bone marrow niches regulate hematopoiesis and osteoblastogenesis. Factors influencing this process occur through cellular, physical, and chemical interactions within the bone marrow microenvironment [58]. In particular, the bone marrow senses the level of calcium, oxygen, and phosphate, as well as some hormonal signals. Hypoactivity is associated with increased bone marrow adipose tissue and low bone mass. With growth hormone deficiency, adipocytes rapidly accumulate within the bone marrow cavity [58]. The process is additionally intensified by estradiol and dihydrotestosterone levels decline. Changes in intracellular calcium levels regulate the proliferation and differentiation of bone marrow stem cells, promoting osteogenesis, angiogenesis, and

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chondroblast differentiation. Senescence leads to the proliferation of damaged ATP and NAD-deficient red blood cells. The process may initiate the massive destruction of red blood cells impairing blood functions in energy metabolism [58].

4. Environmental Adaptation

Muscles and bones have a mechanical interaction, particularly during locomotion [90]. This interaction goes beyond signaling metabolism. Musculoskeletal interaction is also shaped by mechanical forces including the force of gravity. Another example of mechanical interaction is lymph transport in the thoracic duct. Here lymph circulation is forced by the respiratory action of the diaphragm, aided by the duct's smooth muscle and internal valves which prevent the lymph from flowing back down again [91].

High energy-consuming movements such as locomotion stimulate calcium and phosphate metabolism by mechanosensory mechanisms [92]. The bones are highly active tissue that receives up to 10% of overall cardiac output, and thus circulating substrates could meet that demand under normal circumstances [55]. The skeletal system forms an interface between the organism and the environment. Skeletal loading through physical activity is critical for bone health [93]. The gravitational field is an inherent attribute of our environment playing an important role in the development of the musculoskeletal system and its anatomical adaptation [86]. Gravity force plays a vital role in the performance of all movements, particularly locomotion. Bones exposed to gravity forces generate signals that control the systemic metabolism of calcium and phosphate, the two key metabolites of life [3].

The so-called piezoelectric effect plays an important role in the process of bone metabolic activity and repair [94,95]. The effect promotes osteoblast migration and differentiation. In response to piezoelectric stimulation, osteoblasts secrete three times the volume of the matrix in three to four days, and then become osteocytes anchored in them [95]. The electrical signals activate the voltage-gated calcium channel on the cell membrane surface, resulting in an influx of Ca^{2+} ions in the cell. Mechanotransduction by Piezo1 channels regulates osteoblast/osteocyte activity and, thus, strengthens the skeleton enabling it to adapt to a wide range of mechanical loadings [96]. The decline in Piezo1 activity in adulthood results in osteoporosis. Piezo2 channels in sensory neurons might provide another route of skeletal regulation [96]. Piezo channels also regulate the proliferation and differentiation of various types of stem cells.

The process of tissue development and homeostasis is intrinsically regulated using mechanotransduction [92,96]. Piezo channels have also been found to play essential roles in the development of the cardiovascular system, lungs, cartilage, and bones. Piezo1 and Piezo2 channels serve as important mechanosensitive channels for touch, pain, proprioception, hearing, vascular tone, and fluid flow. Piezo channel activation leads to calcium ions influx and triggers various molecular signaling cascades. Piezo2 channels are present in osteoblasts. Mechanotransduction is primarily mediated by Piezo1 regarding bone formation [96]. Piezo2 shows robust expression in peripheral sensory neurons and may regulate bone development and homeostasis in a non-autonomous manner. Transduction of mechanical stimulation into cellular responses by mechanosensitive molecules is crucial for skeletal homeostatic maintenance, and Piezo channels play important roles in this process. Piezo channel activity may affect bones via the regulation of osteoclast differentiation and activation whereas it inhibits adipocyte differentiation and production [96]. Piezo1 signaling in gut epithelia controls gut peristalsis and regulates bone density by serotonin production [96].

Another mediator of body-environment interaction is vitamin D. Vitamin D (calcitriol) circulates in the blood as a hormone, playing a major role in regulating calcium and phosphate concentrations, as well as promoting bone health and bone remodeling. It influences the immune system, by activating several white blood cells, including monocytes, T and B cells [97]. Vitamin D is the essential catalyst for energy homeostasis and glucose metabolism, influencing insulin secretion, and glucose levels.

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In the body, vitamin D is synthesized from its cholesterol precursor (7-dehydrocholesterol), which can be converted in the skin to the active form of the vitamin after sunlight exposure [97]. Moreover, cholesterol and vitamin D are essential for life since their activity is required to build and maintain cellular and mitochondrial phospholipid membranes. Importantly, vitamin D increases the activity of the tyrosine hydroxylase in adrenal medullary cells affecting the synthesis of neurotrophic factors, nitric oxide synthase, and glutathione, which control the body's response and adaption to stress [98]. In this process the enzyme responsible for catalyzing the conversion of the amino acid L-tyrosine L-DOPA, which is a precursor for dopamine, and catecholamines. The half-life of vitamin D is 8–10 h and its levels are affected by changes in calcium, phosphorus, parathyroid hormone, and fibroblast growth factor 23 (FGF 23) levels [97]. Poor nutrition and limited sun exposure are the major factors diminishing vitamin D synthesis and activity. It is estimated that about 3 % of the human genome is regulated by vitamin D which controls two major cellular functions, proliferation and differentiation [97]. Therefore vitamin D deficiency can be associated with senescence, cancer, autoimmune diseases, stress, hypertension, and diabetes.

5. Information Metabolism

Life depends on an organism's ability to stabilize internal bodily mechanisms independently of environmental variations such as food accessibility, changes in their composition and energy value, as well as physical-chemical parameters of our environment, etc. This physiological mechanism of regulation, called allostasis, allows an organism to anticipate and adjust its energy use according to environmental demands. Allostasis depends on several organismal capabilities such as the accumulation of energy and metabolic resources as well as their optimal use and recovery when possible. Toward these aims human body accumulates heat and energy substrates such as glucose and fat. Moreover, the kinetics of all metabolic processes are finely adjusted to internal and external environmental conditions.

The complexity, interplay, and differentiated kinematics of particular biochemical reactions require that particular phases of the biochemical processes should be well-temporary and quantitively coordinated. Therefore, homeostasis and life depend on uninterrupted intracellular and between cells, and tissue, communication. The signaling metabolism being the foundation of life includes self-organizing synergies that optimalize cellular and tissue functioning and interactions, which culminate in cognitive and social processes [100]. The brain is the master controller of energetic and information metabolisms [101]. Communications and interactions at the cellular and organ levels provide feedback for the brain which may have a decisive impact on emotional/motivational states, health, and longevity of individuals.

To live organism must continuously interact and adapt to its environment. Generally, information metabolism with its exogenic and endogenic components evolved to provide such adaptation. Some organismal capabilities such as motivations, emotions, perception, learning, and memory allow humans to adapt socially and maintain homeostasis for a lifetime in our ecosystem. In particular, emotions coordinate the homeostasis of an organism in a complex, dynamic environment and participate in the regulation of social behaviors [102]. Simultaneously, the endogenic homeostatic controls including energy metabolism and intercellular and interorgan signaling and interactions allow for maintaining organismal integrity and life. In these processes, stress-dependent regulation of behavior plays a vital role. Catecholaminergic, dopaminergic, and serotonergic systems contribute to the control of vital life processes such as motor activity, cognition, emotion, and memory [103]. They also co-regulate the brain and immune system interactions. Serotonin and dopamine are neurotransmitters related to fatigue, a feeling that adjusts intensity or interrupts skeletal muscle activity [104]. All changes in peripheral physiological systems such as substrate depletion or metabolite accumulation act as afferent signals which modulate control processes in the brain [104].

The most important product of information metabolism is self-awareness [105]. Perception and memory enable our brain to form a somatosensory representation of our organism and an egocentric representation of the environment [106,107]. These brain networks of consciousness allow us to

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perceive the existence of ourselves in the environment, which is the basis for motivational and emotional control of our behaviors necessary to survive. The hippocampus is the main brain structure that integrates interoceptive information with sensory signals allowing to communicate the body with the environment [108]. At the basic level, communication determines the affective behavior of the organism in the exploration of the environment to obtain food, as well as avoiding life-threatening situations through 'flight or fight' responses, and procreation [108]. The next aim of information metabolism is the formation of social attachments which is a critical component of human life. In the brain, vasopressin and oxytocin neuropeptide systems are critical for the establishment of social bonds and the control of emotional behaviors. In humans, these processes begin early in postnatal life and play a critical role in children's survival and environmental adaptation. Therefore, both neuropeptide systems are associated with social and emotional communication which are the pillars of information metabolism. They allow us to form emotional bonds and, what is also important, reduce stress [109].

The base of information metabolism is multilevel and multimodal communication within organisms as well as with the environment. It allows for maintaining life synergy through integrated endocrine, paracrine, and autocrine signaling at all levels of the organism, from cellular to systemic. Mitochondria are vital in cellular and organismal pathways that direct metabolism, stress responses, immunity, and cellular fate [110]. Towards this aim, mitochondria have established networks of both intra- and extracellular communication [110]. Intracellular communication routes comprise direct contacts between mitochondria and other cellular components using ions, metabolites, and other intracellular messengers [110]. Mitochondrial cytokine (mitokine) factors can provide between-tissue communication and may respond to immune signaling from extracellular sources [110]. Mitochondrial signaling includes the transport of metabolites or small molecule messengers as well as the budding of vesicles carrying mitochondrial cargo to other cellular locations [110]. The mitochondrial release of cytochrome c is pivotal for the control of apoptosis [110]. The physical contact sites with other organelles and subcellular compartments allow for mitochondria-driven transcriptional responses to rewire cellular metabolism in response to stress [110]. The mitochondrial-to-nuclear transcriptional programs direct the activity of nutrient sensors such as mTORC1 and AMPK and protein homeostasis machinery such as lysosomes, as well as the proteasome, chaperones, and small heat shock factors [110]. Mitochondria also participate in systemic signaling to coordinate organismal stress responses and mediate systemic metabolic changes, as well as function as hubs of immune signaling [110].

Integrated interoceptive and exteroceptive control of organismal energy metabolism allows for fine adjustment of energy metabolism to internal and external environment [111]. The living organism is capable of signaling its activity and the signals are sent to all organs and receive feedback about the body's needs. The exchange and processing the sensory information in the brain plays a fundamental role. Internal information metabolism is based on the subconscious exchange of cellular and hormonal signaling, which are the base of subjective motivational and emotional drive [112]. Additionally, the exchange of information with the environment allows us to create in the brain a sphere of self-consciousness and egocentric representation of our environment [107].

The homeostasis is actively regulated with complex feedback mechanisms with the brain as a master controller [101]. The hypothalamus is a brain region that plays a critical role in the regulation of energy homeostasis [101]. It is the central controller of systemic metabolic processes including body temperature, hunger, thirst, fatigue, sleep, and circadian rhythms. The hypothalamus is a key regulator of metabolism, controlling resting metabolism, activity levels, and responses to external temperature and food intake [101]. Supervision by the brain of activities necessary to maintain the body's life is another process characterized by high energy consumption [113]. The sleep phase, in turn, is characterized by a lack of motor activity and the exclusion of conscious and motivational-emotional processes. However, only a small decrease in the brain's energy consumption is observed during sleep [99]. This phenomenon is primarily associated with the activity of the processes of restoring brain homeostasis during sleep, including the removal of waste products of nervous activity. In addition, repair processes and memory-forming processes are carried out in the sleep

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phase [99]. The restructuring of synaptic connections of neural networks and the process of neurogenesis in GABAergic subcortical structures of motor memory require significant energy expenditure [16,114]. The processes of neuronal homeostasis recovery, restoring ionic balance, renewing neurotransmitter resources, and the removal of waste products consume a significant amount of energy, stored in the liver in the form of glycogen and fatty acids. The substantial decline in hepatic glucose resources during sleep is considered energy stress that triggers the sleep-wake transition and restores energy resources by feeding behavior. The transition is controlled by the release of catecholamines [115].

Perception, learning, and memory are important attributes of life. These processes are modulated by emotions affecting and motivating all aspects of human behaviors and supporting survival. Emotional states coordinate also food habits, which are the basis of energy metabolism and homeostasis. The appetitive states usually involve reward signaling including dopamine, serotonin, and oxytocin [116]. On the other hand, major metabolic deficiency is signaled by fear and even panic. The posterior parietal cortex is the area important for sensory-motor integration [117]. Among its functions is the forming of intentions, that is, high-level cognitive plans for movement [117].

Acetylcholine is the primary neurotransmitter of the parasympathetic nervous system. Choline and acetyl-CoA availability determines the rate of acetylcholine synthesis. The cholinergic system is a branch of the autonomic nervous system that plays an important role in memory, digestion, heartbeat control, blood pressure, and movement [66]. The brain contains several cholinergic areas, each with distinct functions, such as arousal, attention, memory, and motivation [112].

Arousal is the physiological state of being awoken or of sense organs stimulated to a point of perception. It involves activating the ascending reticular activating system in the brain, leading to increased heart rate, blood pressure sensory alertness, mobility, and reactivity. Low levels of norepinephrine allow to sleep and rise to initiate wakefulness. ATP acts as either the sole transmitter or a co-transmitter in most nerves in both the peripheral nervous system and the central nervous system [33]. Noradrenaline and ATP are sympathetic co-transmitters. In the pancreas, increased release of glucagon. In the liver, an increase in the production of glucose, either by glycogenolysis or by gluconeogenesis. In skeletal muscles, an increase in glucose uptake. The central effects of noradrenaline are manifested in alertness, arousal, and readiness for action.

Heartbeat control allows for the adjustment of blood circulation to the current life processes while protecting against heart overload. Towards this aim, the blood pressure upstroke induces baroreceptor afferent impulses at each heartbeat, immediately transformed into vagus nerve feedback activity to slow down the sinoatrial node [118]. The vagus nerve innervates numerous organs including the gastrointestinal tract [119]. The vagus is a mixed nerve, with 80% afferent fibers that convey visceral, somatic, and taste signals. The rest are efferent fibers controlling gastrointestinal motility and secretion as well as blood circulation. The tissue signals via vagus nerve afferents are sent directly to sympathetic neurons in hindbrain nuclei, which project to the hypothalamus [41] and to the limbic structures, which affect and motivate all aspects of life [112].

The sympathetic nervous system controls the body's vital organs and functions, such as the cardiovascular and respiratory systems. It contributes to the stress response by releasing epinephrine and norepinephrine from the adrenal medulla. Sympathetic tone may mediate the leptin-dependent regulation of bone-related calcium metabolism [115]. An elevated sympathetic tone accompanies stress related to between-meal glucose decline that motivates organisms to consummatory behaviors to replenish energy fuels and glucose, in particular. The behavioral response is triggered by bone calcium release controlled by catecholamines. However, chronic stress and excessive sympathetic activity may develop osteoporosis that β-blockers can treat [115].

The bone-derived hormone osteocalcin crosses the blood-brain barrier and binds specifically to serotonergic neurons of the raphe nuclei in the brainstem, to neurons of the CA3 region of the hippocampus, and of the dopaminergic nucleus of the ventral tegmental area in the midbrain [120]. In the brain, osteocalcin plays an important role in development and functioning including spatial learning and memory [121]. The osteocalcin deficiency could be traced to a decrease in the synthesis of all monoamine neurotransmitters and to an increase in GABA [120]. This is accompanied by

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behavioral phenotypes such as increased anxiety and a profound deficit in spatial learning and memory [120,121]. Osteocalcin permits manifestations of the acute stress response by inhibiting the post-synaptic parasympathetic neurons, thereby leaving the sympathetic tone unopposed.

Signaling related to the efficiency of energy metabolism is crucial for life. The decrease in NAD levels and the possibility of restoring its physiological level play an important role in the control of motivational and emotional mechanisms that are the basis of information metabolism. In a young, healthy organism, tryptophan catabolism via the kynurenine pathway is the primary source of NAD supplementation. Tryptophan in the blood activates the brain's serotonergic reward system [122]. Additionally, in the ventromedial hypothalamic nuclei, serotonin signals recruit two mediators to inhibit bone mass increase, the neuropeptide cocaine and amphetamine-regulated transcript (CART) and adrenaline [115]. However, high-stress levels or chronic infections can change this process by provoking an immune response that alters the kynurenine pathway. Instead of serotonin in the intermediate steps, several bioactive compounds are produced, such as kynurenic acid and quinolinic acid [122]. These intermediate metabolites have an immunomodulatory effect depending on coexisting inflammatory processes. For example, kynurenine inhibits the synthesis of deoxyribonucleic acid, leading to necrosis and tumorigenesis [122]. In turn, quinolinic acid produced in the brain by microglia excessively stimulates NMDA receptors that may culminate in excitotoxicity and death of overactive dopaminergic neurons of the substantia nigra and striatum. Quinolinic acid is also associated with kidney and liver failure, and neurodegenerative conditions, leading to depression, anxiety, sleep problems, and cognitive changes [122]. Quinolinic neurotoxicity initiates a cascade of events culminating in excitotoxicity, ATP depletion, oxidative stress, neuroinflammation, and selective GABAergic neuron loss [123]. Importantly, the quinolinic acid neurotoxicity can be alleviated by melatonin which acts independently and by different mechanisms in modulating antioxidant enzyme activities [124].

Energy metabolism is mediated by stress hormones epinephrine, norepinephrine, and cortisol [90]. In rest, fatty acid oxidation in the myocardium provides sufficient amounts of ATP supply to maintain the resting energy metabolism of the body. To initiate a movement brain implements a motor program that has been memorized with emotional value. Particularly, stress metabolic response plays an important role in the realization of the program by catecholamine-dependent calcium release in bones. However, stress-related increases in calcium alone may block sodium channels, causing smooth and skeletal muscle hypotonicity, resulting in weakness and low tone of skeletal muscles. Consequently, the excitability of the nerves and muscles may decrease. To avoid such deficiency, the initiation of intensive motor tasks must be accompanied by a rapid change in ATP levels. To avoid cardiac overload and minimize skeletal muscle transition to increase load both tissues use an intracellular phosphocreatine system [125,126]. In this system, creatine kinase catalyzes the reversible conversion of creatine and adenosine triphosphate to phosphocreatine and adenosine diphosphate. Thus, the phosphocreatine serves as a rapidly mobilizable reserve of high-energy phosphates in skeletal muscle, myocardium, and the brain. The phosphocreatine system can produce high levels of ATP in situations of high metabolic demand, such as during the initiation of high-intensity motor activity when the rate of ATP use exceeds its capacity for generation by other metabolic pathways [125,126]. Creatine is particularly abundant in tissues with high and intermittent energy fluctuations, such as skeletal muscle, heart, and brain which allows them to speed up their metabolism during stress-related life-protecting responses such as fight-or-flight. High levels of phosphocreatine in plasma result in damage to the glomerular filtration barrier, excluding kidneys from the erythropoietin-dependent control of erythropoiesis which particularly strikes the oxygen supply to the brain. The phosphocreatine can also cross the blood-brain barrier throughout the fenestrated capillaries in the striatum, hippocampus, and hypothalamus, resulting in damage to systemic homeostasis control.

Skeletal muscle is an endocrine organ, that secretes hundreds of myokines that exert their effects in autocrine, paracrine, or endocrine manners [90]. Myokines allow crosstalk between the muscle and other organs, including the brain, adipose tissue, bone, liver, gut, pancreas, and vascular bed [90]. Myokines are responsible mainly for mediating energy supply, muscle cell proliferation,

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differentiation, and regeneration. Myokine IL-6 affects lipid and glucose metabolism and plays important roles in myogenesis. IL-6 signaling within the muscle can affect glucose uptake and fat oxidation via AMPK activation. Musclin has been identified as an exercise-induced factor promoting skeletal muscle mitochondrial biogenesis. Myostatin is a positive regulator of bone resorption [90]. BAIBA is a molecule produced by contracting muscles [85]. It activates the β-oxidation pathway of hepatic fatty acid and improves insulin sensitivity in skeletal muscle [85]. It also protects osteocytes against reactive oxygen species and prevents bone and muscle loss [85]. The function of BAIBA is lost in aging bones due to the downregulation of its receptor in osteocytes [85].

The energetic processes occurring in the neuromuscular system depend on the intra- and extracellular Ca^{2+} signaling [127,128]. Serum calcium levels are maintained within the physiological range by bone resorption [36]. Calcitonin is secreted by the para-follicular cells of the thyroid gland in response to an increase in serum calcium concentration opposing the effects of parathyroid hormone [129,130]. In bones, calcitonin inhibits osteoclast action and bone resorption [127,131]. Calcitonin in kidneys reduces the reabsorption of calcium, sodium, potassium, chloride, and phosphate. Respiratory alkalosis decreases the serum ionized calcium whereas metabolic acidosis is associated with an increase in calcium excretion, independent of parathormone changes [36]. The activity of calcitonin in the central nervous system may induce eating disorders [130].

Calcium signaling plays a vital role in bone mineralization, muscular contraction, hormone secretion, neurotransmission, intracellular adhesion, and apoptosis [132]. Disruption of calcium signaling can induce apoptosis through a complex interplay involving Ca^{2+}-activated proteases, phospholipases, and endonucleases. Increases in cytoplasmic calcium levels, either through internal release from ER/SR stores or external calcium entry through plasma membrane ion channels, drive intracellular processes by exerting direct and indirect regulatory effects on a multitude of enzymes and proteins [133].

Calcium ions play also a vital role in motor activity. In hypoactivity, calcium excretion is increased while absorption is reduced leading to a sustained negative calcium balance. Osteoblasts and osteoclasts consume up to 20% of the quantity of glucose taken up by muscles [115]. Inside the osteoblast, glucose is metabolized mostly through aerobic glycolysis to generate ATP molecules necessary for bone formation [115]. Insulin signaling in osteoblasts favors osteoclast differentiation and bone resorption by inhibiting the expression of osteoprotegerin [115]. Insulin and IGF-1 signaling in osteoblasts increases the release of osteocalcin, the hormone protein that stimulates insulin secretion [115]. Osteocalcin in contracting muscles intensifies the use of the self-stored glycogen and consequently enables postprandial insulin-dependent glucose uptake [134]. This results in a decline in muscle mass and strength, which limits physical activity. Skeletal tissue is a major storage site for calcium and phosphate ions, and endocrine organs secrete peptides working on other remote organs [135]. Bones secrete osteocalcin, a hormone that participates in glucose and fat metabolism [86]. Osteocalcin stimulates also insulin secretion by the pancreas as well the β-cell proliferation.

Bones communicate with bone marrow, muscle, adipose tissue, kidney, liver, and brain [135]. The bone-derived hormone osteocalcin is the regulator of energy metabolism [121,135]. The hormone contributes to the signaling in muscle, brain, pancreas, and fat tissue [41]. The hormone intensifies the release of insulin in the pancreas with concomitant activation of adiponectin in the adipocytes, which in turn amplifies insulin sensitivity in skeletal muscles, fat, and hepatic tissue [41]. In physiological conditions, plasma levels of osteocalcin are negatively correlated with those of glucose. In turn, hyperglycemia induces a low turnover rate by evoking osteoblast dysfunction and suppressing serum osteocalcin levels [136]. The circulating levels of osteocalcin are the highest in adolescence and gradually decrease in midlife.

In fat cells, osteocalcin triggers the release of the hormone adiponectin, which increases insulin sensitivity [41,137]. Adipokines produced by fat cells, such as leptin and adiponectin, are key mediators of physiological processes in distant organs, such as the brain, liver, and muscle, where they control appetite, digestion of nutrients, energy expenditure and storage, glucose and lipid metabolism and insulin sensitivity. The regulation of bone remodeling by an adipocyte-derived

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hormone implies that bone may exert a feedback control of energy homeostasis [41]. Osteocalcin signaling in myofibers is necessary for adaptation to exercise by favoring the uptake and catabolism of glucose and fatty acids [134]. Circulating levels of osteocalcin double during aerobic exercise at the time those of insulin decrease [134]. In humans circulating levels of osteocalcin decrease during early adulthood but the supplementation of osteocalcin can restore exercise capacity and thus can reverse its age-induced decline [134].

Osteocytes control bone resorption through the osteoclast-released receptor activator of nuclear factor kappa-B ligand (RANKL), bone formation through the local release of sclerostin, which inhibits Wnt/β/catenin, and phosphate metabolism through the systemic production of FGF-23. Prostaglandin (PGE2) and nitrogen released by osteocytes have anabolic effects on osteoblasts. Osteocytes are exposed to hormones, cytokines, inflammatory factors, and signals from other tissues and glands, such as muscles, kidneys, intestines, and parathyroid glands, which regulate the activity of osteocytes [58]. Metabolic activity and bone remodeling are controlled by mechanical factors, endocrine and paracrine signals including insulin-like growth factor, transforming growth factor TGF-β, interleukins IL-1, IL-6, and tumor necrosis factor - α (TNF-α) [58].

Osteopontin is an extracellular structural protein that plays a critical role in bone synthesis mediated by osteoblast activity. The inorganic phosphate is a potent inhibitor of osteopontin which during intensive motor activity inhibits the deposition of hydroxyapatite in bones, increasing calcium ions in circulation [11]. The calcium ions bind to osteocalcin which transports them to the heart, diaphragm, striatal muscles, and brain. In these tissues, using calcium-calcium-induced signaling enables neuromuscular activity [11].

Hypocalcemia and hypophosphatemia stimulate kidney proximal tubule cells to produce calcitriol (1,25-dihydroxy-vitamin D3), which increases osteopontin secretion. Osteopontin is minimally expressed under physiological conditions but accumulates quickly as heart function declines [138]. It stimulates a wide range of physiological processes in the myocardium, including angiogenesis, local production of cytokines, differentiation of myofibroblasts, increased deposition of extracellular matrix, and hypertrophy of cardiomyocytes. Osteopontin acts also as a proinflammatory cytokine that can be secreted from many cells, including activated macrophages and T-lymphocytes [139].

The adipose tissue secretes several adipokines such as leptin, adiponectin, adipsin, resistin, visfatin, and lipokines regulating systemic glucose and lipid metabolism [71,90,140]. Leptin, the satiety hormone secreted by adipocytes in the presence of insulin, prevents overnutrition by inhibiting the enzyme, 5′-adenosine monophosphate-activated protein kinase (AMPK) in the hypothalamus to suppress appetite [141]. Simultaneously, it activates AMPK in skeletal muscles, by increasing the AMP/ATP ratio which stimulates glycolysis and glycogen synthesis [41]. AMPK regulates mitochondrial biogenesis by regulating PGC1α, a cofactor that promotes the transcription of nuclear-encoded mitochondrial genes [141]. The accumulation of three major nutrients, glucose, fatty acids, and amino acids is suggested to suppress AMPK and contribute to insulin resistance [141].

Ghrelin is a hormone primarily produced by enteroendocrine cells of the gastrointestinal tract, especially the stomach, and increases the drive to eat. Ghrelin prepares organisms for food intake by increasing gastric motility and stimulating the secretion of gastric acid. Blood levels of ghrelin are highest when hungry, returning to lower levels after meals. Marrow adipose tissue secretes adiponectin which exerts systemic metabolic effects by regulating glucose levels and fatty acid breakdown [88]. Low levels of adiponectin are symptomatical for mitochondrial dysfunctions related to inflammation, hypoxia, or endoplasmic reticulum stress [88].

The liver-released fetuin-A participates in glucose and lipid metabolic switch [142]. Fetuin-A inhibits insulin receptors in the liver, skeletal muscles, and fat tissue thus reducing glucose uptake and promoting lipid-induced insulin resistance [142,143]. It also acts as an inhibitor of bone calcification. Free fatty acids cause fetuin-A overexpression by increasing the pro-inflammatory protein NF-κB [143].

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6. Senescence and Death

In adult organisms, energy is necessary to carry out all basic life processes, such as metabolism, homeostasis, cellular turnover, reproduction, and environmental adaptation. Progressive system senescence and metabolic dysregulation interfere with the basic life processes. Limited longevity of individuals opens the need for species life based on reproduction. It allows descendants to better adapt to the slowly but continually changing environment. A characteristic feature of ontogeny is the change in the adaptative processes. The most intensive adaptation to the environment is observed in the early developmental period, from birth to maturity. Then the adaptive abilities of the organism gradually weaken with age, which results in a decrease in the body's immunity, and chronic inflammation.

Aging is characterized by chronic, low-grade inflammation. Particularly, dysfunctions of cellular turnover and defective repair processes increase inflammatory processes. Additionally, thymus involution and the resulting failure of the acquired immune system cause exacerbation and chronicity of inflammation. Intracellular protein accumulation, typical of aging highly active cells, reduces the oxygen diffusion coefficient, intensifying the energy crisis. Senescence is a cellular response featuring a stable cell cycle arrest that limits the potential of cell proliferation [58]. The senescent mesenchymal stem cells are characterized by decreased stemness, cell phenotype changes, immunomodulatory property damage, impaired proliferative ability, and higher susceptibility to apoptosis, which highly restricts their therapeutic value [58]. The senescence of the bone marrow strikes particularly the process of hematopoiesis. Erythrocytes, under physiological conditions, are replaced on average every 120 days [81], their lifespan in older organisms is shortened to up to 14 days [144]. As a consequence, intense but not fully efficient hematopoiesis is forced, resulting in the production of dysmorphic red blood cells, which not only causes their rapid use but also intensifies damage to blood vessels. Transport and distribution of energy substrates such as oxygen, glucose, calcium, and phosphates decreases rapidly, causing the development of metabolic dysfunctions. The main of these is the escalating shift of energy metabolism to beta-oxidation.

Due to the inherently limited efficiency of biological processes, the basis of life is multimodal interaction with the environment, the purpose of which is the precise and efficient adaptation of the organism to its natural environment. The process of adaptive adjustment also applies to building immune protective barriers. The thymus involution is an example of a life-limiting process, aiming at dysregulations of immunoreactivity. The thymus is an extraordinary organ of the human body that operates as a “lifetimer”. The thymus is a specialized primary lymphoid organ of the immune system that controls immuno-adaptive processes [145,146,147]. Hemopoietic stem cells of bone marrow are the source of T-cell precursors, which are then transported by blood to the thymus, where they differentiate and mature. Most thymus activity falls during the early developmental period and later on, due to natural involution. Size and activity of the thymus decline steadily and its cells are gradually replaced by fatty tissue, which exhausts the body's adaptive abilities of the organism, culminating in death [146].

Human thymic involution starts as early as 1 year of age [146]. A symptom of involution is a decrease in thymic epithelial cells and their replacement with adipose tissue [146]. At the age of 45 years, adipose tissue constitutes almost 75% of the thymus volume, morphologically consisting of multiple lipid-laden multilocular cells with proinflammatory properties [147]. Consequently, thymic involution is associated with increased susceptibility to many diseases, including cancer, infection, and autoimmunity [146]. In the elderly, nearly all the thymus parenchyma consists of adipocytes. The resultant lymphocyte T deficiency directly impacts the development of inflammation and induces various autoinflammatory disorders, including atherosclerosis [147].

NAD plays a decisive role in ATP production in the neurons and myocytes. Unfortunately, cellular NAD levels decline steadily to reach 100% of the brain's physiological needs by the age of 45 [54]. In old age, the NAD deficit can reach up to 20% of physiological needs, leading to massive death of neurons and disintegration of their neuronal networks. ATP deficiency impacts firstly functioning of the central nervous system which may manifest with metabolic encephalopathy [148]. The

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symptoms of chronic hypophosphatemia may include an altered mental state, irritability, paresthesias, numbness, seizures, or coma [148].

Chronic intracellular ATP deficiency and mitochondrial dysfunction in striatal muscles can cause generalized muscular weakness culminating in dystrophy and rhabdomyolysis, resulting in increased creatinine phosphokinases renal and brain injuries [148]. A concomitant decrease in diaphragm function impacts the availability of oxygen [148]. Also, myocytes become less stable, and arrhythmias become more likely [148]. Gastrointestinal dysfunctions appearing due to ATP deficiency include swallowing difficulties, lack of peristalsis, or constipation [148]. The decline of the myocardium and diaphragm activity results in chronic oxygen deficiency culminating in increased lactate levels which cannot be metabolized efficiently by the liver and kidneys. Consequently, lactate impairs the metabolic functions of these organs and the entire organism. Importantly, the oxygen deficit strikes mainly the respiration process in highly active cells such as neurons and myocytes, which may culminate in lactic acidosis. The excess lactate cannot be metabolized efficiently by the liver and kidneys causing metabolic dysfunctions of these organs and the entire organism. Importantly, the oxygen deficit that increases with age impairs the respiration process, which further intensifies lactic acidosis.

The main problem of energy metabolism leading to organism senescence is insulin resistance. It is a disorder with a multifactorial basis directly related to glucose metabolism or excessive fat accumulation in the body. Insulin has a substantial impact on intestinal lipid metabolism both directly and indirectly by inhibiting the release of fatty acids from adipose tissue. In adipocytes, insulin stimulates glucose uptake to fuel de novo lipogenesis [62]. Additionally, insulin reduces the formation of intestinal lipoproteins. During passage through the hepatic sinusoids, remnant particles are further hydrolyzed by hepatic triglyceride lipase and gain additional apoE, which makes it possible for them to bind to and be taken up by proteins on the surface of liver cells [74]. The accumulation of the remnant lipoproteins plays a pivotal role in fatty liver disease.

The main pathogenic impact of lipid-based energy metabolism is visceral fat accumulation, leading to lipotoxicity [21]. Fat metabolism is combined inextricably with visceral fat accumulation impairs metabolism in all tissues that become resistant to the anti-lipolytic effect of insulin [21]. With the decline of insulin anti-lipolytic action, the intracellular levels of free fatty acid increase rapidly, leading to endoplasmic reticulum stress. Moreover, the excess of free fatty acids induces chronic inflammation that is harmful to multiple organs and systems [21]. Dominance of fat metabolism may induce hepatic steatosis and insulin resistance, concurrent with innate immune system activation [70].

Under physiological conditions and during nutrition with a healthy diet, white adipocytes store excess energy fuel in the form of triglycerides [22]. In a high-fat diet, excess fatty acids cannot be completely removed from the bloodstream, which causes a long-term increase in circulating free fatty acids. This affects intracellular esterified fatty acids, increasing their interactions. Excess energy stimulates lipogenic enzymes that synthesize triglycerides for storage while reduced caloric intake stimulates enzymatic lipid hydrolysis and the release of free fatty acids from fat stores into the bloodstream for metabolism by other organs [88]. As fat deposits expand in states of obesity, the fat tissue undergoes remodeling to facilitate tissue expansion [88]. Dead adipocytes are removed by adipose tissue macrophages that infiltrate the fat tissue in response to adipocyte death, and these macrophages contribute to an increased inflammatory profile in the white adipose tissue depots which are often associated with the development of insulin resistance. As a result, activation of KATP channels leads to insulin resistance, which first hits the tissues with the highest energy metabolism involved in glucose homeostasis, such as the brain, skeletal muscle, and liver [10,22]. Fats, inflammatory cytokines, and other toxic substances are continuously delivered via the thoracic duct and the portal vein to the liver, causing the expansion of visceral adipose tissue and liver metabolic disorders [22]. The lymphatic fluid comprises an interstitial fluid, dietary fat, lymphocytes, immunoglobulins, proteins, metabolites, electrolytes, and vitamins [91], thus lipid overload is associated with liver insulin resistance, metabolic syndrome, and chronic kidney disease [88]. Visceral adipocytes are also more responsive to lipolytic signals which upregulate the transport of

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free fatty acids [88]. All of these pathologies can increase the risk of cardiovascular disease even at a young age [de Ferranti et al. 2019].

Systemic metabolic disorders that increase with age impair homeostasis, the essential for life state of steady internal physical and chemical conditions. In particular, the process of cellular turnover, which contributes significantly to homeostasis, is permanently disturbed by the aging-related switch to lipid-based energy metabolism. The metabolic switch is the next process intensifying lactate acidosis. The impact of acidosis and contamination of the extracellular environment with fatty acids disturbs completely cellular turnover resulting in the formation of dysmorphic and dysfunctional cells initiating the process of carcinogenesis. In addition, the aging of the body increases circulatory problems through the accumulation of damage to blood vessels and especially capillaries by dysmorphic red blood cells. An almost tenfold decrease in the viability of erythrocytes, accompanied by pathomorphological changes in red blood cells, causes further exacerbation of cellular respiration problems. Additionally, angiogenesis, which is an essential element of effective cell exchange, is disturbed.

Senescence occurs in many cell types such as keratinocytes, melanocytes, endothelial cells, epithelial cells, glial cells, adrenocortical cells, T lymphocytes, and even tissue stem cells [149]. The number of cancer cells, that cannot be removed by immanent defense mechanisms, increases rapidly. Senescent cell burden is low in young individuals but increases with aging in several tissues, including adipose, skeletal muscle, kidney, and skin [149]. Cellular senescence can contribute to systemic aging and all age-related pathologies by accelerating the loss of tissue regeneration through the depletion of stem cells and progenitor cells [149]. The accompanying metabolic dysfunctions, especially energy dysmetabolism, lead to the exhaustion and death of the organism.

Concluding, chronic energy deficit is the greatest threat to the body and is signaled in the brain as stress. The aging-related NAD deficit plays a key role in this process. NAD deficiency causes failure of the cellular respiration process and the breakdown of all cellular repair processes dependent on NAD, causing massive cell death. This process can no longer be compensated by cellular turnover. Importantly, in young healthy individuals, the cellular level of NAD is efficiently supplemented by tryptophan. Still, this process breaks down due to chronic stress associated with massive cell death and metabolic diseases. The kynurinic acid pathway produces quinolinic acid instead of NAD, which leads to the breakdown of information metabolism and the loss of the motivational and emotional drive necessary for life.

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References

1. Chaudhry R., Varacallo M. Biochemistry., Glycolysis. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482303/
2. Talley JT., Mohiuddin SS. Biochemistry., Fatty Acid Oxidation. [Updated 2023 Jan 16]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556002/
3. Błaszczyk JW. Metabolites of Life: Phosphate. Metabolites. 2023 Jul 19;13(7):860. https://doi.org/10.3390/metabo13070860.
4. De la Fuente IM. (2010) Quantitative analysis of cellular metabolic dissipative., self-organized structures. Int J Mol Sci. 2010; 11: 3540–3599.
5. De la Fuente IM., Cortés JM., Valero E., Desroches M., Rodrigues S., Malaina I., Martínez L. On the dynamics of the adenylate energy system: homeorhesis vs homeostasis. PLoS One. 2014 Oct 10;9(10):e108676. https://doi.org/10.1371/journal.pone.0108676.
6. Hochachka PW., McClelland GB. Cellular metabolic homeostasis during large-scale change in ATP turnover rates in muscles. J Exp Biol. 1997; 200: 381–386.
7. Nguyen BY., Ruiz-Velasco A., Bui T., Collins L., Wang X., Liu W. Mitochondrial function in the heart: the insight into mechanisms and therapeutic potentials. Br J Pharmacol. 2019 Nov;176(22):4302-4318. https://doi.org/10.1111/bph.14431.

8. Murphy E., Ardehali H., Balaban RS., DiLisa F., Dorn GW 2nd., Kitsis RN., Otsu K., Ping P., Rizzuto R., Sack MN., Wallace D., Youle RJ; American Heart Association Council on Basic Cardiovascular Sciences., Council on Clinical Cardiology., and Council on Functional Genomics and Translational Biology. Mitochondrial Function., Biology., and Role in Disease: A Scientific Statement From the American Heart Association. Circ Res. 2016 Jun 10;118(12):1960-91. https://doi.org/10.1161/RES.0000000000000104.
9. Törnroth-Horsefield S., Neutze R. Opening and closing the metabolite gate. Proc Natl Acad Sci U S A. 2008 Dec 16;105(50):19565-6. https://doi.org/10.1073/pnas.0810654106.
10. Rodríguez-Rivera NS., Barrera-Oviedo D. Exploring the Pathophysiology of ATP-Dependent Potassium Channels in Insulin Resistance. Int J Mol Sci. 2024 Apr 6;25(7):4079. https://doi.org/10.3390/ijms25074079.
11. Fatherazi S., Matsa-Dunn D., Foster BL., Rutherford RB., Somerman MJ., Presland RB. Phosphate regulates osteopontin gene transcription. J Dent Res. 2009 Jan;88(1):39-44. https://doi.org/10.1177/0022034508328072.
12. Martin GM., Patton BL., Shyng SL. KATP channels in focus: Progress toward a structural understanding of ligand regulation. Curr Opin Struct Biol. 2023 Apr;79:102541. https://doi.org/10.1016/j.sbi.2023.102541.
13. Crawford RM, Jovanović S, Budas GR, Davies AM, Lad H, Wenger RH, Robertson KA, Roy DJ, Ranki HJ, Jovanović A. Chronic mild hypoxia protects heart-derived H9c2 cells against acute hypoxia/reoxygenation by regulating expression of the SUR2A subunit of the ATP-sensitive K+ channel. J Biol Chem. 2003;278(33):31444-55. https://doi.org/10.1074/jbc.M303051200.
14. Jensen J., Rustad PI., Kolnes AJ., Lai YC. The role of skeletal muscle glycogen breakdown for regulation of insulin sensitivity by exercise. Front Physiol. 2011 Dec 30;2:112. https://doi.org/10.3389/fphys.2011.00112.
15. Dienel GA. Brain Glucose Metabolism: Integration of Energetics with Function. Physiol Rev 99: 949–1045., 2019. Published December 19., 2018;. https://doi.org/10.1152/phys-rev.00062.2017.
16. Błaszczyk JW. Energy Metabolism Decline in the Aging Brain-Pathogenesis of Neurodegenerative Disorders. Metabolites. 2020;10(11):450. https://doi.org/10.3390/metabo10110450.
17. Wasserman DH. Four grams of glucose. Am J Physiol Endocrinol Metab. 2009 Jan;296(1):E11-21. https://doi.org/10.1152/ajpendo.90563.2008.
18. Brooks GA. The Precious Few Grams of Glucose During Exercise. Int J Mol Sci. 2020 Aug 10;21(16):5733. https://doi.org/10.3390/ijms21165733.
19. Hue L., Taegtmeyer H. The Randle cycle revisited: a new head for an old hat. Am J Physiol Endocrinol Metab. 2009 Sep;297(3):E578-91. https://doi.org/10.1152/ajpendo.00093.2009.
20. Schweiger M., Eichmann TO., Taschler U., Zimmermann R., Zechner R., Lass A. Measurement of lipolysis. Methods Enzymol. 2014;538:171-93.
21. Engin AB. What Is Lipotoxicity? Adv Exp Med Biol. 2017;960:197-220. https://doi.org/10.1007/978-3-319-48382-5_8.
22. Item F., Konrad D. Visceral fat and metabolic inflammation: the portal theory revisited. Obesity Reviews : an Official Journal of the International Association for the Study of Obesity. 2012 Dec;13 Suppl 2:30-39. https://doi.org/10.1111/j.1467-789x.2012.01035.x.
23. O'Hearn LA. Signals of energy availability in sleep: consequences of a fat-based metabolism. Front Nutr. 2024 Aug 29;11:1397185. https://doi.org/10.3389/fnut.2024.1397185.
24. Anton SD., Moehl K., Donahoo WT., Marosi K., Lee SA., Mainous AG 3rd., Leeuwenburgh C., Mattson MP. Flipping the Metabolic Switch: Understanding and Applying the Health Benefits of Fasting. Obesity (Silver Spring). 2018 Feb;26(2):254-268. https://doi.org/10.1002/oby.22065.
25. Catterall WA. Voltage-gated calcium channels. Cold Spring Harb Perspect Biol. 2011 Aug 1;3(8):a003947. https://doi.org/10.1101/cshperspect.a003947.
26. Jankowski V., van der Giet M., Mischak H., Morgan M., Zidek W., Jankowski J. Dinucleoside polyphosphates: strong endogenous agonists of the purinergic system. Br J Pharmacol. 2009 Aug;157(7):1142-53. https://doi.org/10.1111/j.1476-5381.2009.00337.x.
27. Vaughn BP., Robson SC., Longhi MS. Purinergic signaling in liver disease. Dig Dis. 2014;32(5):516-24. https://doi.org/10.1159/000360498.
28. Hu MC., Shiizaki K., Kuro-o M., Moe OW. Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. Annu Rev Physiol. 2013;75:503-33. https://doi.org/10.1146/annurev-physiol-030212-183727.
29. Kaebisch C., Schipper D., Babczyk P., Tobiasch E. The role of purinergic receptors in stem cell differentiation. Comput Struct Biotechnol J. 2014;13:75–84. doi: 10.1016/j.csbj.2014.11.003
30. Burnstock G. Short- and long-term (trophic) purinergic signalling. Phil Trans R Soc B. 2016;371(1700):20150422. doi: 10.1098/rstb.2015.0422.
31. Adamiak M., Ciechanowicz A., Skoda M., Cymer M., Tracz M., Xu B., Ratajczak MZ. Novel evidence that purinergic signaling - Nlrp3 inflammasome axis regulates circadian rhythm of hematopoietic stem/progenitor cells circulation in peripheral blood. Stem Cell Rev Rep. 2020;16(2):335–343. doi: 10.1007/s12015-020-09953-0.

32. Ratajczak MZ., Adamiak M., Bujko K., Thapa A., Pensato V., Kucia M., Ratajczak J., Ulrich H. Innate immunity orchestrates the mobilization and homing of hematopoietic stem/progenitor cells by engaging purinergic signaling-an update. Purinergic Signalling. 2020;16(2):153–166. doi: 10.1007/s11302-020-09698-y.
33. Abbracchio MP., Burnstock G., Verkhratsky A., Zimmermann H. Purinergic signalling in the nervous system: an overview. Trends Neurosci. 2009 Jan;32(1):19-29. https://doi.org/10.1016/j.tins.2008.10.001.
34. Schwarzbaum PJ., Schachter J., Bredeston LM. The broad range di- and tri-nucleotide exchanger SLC35B1 displays asymmetrical affinities for ATP transport across the ER membrane. J Biol Chem. 2022 Apr;298(4):101537. https://doi.org/10.1016/j.jbc.2021.101537.
35. Yong J., Bischof H., Burgstaller S., Siirin M., Murphy A., Malli R., Kaufman RJ. Mitochondria supply ATP to the ER through a mechanism antagonized by cytosolic Ca^2. Elife. 2019 Sep 9;8:e49682. https://doi.org/10.7554/eLife.49682.
36. Blaine J., Chonchol M., Levi M. Renal control of calcium., phosphate., and magnesium homeostasis. Clin J Am Soc Nephrol. 2015 Jul 7;10(7):1257-72. https://doi.org/10.2215/CJN.09750913. Epub 2014 Oct 6. Erratum in: Clin J Am Soc Nephrol. 2015 Oct 7;10(10):1886-7. doi: 10.2215/CJN.08840815.
37. Kuro-O M. Calcium phosphate microcrystallopathy as a paradigm of chronic kidney disease progression. Curr Opin Nephrol Hypertens. 2023 Jul 1;32(4):344-351. https://doi.org/10.1097/MNH.0000000000000890.
38. von Molitor E., Riedel K., Krohn M., Hafner M., Rudolf R., Cesetti T. Sweet Taste Is Complex: Signaling Cascades and Circuits Involved in Sweet Sensation. Front Hum Neurosci. 2021 Jun 22;15:667709. https://doi.org/10.3389/fnhum.2021.667709.
39. Lee AA., Owyang C. Sugars., Sweet Taste Receptors., and Brain Responses. Nutrients. 2017 Jun 24;9(7):653. https://doi.org/10.3390/nu9070653.
40. von Holstein-Rathlou S, BonDurant LD, Peltekian L, Naber MC, Yin TC, Claflin KE, Urizar AI, Madsen AN, Ratner C, Holst B, Karstoft K, Vandenbeuch A, Anderson CB, Cassell MD, Thompson AP, Solomon TP, Rahmouni K, Kinnamon SC, Pieper AA, Gillum MP, Potthoff MJ. FGF21 Mediates Endocrine Control of Simple Sugar Intake and Sweet Taste Preference by the Liver. Cell Metab. 2016 Feb 9;23(2):335-43. https://doi.org/10.1016/j.cmet.2015.12.003.
41. Lee NK., Sowa H., Hinoi E., Ferron M., Ahn JD., Confavreux C., Dacquin R., Mee PJ., McKee MD., Jung DY., Zhang Z., Kim JK., Mauvais-Jarvis F., Ducy P., Karsenty G. Endocrine regulation of energy metabolism by the skeleton. Cell. 2007; 130(3):456-69. https://doi.org/10.1016/j.cell.2007.05.047.
42. *Polonsky KS., Given BD., Van Cauter E. Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. J Clin Invest. 1988;81:442–8. https://doi.org/10.1172/JCI113339.*
43. Arnolds S., Kuglin B., Kapitza C., Heise T. How pharmacokinetic and pharmacodynamic principles pave the way for optimal basal insulin therapy in type 2 diabetes. Int J Clin Pract. 2010 Sep;64(10):1415-24. https://doi.org/10.1111/j.1742-1241.2010.02470.x.
44. Tahimic CG., Wang Y., Bikle DD. Anabolic effects of IGF-1 signaling on the skeleton. Front Endocrinol (Lausanne). 2013 Feb 4;4:6. https://doi.org/10.3389/fendo.2013.00006.
45. Sharples AP., Hughes DC., Deane CS., Saini A., Selman C., Stewart CE. Longevity and skeletal muscle mass: the role of IGF signalling., the sirtuins., dietary restriction and protein intake. Aging Cell. 2015;14(4):511-523. https://doi.org/10.1111/acel.12342.
46. Xie N., Zhang L., Gao W., Huang C., Huber PE., Zhou X., Li C., Shen G., Zou B. NAD^+ metabolism: pathophysiologic mechanisms and therapeutic potential. Signal Transduct Target Ther. 2020 Oct 7;5(1):227. https://doi.org/10.1038/s41392-020-00311-7.
47. Braidy N., Berg J., Clement J., Khorshidi F., Poljak A., Jayasena T., Grant R., Sachdev P. Role of Nicotinamide Adenine Dinucleotide and Related Precursors as Therapeutic Targets for Age-Related Degenerative Diseases: Rationale., Biochemistry., Pharmacokinetics., and Outcomes. Antioxid Redox Signal. 2019 Jan 10;30(2):251-294. https://doi.org/10.1089/ars.2017.7269.
48. Covarrubias AJ, Perrone R, Grozio A, Verdin E. NAD^+ metabolism and its roles in cellular processes during ageing. Nat Rev Mol Cell Biol. 2021 Feb;22(2):119-141. https://doi.org/10.1038/s41580-020-00313-x.
49. Strømland Ø., Diab J., Ferrario E., Sverkeli LJ., Ziegler M. The balance between NAD^+ biosynthesis and consumption in ageing. Mech Ageing Dev. 2021;199:111569. https://doi.org/10.1016/j.mad.2021.111569.
50. Yang Y., Sauve AA. NAD(+) metabolism: Bioenergetics., signaling and manipulation for therapy. Biochim Biophys Acta. 2016 Dec;1864(12):1787-1800. https://doi.org/10.1016/j.bbapap.2016.06.014.
51. Chini CCS, Tarragó MG, Chini EN. NAD and the aging process: Role in life, death and everything in between. Mol Cell Endocrinol. 2017 Nov 5;455:62-74. https://doi.org/10.1016/j.mce.2016.11.003.
52. Andrabi SA., Kim NS., Yu SW., Wang H., Koh DW., Sasaki M., Klaus JA., Otsuka T., Zhang Z., Koehler RC., Hurn PD., Poirier GG., Dawson VL., Dawson TM. Poly(ADP-ribose) (PAR) polymer is a death signal. Proc Natl Acad Sci U S A. 2006 Nov 28;103(48):18308-13. https://doi.org/10.1073/pnas.0606526103.
53. Katsyuba E, Mottis A, Zietak M, De Franco F, van der Velpen V, Gariani K, Ryu D, Cialabrini L, Matilainen O, Liscio P, Giacchè N, Stokar-Regenscheit N, Legouis D, de Seigneux S, Ivanisevic J, Raffaelli N, Schoonjans K, Pellicciari R, Auwerx J. De novo NAD^+ synthesis enhances mitochondrial function and improves health. Nature. 2018 Nov;563(7731):354-359. https://doi.org/10.1038/s41586-018-0645-6.

54. Gomes AP., Price NL., Ling AJ., Moslehi JJ., Montgomery MK., Rajman L., et al. Declining NAD(+) Induces a Pseudohypoxic State Disrupting Nuclear-Mitochondrial Communication During Aging. Cell. 2013; 155(7):1624–38. doi: 10.1016/j.cell.2013.11.037.
55. Rendina-Ruedy E., Rosen CJ. Lipids in the Bone Marrow: An Evolving Perspective. Cell Metab. 2020 Feb 4;31(2):219-231. https://doi.org/10.1016/j.cmet.2019.09.015.
56. Schmiedeknecht K., Kaufmann A., Bauer S., Venegas Solis F. L-lactate as an indicator for cellular metabolic status: An easy and cost-effective colorimetric L-lactate assay. PLoS One. 2022 Jul 22;17(7):e0271818. https://doi.org/10.1371/journal.pone.0271818.
57. Lunt SY., Vander Heiden MG. Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. Annu Rev Cell Dev Biol. 2011;27:441-64. https://doi.org/10.1146/annurev-cellbio-092910-154237.
58. Luo M., Zhao Z., Yi J. Osteogenesis of bone marrow mesenchymal stem cell in hyperglycemia. Front Endocrinol (Lausanne). 2023 Jun 21;14:1150068. https://doi.org/10.3389/fendo.2023.1150068.
59. Semba RD., Ferrucci L., Sun K., Beck J., Dalal M., Varadhan R., Walston J., Guralnik JM., Fried LP. Advanced glycation end products and their circulating receptors predict cardiovascular disease mortality in older community-dwelling women. Aging Clin Exp Res. 2009 Apr;21(2):182-90. https://doi.org/10.1007/BF03325227.
60. Haus JM., Carrithers JA., Trappe SW., Trappe TA. Collagen., cross-linking., and advanced glycation end products in aging human skeletal muscle. J Appl Physiol (1985). 2007 Dec;103(6):2068-76. https://doi.org/10.1152/japplphysiol.00670.2007.
61. Houten SM., Wanders RJ. A general introduction to the biochemistry of mitochondrial fatty acid β-oxidation. J Inherit Metab Dis. 2010 Oct;33(5):469-77. https://doi.org/10.1007/s10545-010-9061-2.
62. Morigny P., Boucher J., Arner P., Langin D. Lipid and glucose metabolism in white adipocytes: pathways, dysfunction and therapeutics. Nat Rev Endocrinol. 2021 May;17(5):276-295. https://doi.org/10.1038/s41574-021-00471-8.
63. Zhang P., He Y., Wu S., Li X., Lin X., Gan M., Chen L., Zhao Y., Niu L., Zhang S., Li X., Zhu L., Shen L. Factors Associated with White Fat Browning: New Regulators of Lipid Metabolism. Int J Mol Sci. 2022;23(14):7641. https://doi.org/10.3390/ijms23147641
64. Palacios-Marin I., Serra D., Jimenez-Chillarón J., Herrero L., Todorčević M. Adipose Tissue Dynamics: Cellular and Lipid Turnover in Health and Disease. Nutrients. 2023;15(18):3968. Published 2023 Sep 14. https://doi.org/10.3390/nu15183968.
65. Kulbacka J., Choromańska A., Rossowska J., Weżgowiec J., Saczko J., Rols MP. Cell Membrane Transport Mechanisms: Ion Channels and Electrical Properties of Cell Membranes. Adv Anat Embryol Cell Biol. 2017;227:39-58. https://doi.org/10.1007/978-3-319-56895-9_3.
66. Zeisel SH. Choline: critical role during fetal development and dietary requirements in adults. Annu Rev Nutr. 2006;26:229-50. https://doi.org/10.1146/annurev.nutr.26.061505.111156.
67. Vance DE. Physiological roles of phosphatidylethanolamine N-methyltransferase. Biochim Biophys Acta. 2013 Mar;1831(3):626-32. https://doi.org/10.1016/j.bbalip.2012.07.017.
68. Zeisel SH., Blusztajn JK. Choline and human nutrition. Annu Rev Nutr. 1994;14:269-96. https://doi.org/10.1146/annurev.nu.14.070194.001413. PMID: 7946521.
69. Etienne Q., Lebrun V., Komuta M., et al. Fetuin-A in Activated Liver Macrophages Is a Key Feature of Non-Alcoholic Steatohepatitis. Metabolites. 2022;12(7):625. Published 2022 Jul 7. https://doi.org/10.3390/metabo12070625.
70. Lanthier N., Lebrun V., Molendi-Coste O., van Rooijen N., Leclercq IA. Liver Fetuin-A at Initiation of Insulin Resistance. Metabolites. 2022;12(11):1023. Published 2022 Oct 25. https://doi.org/10.3390/metabo12111023.
71. Song Z., Xiaoli AM., Yang F. Regulation and Metabolic Significance of De Novo Lipogenesis in Adipose Tissues. Nutrients. 2018 Sep 29;10(10):1383. https://doi.org/10.3390/nu10101383.
72. Panov A., Mayorov VI., Dikalov S. Metabolic Syndrome and β-Oxidation of Long-Chain Fatty Acids in the Brain., Heart., and Kidney Mitochondria. Int J Mol Sci. 2022 Apr 6;23(7):4047. https://doi.org/10.3390/ijms23074047.
73. Ameer F., Scandiuzzi L., Hasnain S., Kalbacher H., Zaidi N. De novo lipogenesis in health and disease. Metabolism. 2014;63(7):895-902. https://doi.org/10.1016/j.metabol.2014.04.003.
74. Gugliucci A. The chylomicron saga: time to focus on postprandial metabolism. Front Endocrinol (Lausanne). 2024;14:1322869. Published 2024 Jan 18. https://doi.org/10.3389/fendo.2023.1322869.
75. Quinville BM., Deschenes NM., Ryckman AE., Walia JS. A Comprehensive Review: Sphingolipid Metabolism and Implications of Disruption in Sphingolipid Homeostasis. Int J Mol Sci. 2021 May 28;22(11):5793. https://doi.org/10.3390/ijms22115793.
76. Pouwels S., Sakran N., Graham Y., Leal A., Pintar T., Yang W., Kassir R., Singhal R., Mahawar K., Ramnarain D. Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology., clinical management and effects of weight loss. BMC Endocr Disord. 2022 Mar 14;22(1):63. https://doi.org/10.1186/s12902-022-00980-1.

77. Roderburg C., Krieg S., Krieg A., et al. Non-alcoholic fatty liver disease (NAFLD) is associated with an increased incidence of chronic kidney disease (CKD). Eur J Med Res. 2023;28(1):153. Published 2023 Apr 17. https://doi.org/10.1186/s40001-023-01114-6.
78. Frayn KN. The glucose-fatty acid cycle: a physiological perspective. Biochem Soc Trans. 2003 Dec;31(Pt 6):1115-9. https://doi.org/10.1042/bst0311115.
79. Abdul-Ghani MA., Muller FL., Liu Y., Chavez AO., Balas B., Zuo P., Chang Z., Tripathy D., Jani R., Molina-Carrion M., Monroy A., Folli F., Van Remmen H., DeFronzo RA. Deleterious action of FA metabolites on ATP synthesis: possible link between lipotoxicity., mitochondrial dysfunction., and insulin resistance. Am J Physiol Endocrinol Metab. 2008 Sep;295(3):E678-85. https://doi.org/10.1152/ajpendo.90287.2008.
80. Kayagaki N., Webster JD., Newton K. Control of Cell Death in Health and Disease. Annu Rev Pathol. 2024;19:157-180. https://doi.org/10.1146/annurev-pathmechdis-051022-014433.
81. Sender R., Milo R. The distribution of cellular turnover in the human body. Nat Med. 2021 Jan;27(1):45-48. https://doi.org/10.1038/s41591-020-01182-9.
82. Dudley AC., Griffioen AW. Pathological angiogenesis: mechanisms and therapeutic strategies. Angiogenesis. 2023 Aug;26(3):313-347. https://doi.org/10.1007/s10456-023-09876-7.
83. Miyajima A., Tanaka M., Itoh T. Stem/progenitor cells in liver development., homeostasis., regeneration., and reprogramming. Cell Stem Cell. 2014 May 1;14(5):561-74. https://doi.org/10.1016/j.stem.2014.04.010.
84. Bonewald LF. The amazing osteocyte. J Bone Miner Res. 2011 Feb;26(2):229-38. https://doi.org/10.1002/jbmr.320.
85. Kitase Y., Vallejo JA., Gutheil W., Vemula H., Jähn K., Yi J., Zhou J., Brotto M., Bonewald LF. β-aminoisobutyric Acid., l-BAIBA., Is a Muscle-Derived Osteocyte Survival Factor. Cell Rep. 2018 Feb 6;22(6):1531-1544. https://doi.org/10.1016/j.celrep.2018.01.041.
86. Confavreux CB., Levine RL., Karsenty G. A paradigm of integrative physiology., the crosstalk between bone and energy metabolisms. Mol Cell Endocrinol. 2009 Oct 30;310(1-2):21-9. https://doi.org/10.1016/j.mce.2009.04.004.
87. Hoffman CM., Han J., Calvi LM. Impact of aging on bone., marrow and their interactions. Bone. 2019 Feb;119:1-7. https://doi.org/10.1016/j.bone.2018.07.012.
88. Hawkes CP., Mostoufi-Moab S. Fat-bone interaction within the bone marrow milieu: Impact on hematopoiesis and systemic energy metabolism. Bone. 2019 Feb;119:57-64. https://doi.org/10.1016/j.bone.2018.03.012.
89. Lv Z., Shi W., Zhang Q. Role of Essential Amino Acids in Age-Induced Bone Loss. Int J Mol Sci. 2022;23(19):11281.
90. Severinsen MCK., Pedersen BK. Muscle-Organ Crosstalk: The Emerging Roles of Myokines. Endocr Rev. 2020 Aug 1;41(4):594–609. https://doi.org/10.1210/endrev/bnaa016. Erratum in: Endocr Rev. 2021 Jan 28;42(1):97-99. doi: 10.1210/endrev/bnaa024.
91. Ratnayake CBB., Escott ABJ., Phillips ARJ., Windsor JA. The anatomy and physiology of the terminal thoracic duct and ostial valve in health and disease: potential implications for intervention. J Anat. 2018 Jul;233(1):1-14. https://doi.org/10.1111/joa.12811.
92. Marahleh A., Kitaura H., Ohori F., Noguchi T., Mizoguchi I. The osteocyte and its osteoclastogenic potential. Front Endocrinol (Lausanne). 2023 May 24;14:1121727. https://doi.org/10.3389/fendo.2023.1121727.
93. Wherry SJ., Swanson CM., Kohrt WM. Acute catabolic bone metabolism response to exercise in young and older adults: A narrative review. Exp Gerontol. 2022 Jan;157:111633. https://doi.org/10.1016/j.exger.2021.111633.
94. Vasquez-Sancho F., Abdollahi A., Damjanovic D., Catalan G. Flexoelectricity in Bones. Adv Mater. 2018 Mar;30(9). https://doi.org/10.1002/adma.201705316.
95. Yang C., Ji J., Lv Y., Li Z., Luo D. Application of Piezoelectric Material and Devices in Bone Regeneration. Nanomaterials (Basel). 2022 Dec 9;12(24):4386. https://doi.org/10.3390/nano12244386.
96. Nie X., Chung MK. Piezo channels for skeletal development and homeostasis: Insights from mouse genetic models. Differentiation. 2022 Jul-Aug;126:10-15. https://doi.org/10.1016/j.diff.2022.06.001.
97. Pop TL., Sîrbe C., Benţa G., Mititelu A., Grama A. The Role of Vitamin D and Vitamin D Binding Protein in Chronic Liver Diseases. Int J Mol Sci. 2022 Sep 14;23(18):10705. https://doi.org/10.3390/ijms231810705.
98. Chau YY., Kumar J. Vitamin D in chronic kidney disease. Indian J Pediatr. 2012 Aug;79(8):1062-8. https://doi.org/10.1007/s12098-012-0765-1.
99. Puchacz E., Stumpf WE., Stachowiak EK., Stachowiak MK. Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells. Brain Res Mol Brain Res. 1996 Feb;36(1):193-6. https://doi.org/10.1016/0169-328x(95)00314-i.
100. Błaszczyk JW. Sleep disorders contribute to the development of dementia and Alzheimer's disease. Explor Neurosci. 2023;2:212–223. https://doi.org/10.37349/en.2023.00022
101. Tran LT., Park S., Kim SK., Lee JS., Kim KW., Kwon O. Hypothalamic control of energy expenditure and thermogenesis. Exp Mol Med. 2022 Apr;54(4):358-369. https://doi.org/10.1038/s12276-022-00741-z.

102. Knapska E., Nikolaev E., Boguszewski P., Walasek G., Blaszczyk J., Kaczmarek L., Werka T. Between-subject transfer of emotional information evokes specific pattern of amygdala activation. Proc Natl Acad Sci U S A. 2006 Mar 7;103(10):3858-62. https://doi.org/10.1073/pnas.0511302103.
103. Li M., Zhou L., Sun X., Yang Y., Zhang C., Wang T., Fu F. Dopamine, a co-regulatory component, bridges the central nervous system and the immune system. Biomed Pharmacother. 2022 Jan;145:112458. https://doi.org/10.1016/j.biopha.2021.112458.
104. Lambert EV., St Clair Gibson A., Noakes TD. Complex systems model of fatigue: integrative homoeostatic control of peripheral physiological systems during exercise in humans. Br J Sports Med. 2005 Jan;39(1):52-62. https://doi.org/10.1136/bjsm.2003.011247.
105. Rochat P. Five levels of self-awareness as they unfold early in life. Conscious Cogn. 2003 Dec;12(4):717-31. https://doi.org/10.1016/s1053-8100(03)00081-3.
106. Azañón E., Haggard P. Somatosensory processing and body representation. Cortex. 2009 Oct;45(9):1078-84. https://doi.org/10.1016/j.cortex.2009.01.006.
107. Hinman JR., Chapman GW., Hasselmo ME. Neuronal representation of environmental boundaries in egocentric coordinates. Nat Commun. 2019 Jun 24;10(1):2772. https://doi.org/10.1038/s41467-019-10722-y.
108. MacLean PD. Psychosomatic disease and the visceral brain; recent developments bearing on the Papez theory of emotion. Psychosom Med. 1949 Nov-Dec;11(6):338-53. https://doi.org/10.1097/00006842-194911000-00003.
109. Wismer Fries AB., Ziegler TE., Kurian JR., Jacoris S., Pollak SD. Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior. Proc Natl Acad Sci U S A. 2005 Nov 22;102(47):17237-40. https://doi.org/10.1073/pnas.0504767102.
110. Shen K., Pender CL., Bar-Ziv R., Zhang H., Wickham K., Willey E., Durieux J., Ahmad Q., Dillin A. Mitochondria as Cellular and Organismal Signaling Hubs. Annu Rev Cell Dev Biol. 2022 Oct 6;38:179-218. https://doi.org/10.1146/annurev-cellbio-120420-015303.
111. Toussaint B., Heinzle J., Stephan KE. A computationally informed distinction of interoception and exteroception. Neurosci Biobehav Rev. 2024 Apr;159:105608. https://doi.org/10.1016/j.neubiorev.2024.105608.
112. Malezieux M., Klein AS., Gogolla N. Neural Circuits for Emotion. Annu Rev Neurosci. 2023 Jul 10;46:211-231. https://doi.org/10.1146/annurev-neuro-111020-103314.
113. Lennie P. The cost of cortical computation. Curr Biol. 2003 Mar 18;13(6):493-7. https://doi.org/10.1016/s0960-9822(03)00135-0.
114. Błaszczyk JW. Parkinson's Disease and Neurodegeneration: GABA-Collapse Hypothesis. Front Neurosci. 2016 Jun 9;10:269. https://doi.org/10.3389/fnins.2016.00269.
115. Karsenty G., Khosla S. The crosstalk between bone remodeling and energy metabolism: A translational perspective. Cell Metab. 2022 Jun 7;34(6):805-817. https://doi.org/10.1016/j.cmet.2022.04.010.
116. Berridge KC., Kringelbach ML. Pleasure systems in the brain. Neuron. 2015; 86(3):646–64.
117. Andersen RA., Buneo CA. Intentional maps in posterior parietal cortex. Annu Rev Neurosci. 2002;25:189-220. https://doi.org/10.1146/annurev.neuro.25.112701.142922.
118. Karemaker JM. How the vagus nerve produces beat-to-beat heart rate variability; experiments in rabbits to mimic in vivo vagal patterns. J Clin Transl Res. 2015 Dec 20;1(3):190-204.
119. Bonaz B., Sinniger V., Pellissier S. Vagus nerve stimulation: a new promising therapeutic tool in inflammatory bowel disease. J Intern Med. 2017 Jul;282(1):46-63. https://doi.org/10.1111/joim.12611. Epub 2017 Apr 18. PMID: 28421634.
120. Karsenty G., Olson EN. Bone and Muscle Endocrine Functions: Unexpected Paradigms of Inter-organ Communication. Cell. 2016 Mar 10;164(6):1248-1256. https://doi.org/10.1016/j.cell.2016.02.043.
121. Obri A., Khrimian L., Karsenty G., Oury F. Osteocalcin in the brain: from embryonic development to age-related decline in cognition. Nat Rev Endocrinol. 2018 Mar;14(3):174-182. https://doi.org/10.1038/nrendo.2017.181.
122. Saade MC., Clark AJ., Parikh SM. States of quinolinic acid excess in urine: A systematic review of human studies. Front Nutr. 2022 Dec 16;9:1070435. https://doi.org/10.3389/fnut.2022.1070435.
123. Jamwal S., Singh S., Gill JS., Kumar P. L-theanine prevent quinolinic acid induced motor deficit and striatal neurotoxicity: Reduction in oxido-nitrosative stress and restoration of striatal neurotransmitters level. Eur J Pharmacol. 2017 Sep 15;811:171-179. https://doi.org/10.1016/j.ejphar.2017.06.016.
124. Vega-Naredo I., Poeggeler B., Sierra-Sánchez V., Caballero B., Tomás-Zapico C., Alvarez-García O., Tolivia D., Rodríguez-Colunga MJ., Coto-Montes A. Melatonin neutralizes neurotoxicity induced by quinolinic acid in brain tissue culture. J Pineal Res. 2005 Oct;39(3):266-75. https://doi.org/10.1111/j.1600-079X.2005.00243.x.
125. Guimarães-Ferreira L. Role of the phosphocreatine system on energetic homeostasis in skeletal and cardiac muscles. Einstein (Sao Paulo). 2014 Jan-Mar;12(1):126-31. https://doi.org/10.1590/s1679-45082014rb2741.

126. Del Franco A., Ambrosio G., Baroncelli L., Pizzorusso T., Barison A., Olivotto I., Recchia FA., Lombardi CM., Metra M., Ferrari Chen YF., Passino C., Emdin M., Vergaro G. Creatine deficiency and heart failure. Heart Fail Rev. 2022 Sep;27(5):1605-1616. https://doi.org/10.1007/s10741-021-10173-y.
127. Pike JW., Christakos S. Biology and Mechanisms of Action of the Vitamin D Hormone. Endocrinol Metab Clin North Am. 2017 Dec;46(4):815-843. https://doi.org/10.1016/j.ecl.2017.07.001.
128. Giudice ML., Mihalik B., Dinnyés A., Kobolák J. The Nervous System Relevance of the Calcium Sensing Receptor in Health and Disease. Molecules. 2019 Jul 12;24(14):2546. https://doi.org/10.3390/molecules24142546.
129. Felsenfeld AJ., Levine BS. Calcitonin., the forgotten hormone: does it deserve to be forgotten? Clin Kidney J. 2015;8(2):180–187.
130. Srinivasan A., Wong FK., Karponis D. Calcitonin: A useful old friend. J Musculoskelet Neuronal Interact. 2020 Dec 1;20(4):600-609.
131. Horne WC., Shyu JF., Chakraborty M., Baron R. Signal transduction by calcitonin Multiple ligands, receptors, and signaling pathways. Trends Endocrinol Metab. 1994 Dec;5(10):395-401. https://doi.org/10.1016/1043-2760(95)92521-j.
132. Llorente-Folch I, Rueda CB, Pardo B, Szabadkai G, Duchen MR, Satrustegui J. The regulation of neuronal mitochondrial metabolism by calcium. J Physiol. 2015 Aug 15;593(16):3447-62. https://doi.org/10.1113/JP270254.
133. Clapham DE. Calcium signaling. Cell. 2007 Dec 14;131(6):1047-58. https://doi.org/10.1016/j.cell.2007.11.028.
134. Mera P., Laue K., Ferron M., Confavreux C., Wei J., Galán-Díez M., Lacampagne A., Mitchell SJ., Mattison JA., Chen Y., Bacchetta J., Szulc P., Kitsis RN., de Cabo R., Friedman RA., Torsitano C., McGraw TE., Puchowicz M., Kurland I., Karsenty G. Osteocalcin Signaling in Myofibers Is Necessary and Sufficient for Optimum Adaptation to Exercise. Cell Metab. 2016 Jun 14;23(6):1078-1092. https://doi.org/10.1016/j.cmet.2016.05.004.
135. Zaidi M., Kim SM., Mathew M., Korkmaz F., Sultana F., Miyashita S., Gumerova AA., Frolinger T., Moldavski O., Barak O., Pallapati A., Rojekar S., Caminis J., Ginzburg Y., Ryu V., Davies TF., Lizneva D., Rosen CJ., Yuen T. Bone circuitry and interorgan skeletal crosstalk. Elife. 2023 Jan 19;12:e83142. https://doi.org/10.7554/eLife.83142.
136. Fernandes TAP., Gonçalves LML., Brito JAA. Relationships between Bone Turnover and Energy Metabolism. J Diabetes Res. 2017;2017:9021314. https://doi.org/10.1155/2017/9021314.
137. Ghoshal K.., Chatterjee T.., Chowdhury S.., Sengupta S.., Bhattacharyya M. Adiponectin Genetic Variant and Expression Coupled with Lipid Peroxidation Reveal New Signatures in Diabetic Dyslipidemia. Biochem Genet. 2021 Jun;59(3):781-798. https://doi.org/10.1007/s10528-021-10030-5. Epub 2021 Feb 4. PMID: 33543406.
138. Abdelaziz Mohamed I., Gadeau AP., Hasan A., Abdulrahman N., Mraiche F. Osteopontin: A Promising Therapeutic Target in Cardiac Fibrosis. Cells. 2019 Dec 3;8(12):1558. https://doi.org/10.3390/cells8121558.
139. Yu H., Liu X., Zhong Y. The Effect of Osteopontin on Microglia. Biomed Res Int. 2017:1879437.. https://doi.org/10.1155/2017/1879437.
140. Song Z., Chen W., Athavale D., Ge X., Desert R., Das S., Han H., Nieto N. Osteopontin Takes Center Stage in Chronic Liver Disease. Hepatology. 2021 Apr;73(4):1594-1608. https://doi.org/10.1002/hep.31582.
141. Jeon SM. Regulation and function of AMPK in physiology and diseases. Exp Mol Med. 2016 Jul 15;48(7):e245. https://doi.org/10.1038/emm.2016.81.
142. Ramírez-Vélez R., García-Hermoso A., Hackney AC., Izquierdo M. Effects of exercise training on Fetuin-a in obese., type 2 diabetes and cardiovascular disease in adults and elderly: a systematic review and Meta-analysis. Lipids Health Dis. 2019 Jan 22;18(1):23. https://doi.org/10.1186/s12944-019-0962-2.
143. Pal D., Dasgupta S., Kundu R., Maitra S., Das G., Mukhopadhyay S., Ray S., Majumdar SS., Bhattacharya S. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance. Nat Med. 2012 Aug;18(8):1279-85. https://doi.org/10.1038/nm.2851.
144. Groarke EM., Young NS. Aging and Hematopoiesis. Clin Geriatr Med. 2019 Aug;35(3):285-293. https://doi.org/10.1016/j.cger.2019.03.001.
145. Langhi LG., Andrade LR., Shimabukuro MK., van Ewijk W., Taub DD., Borojevic R., de Mello Coelho V. Lipid-Laden Multilocular Cells in the Aging Thymus Are Phenotypically Heterogeneous. PLoS One. 2015 Oct 28;10(10):e0141516. https://doi.org/10.1371/journal.pone.0141516.
146. Liang Z., Dong X., Zhang Z., Zhang Q., Zhao Y. Age-related thymic involution: Mechanisms and functional impact. Aging Cell. 2022 Aug;21(8):e13671. https://doi.org/10.1111/acel.13671.
147. Kologrivova IV., Naryzhnaya NV., Suslova TE. Thymus in Cardiometabolic Impairments and Atherosclerosis: Not a Silent Player? Biomedicines. 2024 Jun 25;12(7):1408. https://doi.org/10.3390/biomedicines12071408.
148. Sharma S., Hashmi MF., Kaur J., et al. Hypophosphatemia. [Updated 2024 Feb 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493172/

 doi:10.20944/preprints202411.2328.v1

149. Regulski MJ. Cellular Senescence: What, Why, and How. Wounds. 2017 Jun; 29(6):168-174.