Review

The Kinome-Microbiota Axis in Precision Nutrition as a Target for Restoration and Maintenance of Cellular Flexibility

Vincenzo Sorrenti *, Stefano Fortinguerra, Lorenzo Mauro, Alessandro Buriani *

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Review

The Kinome-Microbiota Axis in Precision Nutrition as a Target for Restoration and Maintenance of Cellular Flexibility

Vincenzo Sorrenti [1,2,3,*], Stefano Fortinguerra [2,4], Lorenzo Mauro [1,5] and Alessandro Buriani [2,*]

[1] NutriHealth Genomics Srl, 71 Viale Giulio Cesare, 00192 Rome, Italy
[2] Maria Paola Belloni Center for Personalized Medicine, Data Medica (Synlab Limited), 35100 Padova, Italy
[3] Department of Pharmaceutical and Pharmacological Sciences, University of Padova, 35131 Padova, Italy
[4] SYNLAB Data Medica Srl, 89 Via Zanchi, 35133 Padua, Italy
[5] Link Campus University, Department of Life Sciences, Health, and Health Professions, 44 Via del Casale di S. Pio V, 00165 Rome, Italy
* Correspondence: vincenzosorrenti88@gmail.com (V.S.); alessandro.buriani@gmail.com (A.B.)

Abstract

This review explores the modulation of the host cellular flexibility "kinome" (protein kinases) and "phosphatome" (protein phosphatases) by dietary nutrients and gut microbiota metabolites, proposing a potential paradigm in the strategies for healthy aging and metabolic disease prevention. While mainstream nutrition approaches focus on population-wide guidelines, precision nutrition exploits the innovations in personal molecular networks and systems medicine, integrating genomics and metabolomics to address "metabolic rigidity"—the cell inability to switch between fuel sources. The review examines how master molecular regulators like AMPK and mTOR, and "metabolic brakes" like PTP1B and PTEN, are affected by single nucleotide polymorphisms (SNPs) and microbial signals (SCFAs, secondary bile acids, indoles). Specifically, the "microbial kinomic interference" hypothesis is discussed, where gut metabolites act as remote ligands for host signaling enzymes. Finally, the potential role of a personalized phosphoproteomics strategy is highlighted as an effective functional readout to guide nutritional interventions, aiming to restore metabolic plasticity through a gut microbiota/multi-omics approach.

Keywords: precision nutrition; kinome; microbiota; metabolic flexibility; PTP1B; AMPK; mTOR; nutrigenomics; phosphoproteomics

1. Introduction

The advent of precision nutrition marks a paradigmatic shift in how we conceive the interaction between diet and human health [1]. Historically, nutritional recommendations relied on population-based approaches, ignoring the vast biological heterogeneity that characterizes individual responses to nutrients [2]. Standard dietary guidelines have long operated under the assumption of a "reference human", a statistical average that fails to capture the dynamic and individualized nature of metabolism [2,3]. However, recent advances in clinical biochemistry and molecular biology have revealed that metabolic balance and wellness is not a static entity, but depends on the capacity for dynamic cellular adaptation to different energy substrates defined as "metabolic flexibility" [4].

This concept moves beyond the simplistic view of calories-in versus calories-out, positing that health is determined by the efficiency with which an organism switches between energy substrates—glucose and fatty acids—in response to fluctuating environmental conditions [4,5]. As highlighted in recent clinical discussions regarding metabolic rigidity, the ability of an organism to efficiently switch between carbohydrate oxidation and lipid oxidation in response to substrate availability and energy demand is the hallmark of homeostatic health [5]. In a healthy phenotype, the transition from fasting

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a fasted state to the postprandial state engages a coordinated cascade of hormonal and enzymatic signals [6]. Skeletal muscle and the liver, the primary sites of oxidative metabolism, rapidly transition from lipid oxidation (fat burning) during fasting, to glucose oxidation (sugar burning) in the post-prandial state under the stimulation of insulin [6,7]. This seamless transition, primarily mediated by mitochondrial respiratory chain adaptations and peroxisome proliferator-activated receptor (PPAR) signaling pathways, ensures that fuel stores are utilized appropriately, preventing the accumulation of ectopic lipids or the persistence of hyperglycemia [7,8].

Conversely, the loss of this plasticity—defined as "metabolic rigidity"—represents a state of impaired capacity of substrate switching, characterized by persistent reliance on a single fuel source usually associated with mitochondrial dysfunction, ectopic lipid accumulation, and reduced oxidative capacity [9]. This phenomenon has been quantified through respiratory quotient (RQ) measurements during fasting-feeding transitions, where rigid profiles correlate with early insulin signaling defects in skeletal muscle and adipose tissue [10]. Metabolic rigidity is thus a molecular prelude to chronic, progressive conditions such as insulin resistance, type 2 diabetes (T2DM), and metabolic syndrome, often manifesting at the cellular level long before traditional clinical markers like HbA1c or fasting glucose are altered [11] (see Figure 1).

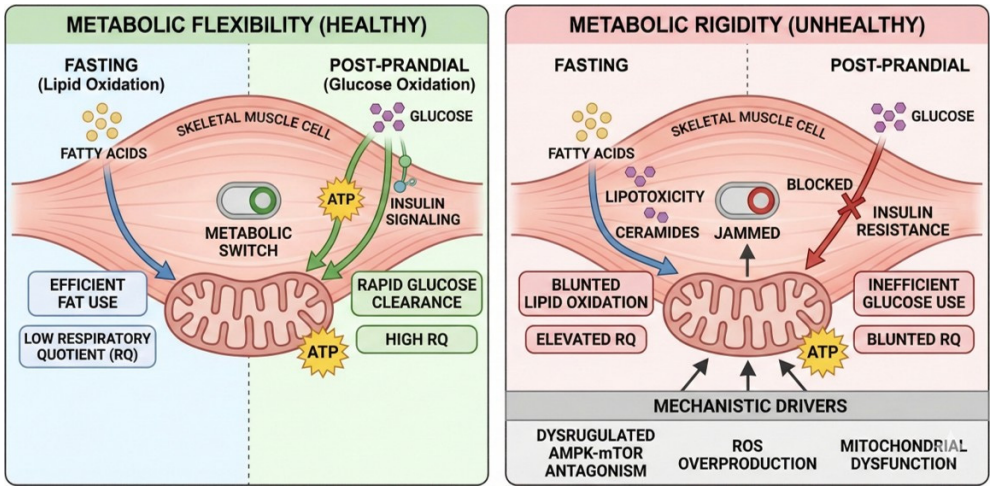

Figure 1.

Clinically, metabolic rigidity explains the patient who struggles with weight loss despite caloric restriction, the individual who experiences profound drowsiness after a carbohydrate-rich meal, and the patient with "normal" glucose levels but pathologically elevated insulin [12]. This state reflects a persistent misalignment of metabolic fluxes, with impaired substrate switching despite nutrient availability [13].

The clinical manifestation of metabolic rigidity is profound and multifaceted. Dysfunction of mitochondria reduces oxidative capacity, leading to inefficient running of the cellular engines [14]. Even when fatty acids are mobilized, they cannot be fully oxidized, leading to a backlog of acetyl-CoA and other metabolites [13,14]. Consequently, the cell is congested with toxic lipid intermediates such as diacylglycerols (DAGs) and ceramides, leading to lipotoxicity [15]. These lipid species are not inert; they actively interfere with signaling pathways, triggering Endoplasmic Reticulum (ER) stress and chronic low-grade inflammation—often termed "meta-inflammation"—which further alters intracellular signals [16]. Insulin thus progressively loses efficacy as a pivotal metabolic regulator, not necessarily because the hormone is absent, but because the downstream signaling infrastructure is blocked as a consequence of metabolic rigidity [17].

A healthy organism is flexible, using energy-providing substrates dynamically. In diabetes and insulin resistance, this flexibility is reduced; the cellular metabolic machinery loses the capacity to modulate fuel use and becomes more rigid [18]. This rigidity is the root cause of the "energy crisis"

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seen in metabolic syndrome: the body is awash in fuel (high glucose, high triglycerides) yet the tissues are starving for energy, trapped in an inflexible state unbalanced towards storage over utilization [13,18].

At the heart of this cellular metabolic regulation lies the "kinome", the set of protein kinases, and the "phosphatome," the set of protein phosphatases [19]. These enzymes act as reversible molecular switches, orchestrating nearly every aspect of cellular life through the phosphorylation and dephosphorylation of target proteins [20]. Phosphorylation acts as the binary code of the cell, turning pathways on and off with millisecond precision. Understanding the "kinome" is therefore essential for understanding the controls of the metabolic engine [19,21].

Indeed, two kinases are known to act as master regulators, AMPK (AMP-activated protein kinase) and mTOR (mechanistic target of rapamycin), along with two critical phosphatases, PTP1B (Protein Tyrosine Phosphatase 1B) and PTEN, playing a central role in the cell's decision-making pathways, and determining whether to store energy (anabolism) or consume it (catabolism) [22]. This network is not arbitrarily chosen; it represents the fundamental "yin and yang" of cellular energetics [22,23]. AMPK and mTOR serve as the primary sensors of energy status and nutrient availability, respectively, and their reciprocal regulation is the molecular basis of metabolic flexibility [24]. When this balance is disrupted—when the "switch" gets stuck—metabolic rigidity ensues.

This signaling network receives many different endogenous and exogenous stimuli. In recent years, a crucial and previously underestimated actor has emerged: the gut microbiota [25]. This microbial supersystem or "organ" provides a wide array of bioactive metabolites, including short-chain fatty acids (SCFAs), secondary bile acids, and indole derivatives, that translocate from the intestinal lumen to the systemic circulation [26]. These metabolites act as remote ligands or allosteric modulators of host kinases and phosphatases, effectively functioning as signaling molecules bridging together the gut environment and host cellular metabolism [26,27].

SCFAs such as butyrate, for instance, activate AMPK while inhibiting mTORC1 signaling, thereby modulating autophagy and lipid metabolism in a microbiota-dependent manner [28]. This phenomenon reflects the capacity of microbial metabolites to directly influence host phosphoproteomic networks, including inactivation of negative regulators like PTP1B and PTEN via reactive oxygen species intermediates [29]. Consequently, dysbiosis-induced alterations in metabolite profiles contribute to metabolic rigidity by impairing kinase-phosphatase balance and substrate switching in insulin-sensitive tissues [30]. Response to nutrients is dictated not only by the host's genetic polymorphisms (SNPs), but also by the composition and functionality of the individual gut microbiome, with specific SNP-microbiota interactions (e.g., FUT2 variants enriching Ruminococcus torques) modulating metabolite production and kinomic responsiveness [31].

The microbiota acts as a variable filter, processing dietary inputs into signaling outputs that can either reinforce metabolic flexibility or promote rigidity [32]. For example, a microbiome deficient in butyrate-producing bacteria may fail to provide the necessary HDAC inhibition to regulate phosphatase expression, thereby removing a critical layer of metabolic control [33]. This review aims to explore the functional connections between personalized nutrition, genomics, and microbiota, focusing on signaling mechanisms mediated by kinases and phosphatases and how metabolic rigidity may emerges from a dysfunction of these pathways, how genetic polymorphisms (SNPs) can predispose individuals to such dysfunctions, and how targeted interventions on the microbiota and diet can contribute to restore metabolic flexibility. Furthermore, potential clinical applications of these concepts will be taken into consideration, suggesting how this molecular network dysfunctions can help understanding common clinical presentations such as post-prandial drowsiness, weight loss resistance, and the progression from pre-diabetes to overt T2DM. Finally, the emerging role of phosphoproteomics as an advanced diagnostic tool for individual metabolic multilayer phenotyping will be discussed, proposing it as a possible linking tool between personalized genomic, metabolomic and microbiota data to provide dynamic, actionable clinical insights [34].

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2. Metabolic Rigidity vs. Flexibility: The Role of Master Regulators

Metabolic flexibility is defined as an organism's ability to adapt cellular oxidation processes to fuel availability [35]. Today, this concept is central to understanding the pathophysiology of metabolic diseases. In a healthy state, skeletal muscle—the primary site of insulin-stimulated glucose consumption—rapidly transitions from lipid oxidation (fasting) to glucose oxidation (post-prandial) under insulin regulation [36]. This allows the body to efficiently clear glucose from the bloodstream after a meal and to tap into fat stores for energy between meals.

In metabolic rigidity, this "switch" is compromised: the muscle struggles to uptake and oxidize glucose even in the presence of insulin (insulin resistance) and simultaneously fails to suppress lipolysis or efficiently oxidize fats during fasting [37]. This state of "metabolic indecision" leads to the accumulation of toxic lipid intermediates (lipotoxicity) and mitochondrial dysfunction [38]. The clinical consequence is a patient who feels constantly tired ("cellular starvation") despite having ample fat stores, and who experiences blood sugar swings due to inefficient clearance. The cells are effectively "deaf" to the context of their environment, locked in a rigid metabolic program that matches neither the fasted nor the fed state [38,39].

Metabolic rigidity manifests as persistently elevated mitochondrial respiratory quotients during fasting and blunted shifts postprandially, reflecting impaired respiratory chain adaptations and ectopic lipid deposition in insulin-sensitive tissues [40]. This state is exacerbated by persistent nutrient oversupply, promoting reactive oxygen species (ROS) overproduction and ceramide accumulation, which further desensitize insulin signaling pathways via serine/threonine kinase crosstalk [41].

This orchestration depends on the balance between two antagonistic kinase complexes: AMPK and mTOR [42] (see Figure 2). In metabolic rigidity, dysregulated AMPK-mTOR antagonism disrupts autophagic flux and substrate selection, perpetuating a catabolic-anabolic imbalance that underlies progression to type 2 diabetes [43]. These two kinases form the core decision-making unit of cellular metabolism, integrating thousands of upstream signals to determine the cell's energetic fate.

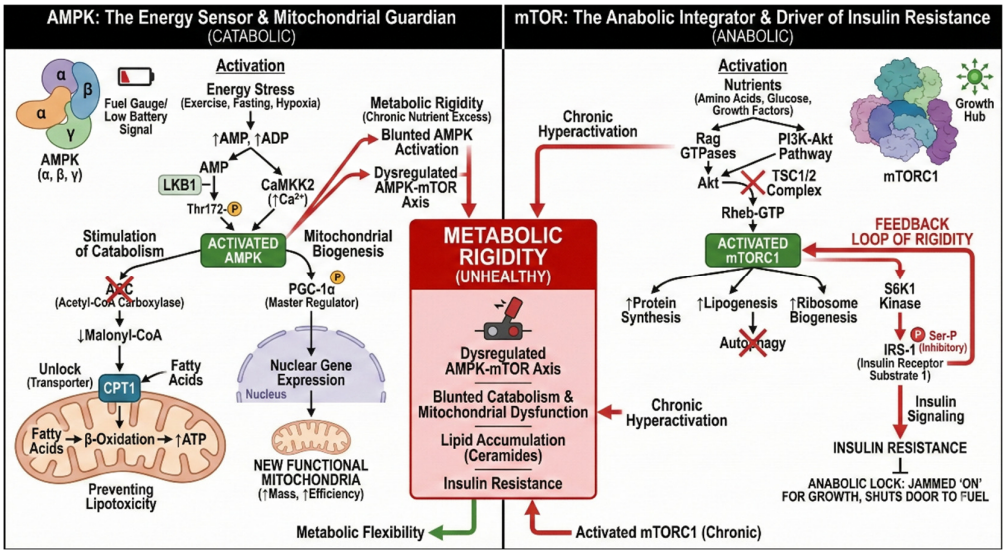

Figure 2.

2.1. AMPK: The Energy Sensor and Mitochondrial Guardian.

AMPK (AMP-activated protein kinase) is an evolutionarily conserved heterotrimer composed of a catalytic subunit (alpha) and two regulatory subunits (beta and gamma) [44]. It functions as a cellular "fuel gauge" or "low battery signal." Under conditions of energy stress (e.g., exercise, fasting, hypoxia), ATP consumption leads to a rise in AMP and ADP levels. AMP binds to the gamma subunit, inducing a conformational change that protects the protein from dephosphorylation and

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exposes the Thr172 phosphorylation site on the alpha subunit. Phosphorylation of Thr172, mediated by the upstream kinase LKB1 (Liver Kinase B1) or CaMKK2 (Calcium/Calmodulin-dependent Protein Kinase Kinase 2) in response to intracellular calcium flux, activates AMPK up to 1000-fold [44,45]. This extreme sensitivity ensures that even minor deficits in cellular energy charge trigger a robust restorative response.

Once activated, AMPK restores energy homeostasis through two main mechanisms that are critical for preventing metabolic rigidity (see Figure 2):

Stimulation of Catabolism: AMPK promotes fatty acid oxidation by phosphorylating and inhibiting Acetyl-CoA Carboxylase (ACC). ACC is the rate-limiting enzyme that converts acetyl-CoA to malonyl-CoA. Malonyl-CoA is a crucial metabolic regulator because it acts as a potent inhibitor of Carnitine Palmitoyltransferase 1 (CPT1), the transporter responsible for shuttling fatty acids into the mitochondria for beta-oxidation [46]. Through the inhibition of ACC, AMPK lowers malonyl-CoA levels, effectively "unlocking the door" (CPT1) for fatty acids to enter the mitochondria. This mechanism is crucial for preventing the lipotoxicity described in metabolic rigidity. In patients experiencing this condition, this pathway is often blunted; AMPK fails to activate, ACC remains active, malonyl-CoA stays high, and fatty acids are trapped in the cytoplasm where they are re-esterified into toxic lipid species like ceramides, which directly impair insulin signaling [46,47].

Mitochondrial Biogenesis: AMPK phosphorylates and activates PGC-1alpha (PPARgamma coactivator 1alpha), the master regulator of mitochondrial biogenesis [48]. This transcription coactivator drives the expression of nuclear genes encoding mitochondrial proteins, thereby increasing mitochondrial mass and efficiency. This directly counters the mitochondrial dysfunction that reduces oxidative capacity in metabolic syndrome [49]. A rigid metabolism is often characterized by a paucity of functional mitochondria ("mitochondrial rarefaction"). Without a robust AMPK signal—often due to sedentary behavior or chronic nutrient excess—the cell cannot generate the machinery needed to burn fuel efficiently, perpetuating the self-amplifying cycle of rigidity [50].

In metabolic rigidity, AMPK activation is often blunted or desensitized due to chronic hyperactivation of antagonistic mTOR signaling, which sustains an inappropriate anabolic state despite energy deficits. Without a robust AMPK signal, the cell fails to suppress mTORC1-mediated protein synthesis, perpetuating defective autophagic flux, ceramide buildup, and inflexible substrate utilization that hallmark insulin resistance progression [51]. This dysregulated AMPK-mTOR axis thus entrenches metabolic rigidity, limiting adaptive responses to nutrient fluctuations. Exercise, time-restricted feeding, and selected bioactive compounds (e.g., berberine and resveratrol) have been shown to activate AMPK in preclinical models, although clinical responses are heterogeneous and influenced by both contextual and genetic determinants [52].

2.2. mTOR: The Anabolic Integrator and Driver of Insulin Resistance

Balancing AMPK's pro-catabolic functions is mTOR (mechanistic target of rapamycin), a serine/threonine kinase that serves as a central hub for cell growth and anabolism [53]. While AMPK flags energetic needs, mTOR signals the cell to stop using substrates for energy production and focus on growth. mTOR exists in two distinct complexes: mTORC1 and mTORC2. mTORC1 (Rapamycin-sensitive) is the primary nutrient sensor. It integrates signals from amino acids (particularly leucine and arginine), glucose, and growth factors (insulin/IGF-1) to promote protein synthesis, lipogenesis, and ribosome biogenesis, while simultaneously inhibiting autophagy [53,54].

mTORC1 activation is a two-step process requiring both amino acids (signaled via Rag GTPases on the lysosome) and insulin signaling (mediated by the PI3K-Akt pathway). Akt phosphorylates and inhibits the TSC1/2 complex (Tuberous Sclerosis Complex). Since TSC2 acts as a GAP (GTPase Activating Protein) for the small GTPase Rheb, TSC2 inhibition allows Rheb to accumulate in its active GTP-bound form, thereby activating mTORC1 [55].

While acute activation of mTORC1 is essential for muscle growth and post-prandial recovery (anabolism), its chronic hyperactivation—caused by constant nutrient excess (overfeeding) and lack of fasting intervals—favors the development of insulin resistance [56]. The "Feedback Loop of

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Rigidity" consists in the activation of S6K1 kinase by mTORC1, which in turn phosphorylates Insulin Receptor Substrate 1 (IRS-1) on inhibitory serine residues [57]. This negative feedback mechanism desensitizes the cell to insulin. Physiologically, this prevents the cell from taking in more nutrients than it can handle. However, in the context of constant availability of calories, this feedback becomes constitutive. Sustained mTORC1 hyperactivation in the context of caloric surplus enhances S6K1-mediated inhibitory phosphorylation of IRS-1, a key mechanism underlying insulin resistance [57,58] (see Figure 2).

This explains the clinical paradox of high circulating insulin and glucose coexisting with cellular "starvation." The machinery is jammed in an "on" position for growth (mTOR) that paradoxically shuts the door (IRS-1) to the fuel needed for that growth [59]. This "anabolic lock" prevents the metabolic flexibility required to switch back to fat oxidation when glucose drops, leading to the hypoglycemic symptoms and cravings often reported by patients with insulin resistance.

2.3. The AMPK-mTOR Crosstalk and PP2A

Metabolic flexibility relies on the cellular ability to oscillate between these two kinase-induced states. The pathways are not parallel; they are deeply intertwined in a reciprocal inhibitory relationship. Under energy deficit, AMPK phosphorylates TSC2 (activating it) and directly phosphorylates Raptor (an essential component of mTORC1), thereby shutting down mTORC1 to conserve energy and induce autophagy [60]. This molecular switch ensures that anabolic processes do not consume ATP when supplies are critically low.

Recently, a crucial role has emerged for Protein Phosphatase 2A (PP2A) in this balance. PP2A is responsible for dephosphorylating targets in the Akt/mTOR pathway, ensuring that mTORC1 is rapidly turned off when building blocks for protein synthesis are unavailable [61]. Dysfunction of PP2A can thus lead to constitutively active mTORC1, locking the cell in a state of pseudo-growth and preventing the activation of reparative catabolic processes like autophagy. This represents a failure of the "off switch". If PP2A cannot dephosphorylate its targets, mTOR remains active even in the absence of optimal nutrients, perpetuating the insulin-resistant state and contributing to the "stiffness" of the metabolic response [62] (see Figure 2).

This dysregulation entrenches metabolic rigidity, characterized by an inflexible commitment to anabolic signaling despite fluctuating nutrient availability, resulting in defective substrate switching (e.g., persistent lipid oxidation during fed states) and progressive mitochondrial overload [63]. In metabolic rigidity phenotypes, impaired phosphatase activity sustains TSC2/Rheb hyperactivity, exacerbating mTORC1-S6K1 feedback on IRS-1 and fostering insulin desensitization alongside ectopic lipid accumulation in skeletal muscle and liver. Preclinical studies have examined pharmacological modulation of PP2A, yet its clinical applicability and long-term safety remain insufficiently characterized [64].

This network—AMPK, mTOR, and their regulators—provides the core logic of metabolic flexibility. Its dysregulation can be the determinant factor in the development of pathologic nutritional conditions, and explains why simply reducing calories may be ineffective if this signaling network remains locked in a rigid, mTOR-dominant, AMPK-suppressed state.

3. Metabolic Brakes: The Role of Protein Phosphatases

While kinases propagate intracellular signals, phosphatases terminate or finely modulate them, acting as essential metabolic "brakes" within signaling networks. In the pathogenesis of metabolic rigidity, hyperactivity of specific phosphatases can pathologically suppress insulin signaling, effectively maintaining an inhibitory state even in the presence of anabolic stimuli. This persistent dampening of insulin-dependent pathways impairs metabolic flexibility by limiting appropriate fuel switching, thereby promoting a chronic reliance on glycolytic metabolism despite adequate lipid availability [65].

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3.1. PTP1B: The Negative Regulator of Insulin and Leptin

Protein Tyrosine Phosphatase 1B (PTP1B) is localized on the cytoplasmic face of the endoplasmic reticulum (ER) [66]. It is widely recognized as the principal negative regulator of the insulin signaling pathway and the most important phosphatase in the context of insulin resistance development. PTP1B dephosphorylates tyrosine residues on the activated insulin receptor (IR) and receptor substrates (IRS-1/2), terminating signal transduction. Under physiological conditions, this prevents excessive insulin signaling and hypoglycemia [66,67].

In conditions of obesity, hyperglycemia, and chronic low-grade inflammation (meta-inflammation), PTP1B levels and activity increase drastically in the liver and skeletal muscle [68]. This hyperactivity creates a formidable barrier to insulin signaling. Even in the presence of hyperinsulinemia, the insulin receptor is rapidly dephosphorylated by PTP1B before the signal can effectively propagate downstream through the PI3K–Akt axis to promote GLUT4 translocation. Consequently, cells enter a state of profound insulin resistance in which they are functionally insensitive to the hormone [68] (see Figure 3).

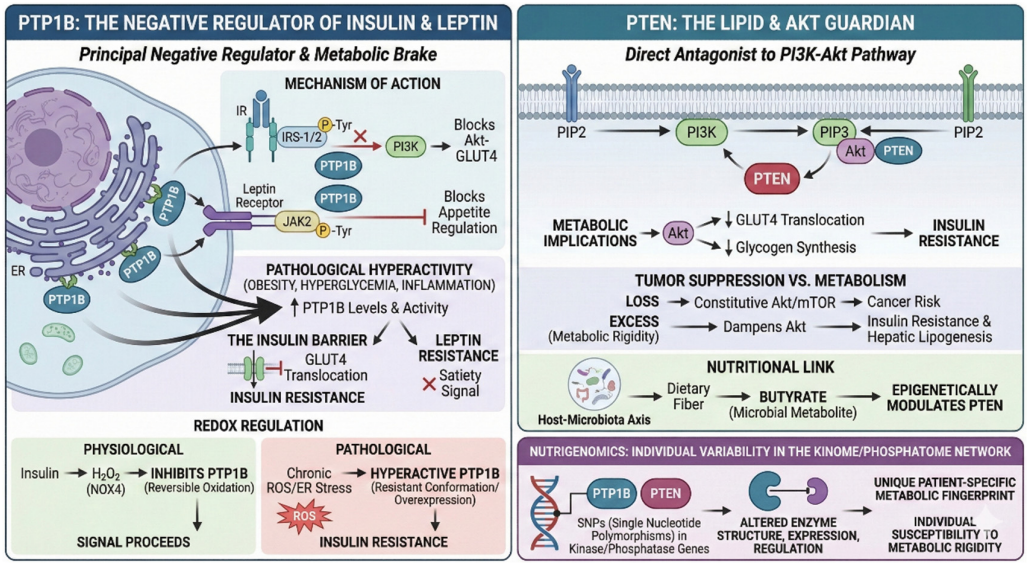

Figure 3.

In parallel, PTP1B-mediated dephosphorylation of JAK2, a critical kinase associated with the leptin receptor, contributes to leptin resistance, impairing central regulation of appetite and energy expenditure [69]. Within the broader framework of metabolic rigidity, sustained PTP1B overactivity perpetuates defective glucose uptake, mitochondrial substrate inflexibility, and incomplete lipid oxidation, thereby exacerbating lipotoxicity and accelerating the progression toward type 2 diabetes mellitus. Patients with high PTP1B activity are thus doubly affected: they cannot utilize glucose efficiently (insulin resistance) and they lack the satiety signals to stop eating (leptin resistance). This duality makes PTP1B a critical target for restoring metabolic flexibility [70].

PTP1B is finely regulated by the cell's redox state. Its active site contains an essential catalytic cysteine (Cys215) that is highly susceptible to oxidation by Reactive Oxygen Species (ROS) [71]. In physiological conditions, insulin itself induces transient H2O2 production (via NOX4) that reversibly oxidizes and inhibits PTP1B, allowing the signal to proceed. However, under conditions of chronic oxidative stress (common in mitochondrial dysfunction and obesity), this fine regulation may be lost. The sustained high levels of ROS might paradoxically lead to compensatory overexpression of PTP1B protein, or the specific redox environment in the ER (ER stress) may maintain PTP1B in a hyperactive conformation that is resistant to normal regulation [72]. This links mitochondrial health directly to insulin sensitivity via this phosphatase "brake" [73].

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3.2. PTEN: The Lipid and Akt Guardian

The phosphatase PTEN (Phosphatase and Tensin Homolog) acts as a direct antagonist to the PI3K-Akt pathway [74]. While PI3K phosphorylates the membrane lipid PIP2 into PIP3 to recruit Akt, PTEN removes the phosphate at position 3, converting PIP3 back to PIP2. Since Akt is essential for GLUT4 glucose transporter translocation and glycogen synthesis, PTEN activity directly reduces insulin sensitivity [75]. Although PTEN is primarily known as a tumor suppressor (its loss leads to uncontrolled cell growth via constitutive Akt/mTOR signaling), its regulation in a metabolic context is subtle [76].

In metabolic rigidity, PTEN overexpression in adipose and skeletal muscle tissues attenuates Akt-dependent oxidative and mitochondrial adaptations, effectively constraining cells within rigid glycolytic metabolic states and amplifying metaflammation-driven dysfunction [77]. Within this framework, nutritional modulation of PTEN emerges as a key regulatory component of the host–microbiota axis. Microbiota-derived metabolites such as butyrate can function as epigenetic modulators (via HDAC inhibition) influencing PTEN expression and activity, thereby establishing a direct mechanistic link between dietary fiber intake, microbial metabolic output, and the regulation of this critical signaling node [78] (see Figure 3).

3.3. From Cellular Energy Sensing to Systemic Adaptation: Integrative Control of Metabolic Flexibility by AMPK–mTOR–GLP-1 Axis

Within the broader landscape of metabolic flexibility, the AMPK–mTOR signaling axis operates as a central, hierarchically organized systems-level hub that enables cells and tissues to reprogram substrate utilization in response to dynamic fluctuations in energetic, hormonal, and nutritional inputs [79]. AMPK activation triggers a coordinated catabolic program that enhances fatty acid oxidation, mitochondrial biogenesis, and autophagic flux, thereby facilitating rapid and reversible transitions between nutrient abundance and scarcity, while simultaneously restraining anabolic outputs mediated by mTOR complex 1 (mTORC1). Through direct phosphorylation of key upstream regulators, AMPK imposes an energy-conserving brake on mTORC1 activity, ensuring metabolic prioritization under conditions of energetic stress [80].

Conversely, chronic mTORC1 hyperactivation—characteristic of insulin-resistant, obesogenic, and inflammatory states—imposes a persistent anabolic bias that decouples nutrient availability from appropriate metabolic responses, diminishes fuel-switching capacity, and entrenches metabolic inflexibility. This pathological state reflects not merely excessive nutrient signaling, but a failure of adaptive feedback control across the AMPK–mTOR axis. This maladaptive signaling configuration is further reinforced by increased activity of inhibitory phosphatases such as PTEN and PTP1B, which blunt PI3K–AKT signaling upstream of mTOR and functionally uncouple insulin and growth factor inputs from downstream metabolic reprogramming [81] (see Figure 3).

Glucagon-like peptide 1 (GLP-1) receptor agonists counterbalance this rigid signaling states by engaging cAMP-dependent and protein kinase A–mediated pathways that converge on AMPK activation and secondarily attenuate mTORC1 activity [82]. Beyond their canonical incretin effects, GLP-1 receptor agonists thus act as modulators of intracellular energy sensing, restoring signaling plasticity across multiple metabolic tissues. In parallel, bile acid–sensitive TGR5 signaling amplifies cAMP generation and enhances mitochondrial oxidative capacity, particularly in enteroendocrine cells, brown adipose tissue, and skeletal muscle, thereby reinforcing AMPK-dependent oxidative and thermogenic programs [83].

Importantly, the gut microbiome emerges as an upstream ecological driver of this network, shaping host metabolic flexibility through the production of short-chain fatty acids, secondary bile acids, indoles, and additional metabolites that modulate AMPK activity, TGR5 signaling, and insulin sensitivity [84]. Microbiome-derived signals thus provide a contextual layer of regulation that links dietary patterns, bile acid metabolism, and host energy sensing pathways. Through the integrated modulation of AMPK–mTOR dynamics, inhibitory phosphatases, bile acid–responsive receptors, and microbiome-derived cues, GLP-1–based therapies promote a systems-level reconfiguration of

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metabolic signaling networks, shifting cellular and organismal physiology toward metabolic adaptability [85]. This framework offers a unifying mechanistic rationale for targeting disorders defined by chronic signaling rigidity, impaired fuel flexibility, and maladaptive anabolic dominance.

4. Nutrigenomics: Individual Variability in the Kinome/Phosphatome Network

"Metabolic rigidity" does not affect all individuals equally even in the presence of the same dietary conditions. Host genetics play a fundamental role in determining individual susceptibility [86]. Single Nucleotide Polymorphisms (SNPs) in genes encoding these kinases and phosphatases can alter enzyme structure, expression, or regulatory dynamics, thereby generating a unique, patient-specific metabolic fingerprint. Such genetic variability predisposes certain genotypes to impaired substrate switching and a pathogenetic reliance on fuel sources under conditions of nutrient excess or metabolic stress, contributing to interindividual differences in metabolic flexibility and disease susceptibility [87] (see Figure 4).

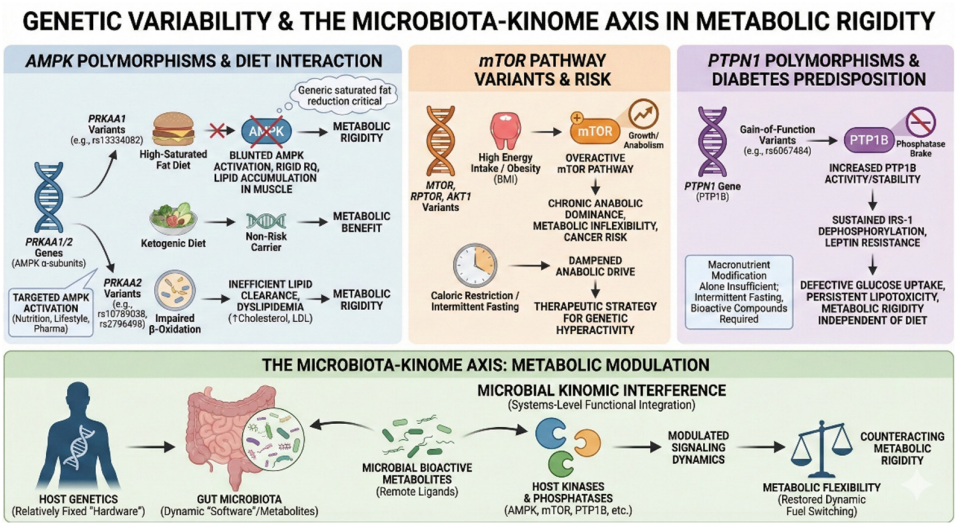

Figure 4.

4.1. AMPK Polymorphisms (PRKAA1/2) and Saturated Fat Interaction

The PRKAA1 and PRKAA2 genes encode the alpha1 and alpha2 isoforms of the AMPK catalytic subunit. Variants in these genes have been associated with various metabolic traits and susceptibility to type 2 diabetes [88] (see Figure 4). Variants in the PRKAA1 gene have been shown to modulate the metabolic response to dietary fats. In particular, carriers of specific risk alleles exhibit increased susceptibility to insulin resistance and obesity when exposed to high–saturated-fat diets [89]. These genotype-dependent effects indicate that impaired AMPK signaling compromises adaptive fuel sensing and substrate switching, thereby accelerating the onset of metabolic rigidity.

From a clinical and translational perspective, this evidence underscores that a general recommendation to "reduce saturated fats" may be critical for individuals harboring a functionally attenuated AMPK response, while being less relevant for others. Indeed, dietary patterns such as high–saturated-fat ketogenic diets may confer metabolic benefit in some patients but precipitate the development of metabolic inflexibility in carriers of PRKAA1 risk variants, highlighting the importance of a precision nutrition approach [90].

Variants in the PRKAA2 gene have been consistently associated with interindividual differences in total cholesterol and LDL levels, reflecting a genetically determined variability in basal AMPK activation and lipid-handling capacity [91]. These variants likely impair AMPK-mediated β-oxidation, thereby predisposing carriers to inefficient lipid clearance and metabolic rigidity under conditions of lipid overload. Consequently, individuals harboring PRKAA2 risk alleles may exhibit increased susceptibility to dyslipidemia and may require more targeted interventions—nutritional,

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lifestyle, or pharmacological—aimed at enhancing AMPK activity to restore and maintain metabolic flexibility [92].

4.2. mTOR Pathway Variants and Oncological/Metabolic Risk

Given mTOR's central role in cell growth, genetic variants in this pathway influence both cancer development and metabolic risk, often interacting with caloric intake [93]. Epidemiological studies have highlighted these variants in MTOR (formerly FRAP1) and RPTOR (component of mTORC1) influence cancer risk, but this risk is often modified by obesity (BMI) and energy intake [94] (see Figure 4). In some populations, variants in the AKT1 gene show a protective effect only in contexts of specific energy balance, suggesting that caloric restriction could be a key therapeutic strategy for individuals with a genetically hyperactive mTOR pathway prone to chronic anabolic dominance [95].

For these patients, intermittent fasting might not just be a weight loss tool, but a critical mechanism to dampen a genetically overactive anabolic drive that predisposes them to both metabolic rigidity and malignancy [96].

4.3. PTPN1 Polymorphisms and Diabetes Predisposition

The PTPN1 gene (encoding PTP1B) is highly polymorphic. Variants in the promoter region or coding regions can lead to increased mRNA stability or increased specific enzymatic activity [97]. In metabolic rigidity, these "gain-of-function" variants sustain IRS-1 dephosphorylation and leptin resistance, locking insulin-sensitive tissues into defective glucose uptake and persistent lipotoxicity independent of dietary triggers [98] (see Figure 4).

Carriers of these variants have a genetic predisposition to higher phosphatase activity, rendering them intrinsically more resistant to insulin and leptin. For these individuals, macronutrient modification alone may be insufficient to overcome a genetically driven, persistently overactive anabolic signaling milieu. In this context, intermittent fasting should be viewed as a potent long-term intervention capable of attenuating excessive anabolic drive, thereby restoring dynamic kinase–phosphatase balance and mitigating the progression toward metabolic rigidity [99]. Moreover, adjunctive use of targeted bioactive compounds—such as specific polyphenols like resveratrol or berberine with documented modulatory effects on these signaling nodes—may directly help balance dysregulated pathways [100]. Together, these approaches offer a phosphatome-targeted strategy to counteract genetically encoded anabolic hyperactivation that predisposes affected individuals not only to metabolic inflexibility but also to increased oncogenic risk.

PTPN1 related susceptibility should be viewed within a broader, hierarchical organisation of insulin signalling. Variants affecting the insulin receptor (INSR), scaffolding adaptors (IRS1/2), and the PI3K–AKT axis (for example PIK3CA, PIK3R1, AKT1/2) can exert dominant, upstream constraints on cellular insulin responsiveness and thereby shape, or even override, downstream kinase–phosphatase dynamics. Consequently, genotype informed strategies aimed at PTP1B or adjacent phosphatase nodes should be embedded within a systematic appraisal of upstream lesions to ensure that proposed interventions are aligned with the patient's principal molecular drivers.

5. The Microbiota-Kinome Axis: A Potential Target for Metabolic Modulation

If host genetics defines the "hardware" of intracellular signaling architectures, the gut microbiota supplies a continuous and highly dynamic layer of chemical "software" in the form of bioactive metabolites [101]. These microbial-derived compounds can function as remote, exogenous ligands for host kinases and phosphatases, directly or indirectly modulating their activity and thereby reshaping intracellular signaling dynamics [102]. Through this mechanism, gut microbial metabolites influence metabolic flexibility by fine-tuning insulin signaling, mitochondrial substrate selection, and oxidative capacity in insulin-sensitive tissues, effectively counteracting metabolic rigidity and restoring dynamic fuel switching [103]. This conceptual framework constitutes the innovative core of the present review, describing what could be defined as an acquired "Microbial Kinomic Defense

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System"—an intersystemic crosstalk through which the gut microbiota functionally integrates with host signaling networks to regulate metabolic homeostasis (see Figure 4).

5.1. Short-Chain Fatty Acids (SCFA): Epigenetic and Kinase Regulators

SCFAs (butyrate, propionate, acetate), produced by gut bacterial fermentation of dietary fibers, are among the primary mediators of host-microbiota dialogue [104]. They represent a direct link between diet (fiber intake) and host kinase regulation.

Butyrate is a potent Histone Deacetylase (HDAC) inhibitor. Through this epigenetic mechanism, butyrate maintains chromatin in an "open" acetylated state [105]. It has been demonstrated that butyrate induces PTEN expression in intestinal epithelial cells by inhibiting HDACs that normally repress the PTEN promoter [106]. By restoring PTEN levels, butyrate negatively modulates the PI3K-Akt pathway, promoting cell differentiation and preventing cancerous hyperproliferation (the Warburg effect). However, excessive or dysregulated PTEN activity at the systemic level could theoretically compromise insulin sensitivity in host target tissues, undermining its critical metabolic role [107]. Localized PTEN upregulation in the intestinal epithelium is associated with protective, tumor-suppressive functions; however, dysbiosis-driven alterations, including butyrate-mediated induction of PTEN expression in preclinical settings, have not been shown to translate into systemic pro–insulin-resistance effects in humans [107,108]. Notably, concomitant effects of PTEN on AMPK-related pathways may partially offset these outcomes, highlighting a delicate balance in which spatial regulation and signaling compartmentalization ultimately determine whether PTEN activity favors metabolic flexibility or dysfunction.

Short-chain fatty acids (SCFAs) are also potent physiological activators of AMP-activated protein kinase (AMPK) through complementary and convergent signaling pathways [109]. First, SCFAs bind to G-protein–coupled receptors GPR43 and GPR41, triggering intracellular calcium fluxes that activate calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2), which subsequently phosphorylates AMPK at the critical Thr172 residue [110]. Second, the hepatic metabolism of SCFAs alters the intracellular AMP/ATP ratio, leading to AMPK activation via the canonical LKB1-dependent pathway [111].

Through sustained AMPK activation, SCFAs enhance systemic fatty acid oxidation, improve insulin sensitivity, and promote mitochondrial adaptability, thereby facilitating dynamic respiratory quotient shifts between lipid and glucose oxidation [112]. This integrated response functionally mimics key metabolic effects of fasting and physical exercise, effectively acting as an endogenous "exercise-mimetic" signal. Importantly, this mechanistic chain of events provides a biological explanation for the efficacy of high-fiber diets in counteracting metabolic rigidity: by continuously supplying microbiota-derived SCFAs, dietary fibers deliver a persistent, low-amplitude activation signal to cellular energy-sensing networks, maintaining metabolic flexibility and preventing maladaptive fuel locking [113].

5.2. Secondary Bile Acids: Signaling via TGR5 and FXR

Microbial transformation of primary bile acids into secondary ones (e.g., deoxycholic acid, lithocholic acid) via 7α-dehydroxylation profoundly alters the signaling pool reaching the liver and peripheral tissues [114]. The membrane receptor TGR5 (Takeda G-protein-coupled receptor 5) is one of the targets preferentially activated by secondary bile acids. TGR5 activation triggers cAMP production and Protein Kinase A (PKA) activation [115]. PKA phosphorylates CREB, inducing the expression of key genes for energy expenditure (e.g., UCP1 in brown adipose tissue) and GLP-1 secretion from L-cells [116], thereby countering metabolic rigidity through enhanced thermogenesis and postprandial glucose disposal. This pathway directly modulates metabolic rigidity by increasing energy expenditure (wasting calories as heat) and enhancing insulin secretion.

The nuclear receptor FXR (Farnesoid X Receptor) plays a central role in coordinating bile acid and energy metabolism. Upon activation, FXR induces the secretion of fibroblast growth factor 19 (FGF19; FGF15 in rodents), which circulates to the liver and engages the FGFR4 receptor, triggering

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downstream MAPK signaling via ERK1/2 [117]. This pathway represses CYP7A1-mediated bile acid synthesis while simultaneously modulating hepatic glucose and lipid homeostasis [118]. Dysbiosis that diminishes populations of secondary bile acid-producing microbes disrupts this gut–liver signaling axis, leading to impaired feedback inhibition of bile acid synthesis, accumulation of hepatic lipids, and rigid lipid oxidation profiles [119]. Such perturbations can reinforce hallmarks of metabolic syndrome, including hepatic steatosis, impaired metabolic flexibility, and diminished capacity for adaptive substrate switching in response to nutritional or hormonal cues.

5.3. Indoles and Interaction with AhR

Tryptophan metabolism by the microbiota generates indoles (e.g., indole-3-propionate, indole-3-aldehyde), which act as ligands for the AhR (Aryl Hydrocarbon Receptor) [120]. Although the aryl hydrocarbon receptor (AhR) is primarily a ligand-activated transcription factor, its activation intersects with multiple kinase signaling pathways. AhR modulates Src kinase activity and engages p38 MAPK and NF-κB cascades, thereby regulating both immune responses and intestinal barrier integrity [121]. This crosstalk provides an additional molecular framework through which microbial metabolites can influence systemic metabolic homeostasis.

Indole derivatives produced by commensal bacteria act as endogenous AhR ligands that support gut barrier function. Loss of indole production compromises intestinal integrity, promoting translocation of lipopolysaccharides (LPS) and triggering chronic low-grade inflammation (meta-inflammation) [122]. This inflammatory milieu hyperactivates PTP1B and suppresses AMPK signaling, leading to persistent serine phosphorylation of IRS-1, defective GLUT4 translocation, and impaired mitochondrial substrate flexibility [123]. Through this mechanism, the microbiota–indole–AhR axis may contribute to mitigate the inflammatory activation of metabolic "brakes," preserving dynamic substrate switching and maintaining metabolic flexibility in insulin-sensitive tissues [124].

6. Personalized Multi-omics: Genomics and Phosphoproteomics for a Multilayer Picture of the Kinome/Phosphatome

While genomics provides valuable information on host susceptibility, xenobiotic sensitivity, and potential metabolic risks, it represents a static blueprint, reflecting probabilities rather than real-time cellular states [125]. However, the phosphorylation status of kinases and phosphatases constitutes a dynamic readout of functional signaling networks. By combining genomics with phosphoproteomics—the large-scale profiling of phosphorylated proteins—an instantaneous snapshot of the kinome and phosphatome can be captured, revealing which pathways are actively engaged or dysregulated in a given individual [126], a strategy that can be also utilized to monitor the effectiveness of therapeutic intervention.

This multi-omics integration enables a dual strategy: genomics predicts inherent susceptibilities, as well as the individual capability of responding to interventions, while phosphoproteomics monitors the real-time functional response of signaling networks, particularly those perturbed in metabolic rigidity. Applied to interventions targeting the gut microbiota, this approach allows personalized tracking of how microbial metabolites modulate host signaling, providing a mechanistically informed, comprehensive diagnostic framework guiding precision nutrition [127]. By linking static genetic predispositions with dynamic signaling states, this strategy supports the development of individualized nutritional interventions aimed at restoring metabolic flexibility and counteracting rigid fuel utilization.

6.1. Functional Phenotyping

Recent advances in mass spectrometry-based phosphoproteomics have enabled high-resolution mapping of individual responses to metabolic interventions such as exercise, nutrient intake, and dietary challenges [128]. These studies reveal extensive inter-individual variability in insulin signaling and substrate utilization that cannot be predicted by genomic data alone, highlighting the

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importance of functional, real-time profiling of the kinome and phosphatome, thus providing an individual functional phenotyping of diagnostic/prognostic value [129].

A personalized phosphoproteomics approach has uncovered novel regulatory interactions, thus shedding light on the molecular basis of metabolic rigidity. Notably, inhibitory phosphorylation of AMPK has been predominantly reported at Ser345/Ser347 by Akt/S6K1; a direct mTORC1-mediated phosphorylation remains under investigation and is not universally accepted [130]. This provides a molecular explanation for the so-called "anabolic lock" observed in metabolically rigid individuals, where persistent growth signaling physically suppresses fat oxidation and mitochondrial adaptability.

Complementary phosphosite analyses reveal hyperpersistent S6K1-IRS1 serine phosphorylation alongside hypo-phosphorylation of canonical AMPK substrates, reflecting sustained anabolic dominance, impaired mitochondrial biogenesis, and defective substrate switching [131]. These dysregulated signaling patterns precede overt dysglycemia and underscore how personalized phosphoproteomics can identify actionable targets for interventions aimed at restoring metabolic flexibility and preventing insulin resistance [132].

7. Precision Nutrition Strategies: Clinical Applications

Building on this framework of integrated molecular networks, it is possible to delineate precision nutrition strategies that extend far beyond common calorie counting [133]. By leveraging multi-omics insights—including kinome and phosphatome dynamics, genotype-specific susceptibilities, and microbiota-derived signaling—this approach allows tailored interventions to individual metabolic phenotypes [134]. Such personalized strategies aim to restore adaptive substrate switching, recalibrate kinase–phosphatase antagonism in real time, and prevent the progression from metabolic rigidity to overt metabolic disease.

"Nutritional Network Medicine" thus operationalizes systems biology at the patient's plate: interventions can combine targeted bioactive compounds, dietary modulation of microbial metabolites, and gene–diet interactions to selectively enhance catabolic or attenuate hyperactive anabolic pathways [135]. This paradigm provides a mechanistically informed, dynamic approach for nutrition, evolving from static dietary recommendations into actionable, personalized multi-omic diagnostics for metabolic therapeutics that can reshape cellular signaling networks.

7.1. Post-Prandial Heterogeneity

Post-prandial glycemic and lipid responses exhibit remarkable inter-individual variability, even among monozygotic twins, highlighting the critical contribution of non-genetic factors such as gut microbiota composition [136]. Integrating phosphoproteomics— easily performed on peripheral blood mononuclear cells (PBMCs) following nutrient intake—with continuous glucose monitoring (CGM) and comprehensive microbiota profiling enables high-resolution, real-time mapping of relevant intracellular signaling dynamics [137]. This approach can pinpoint specific molecular "blocks" that underlie metabolic rigidity, such as blunted Akt phosphorylation, PTP1B hyperactivity, or impaired AMPK activation, which manifest clinically as rigid respiratory quotient patterns, ectopic lipid accumulation, and defective substrate switching [138].

Inter individual variability in post prandial signalling should be interpreted in the context of potential upstream defects that precede AMPK–mTOR and phosphatase circuitry. Pathogenic or hypomorphic variants in INSR or IRS1/2 can blunt, distort or uncouple phosphorylation dynamics in circulating immune cells independently of microbiota derived metabolites or nutrient sensing kinases [139]. Accordingly, functional phosphoproteomic profiling should be integrated with targeted genotyping of canonical insulin signalling components to avoid misattribution of post prandial 'rigidity' to downstream pathways when the primary lesion resides upstream.

By distinguishing between mechanistically distinct forms of insulin resistance—those driven primarily by receptor downregulation versus those driven by phosphatase hyperactivity—clinicians can tailor nutritional and pharmacological interventions with unprecedented specificity. For

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example, patients with AMPK suppression may benefit from SCFA precursors or bioactive polyphenolic compounds that restore catabolic signaling, whereas individuals with PTP1B hyperactivity may require targeted inhibitors to relieve the "metabolic brake" [140]. Such real-time phenotyping provides a mechanistically informed strategy to reinstate dynamic substrate oxidation and avert progression toward type 2 diabetes.

7.2. Natural Compound Inhibition of PTP1B in Insulin Resistance

Insulin resistance emerges from a multilayered hierarchy of molecular alterations rather than from a single signalling fault. In individuals harbouring deleterious variants upstream of the kinase–phosphatase network — for example in INSR, IRS1 or PIK3R1 [141]— the capacity of PTP1B directed or AMPK activating interventions (such as curcumin, berberine or lipid derived modulators) to restore glucose handling may be constrained. Thus, any nutraceutical or dietary approach should be considered genotype contingent and evaluated against the integrity of proximal insulin receptor signalling.

Given PTP1B's pivotal role in attenuating insulin and leptin signaling—the so-called "metabolic brake" phenomenon—selective inhibition of this phosphatase represents a cornerstone strategy for precision nutrition in insulin-resistant individuals [142]. Dietary bioactive compounds, often present in phytocomplexes or nutraceutical formulations, can act as molecular modulators capable of allosterically or functionally attenuating PTP1B, thereby restoring dynamic kinase–phosphatase balance and improving metabolic flexibility [143].

Curcumin: Curcumin has been shown to significantly reduce hepatic PTP1B expression and enzymatic activity, primarily via NF-κB suppression [144]. This downregulation enhances tyrosine phosphorylation of the insulin receptor and JAK2, improving insulin and leptin sensitivity, reducing hepatic steatosis, and mitigating postprandial hyperglycemia. Genotype-stratified studies suggest that individuals with insulin-resistant or "rigid" phenotypes—particularly those with central adiposity—derive pronounced benefit from curcumin supplementation [145]. The clinical benefit of curcumin is therefore unlikely to be uniform and may be attenuated where receptor level or IRS associated defects dominate the phenotype.

Lipid Derivatives: Certain lithocholic acid congeners and specific fatty acids exert non-competitive, allosteric inhibition of PTP1B [146]. This action selectively potentiates Akt–GLUT4 translocation, exemplifying precision modulation of phosphatase hyperactivity. By targeting specific molecular nodes, these lipid-derived compounds can restore adaptive substrate switching and alleviate ectopic lipid accumulation.

Berberine: While primarily recognized as an AMPK activator, berberine also directly inhibits PTP1B, providing a dual mechanism to restore metabolic flexibility [147]. Through simultaneous enhancement of catabolic signaling and attenuation of maladaptive anabolic hyperactivity, berberine represents a prototypical bioactive for counteracting the "rigid" metabolic phenotype [148].

Collectively, these interventions illustrate how naturally derived compounds can serve as "molecular balancers" to recalibrate dysregulated phosphatase activity, offering a mechanistically informed, genotype-sensitive approach to precision nutrition and the management of insulin-resistant states.

7.3. Microbiota Modulation for Kinase Control

Precision nutrition can strategically exploit diet-induced reconfiguration of the gut microbiota to deliver targeted molecular signals that optimize the dynamic reciprocity between AMPK and mTORC1, thereby restoring metabolic flexibility in individuals with rigid phenotypes [149].

Fermentable Fibers (Prebiotics): Specific fermentable fibers—such as inulin-type fructans, resistant starches, and beta-glucans—selectively enrich butyrate-producing taxa (e.g., Faecalibacterium prausnitzii) [150]. Butyrate acts through dual mechanisms: histone deacetylase (HDAC) inhibition, which modulates PTEN expression, and activation of AMPK via GPR41/GPR43–CaMKK2 signaling [151]. Functionally, this constitutes an "eating-for-your-kinases" strategy. Dietary

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fibers, indeed, not only promote bowel health but can provide a controlled "energy stress" signal, thus contributing to mitochondrial activity, substrate switching, and catabolic capacity in conditions of metabolic rigidity.

Precision Probiotics: Targeted probiotic strains can be used to restore critical signaling axes disrupted by dysbiosis. For example, Clostridium sporogenes produces indole-3-propionate, activating AhR to reinforce intestinal barrier integrity and suppress PTP1B, whereas Clostridium scindens generates secondary bile acids that engage TGR5, stimulating PKA-dependent thermogenesis and enhancing lipid oxidation [152]. By providing these exogenous ligands, precision probiotics can contribute to recalibrate kinase–phosphatase networks in real time, effectively restoring host metabolic flexibility through microbiota-mediated signaling [153].

Through the combination of fermentable fibers and precision probiotics, diet can be purposefully employed to "program" the microbiota as a dynamic producer of bioactive metabolites that act as remote modulators of the host kinome and phosphatome, thereby bridging microbial ecology with molecular metabolic control.

7.4. Genotype-Based Personalization

Genotype based personalization should extend beyond variants directly impacting AMPK, mTOR or phosphatases to encompass upstream and downstream determinants of insulin signalling. Pathogenic or functional alleles in INSR, IRS1/2, PIK3CA/PIK3R1, AKT1/2 and downstream transcriptional regulators can substantially reframe the intracellular context within which nutrient and microbiota derived cues operate. A comprehensive genotypic scaffold is therefore required to prevent over attribution of metabolic inflexibility to a single signalling layer and to prioritise interventions that address the dominant molecular bottlenecks in a given patient. Leveraging genomic information to tailor dietary interventions exemplifies precision nutrition, allowing clinicians to preempt dysregulation of key signaling networks and mitigate the onset of metabolic rigidity [154]. By aligning nutrient composition and timing with individual kinase–phosphatase genotypes, interventions can be mechanistically targeted to restore metabolic flexibility.

AMPK Genotype (PRKAA1): Carriers of specific PRKAA1 risk variants exhibit heightened susceptibility to saturated fat–induced S6K1 hyperactivation and downstream anabolic dominance [155]. For these individuals, diets with strict saturated fat limitation are critical to prevent lipotoxicity, rigid respiratory quotient patterns, and early insulin resistance. High-fat ketogenic regimens, while therapeutic in other contexts, may be deleterious in these genotypes, accelerating the very metabolic rigidity they aim to correct [156].

mTOR Genotype (MTOR/AKT1): Individuals harboring hyperactive MTOR or AKT1 variants display an intrinsic anabolic bias, predisposing them to tonic mTORC1 overactivation and impaired autophagic flux [157]. Time-restricted feeding protocols (e.g., 16:8) and reduction of branched-chain amino acid intake—particularly leucine—can selectively attenuate mTORC1 signaling, enhance autophagy, and improve insulin sensitivity in genotype-stratified cohorts, as demonstrated in controlled trials [158].

This genomics-driven approach enables a nuanced, mechanism-based strategy in which nutrient composition, timing, and caloric load are individualized to counteract genetically encoded vulnerabilities, recalibrate kinase–phosphatase dynamics, and maintain adaptive substrate switching. By aligning dietary interventions with the patient's signaling genotype, precision nutrition moves beyond population-level recommendations toward personalized, metabolically informed therapy (see Table 1).

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Table 1. Key Interactions in Genetic Predictors for Nutritional Interventions on the Kinome-Microbiota Axis.

Component	Primary Function	Microbial/Nutritional Modulator	Enzymatic Target	Nutritional Implication	Bibliography
mTORC1	Anabolism, Protein Synthesis	Amino acids, Insulin	Kinase	Protein/caloric restriction to reduce hyperactivity (aging/cancer).	[53,54]
AMPK	Energy Sensor, Catabolism	SCFA (Butyrate, Acetate)	Kinase	Fermentable fibers mimic fasting/exercise signals.	[44–46]
PTP1B	Insulin/Leptin Brake	Curcumin, ROS, Specific Lipids	Phosphatase	Polyphenols (Curcumin, Berberine) to sensitize to insulin by inhibiting PTP1B.	[66–68]
PTEN	PI3K Antagonist (Tumor Suppressor)	Butyrate (via HDAC inhibition)	Phosphatase	Fibers as chemopreventive agents by restoring PTEN.	[75–78]
TGR5	Metabolism, GLP-1	Secondary Bile Acids (LCA, DCA)	GPCR -> PKA	Modulation of bile acid pool (Probiotics) to stimulate metabolism.	[115–118]

8. Towards a Translational Network-Based Framework for Precision Nutrition

The clinical translation of a network-based precision nutrition paradigm grounded in the kinome–phosphatome–microbiota axis would require a shift from purely conceptual representations toward operationally defined, scalable, and context-aware frameworks [159]. In this perspective, metabolic regulation may be more appropriately conceptualized as an adaptive, multilayered network whose functional state emerges from the dynamic integration of genetic architecture, microbial-derived signals, and intracellular phosphorylation-dependent signaling [160].

A translational model informed by network medicine and systems biology could be envisaged as a methodological scaffold to bridge mechanistic insights with clinically relevant interpretation, while remaining primarily oriented toward research-grade stratification rather than immediate clinical deployment [161]. At the analytical level, the integration of multi-omic data would necessitate standardized, reproducible, and context-dependent analytical pipelines, explicitly acknowledging variability in technical depth and resource availability. Genomic profiling could contribute structural information on network susceptibility through the identification of functional variants in genes governing energy sensing (e.g., PRKAA1, MTOR) and insulin signaling (e.g., PTPN1), here cited as representative nodes rather than exhaustive determinants [162]. In parallel, functional characterization of the gut microbiota, with particular emphasis on short-chain fatty acid production, bile acid transformation, and tryptophan metabolism, would capture a major component of the environmental chemical input modulating host signaling networks [163].

Central to this framework, dynamic phosphoproteomic profiling could serve as a functional layer of integration, ideally performed under standardized pre- and post-prandial conditions, enabling the assessment of pathway activity states over time [164]. By focusing on phosphorylation sites with high inferred network centrality—such as those regulating AMPK (Thr172), mTORC1 (Ser2448), and insulin receptor substrate signaling (Ser636/639), used here as illustrative examples—phosphoproteomics could transition from a predominantly descriptive approach to a context-dependent functional readout of network behavior, without implying a fixed or universal marker set [165].

The integration of these heterogeneous data layers could allow for the reconstruction of patient-specific molecular networks in a research setting, in which nodes represent signaling proteins and metabolic regulators, while weighted edges reflect functional interactions modulated by genetic predisposition and microbial inputs [166]. Such an approach might enable the identification of recurrent functional modules and network configurations associated with impaired metabolic

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adaptability, thereby reframing metabolic disease not as the result of isolated pathway dysfunctions, but as the emergence of stable yet maladaptive network states [167].

Within this conceptual framework, the molecular highlights of metabolic flexibility, identified with a multilayer -omic approach, as well as other relevant diagnostic analytes, could be presented as an integrative, systems-level construct aimed at capturing the adaptive capacity of metabolic signaling networks in response to defined nutritional or energetic perturbations. Such a construct would not be intended as a single measurable variable, but rather as a composite descriptor that could reflect coordinated behavior across molecular, microbial, and clinical layers of regulation [168].

From a conceptual standpoint, this approach could integrate information derived from dynamic signaling responses, structural properties of inferred molecular networks, functional outputs of the gut microbiota, and established clinical indicators of insulin sensitivity, including fasting insulin levels and HOMA-IR [169]. By combining these complementary dimensions, the framework would aim to move beyond the current segmented and incomplete static representations of metabolic state and might offer a means to characterize the system's capacity for reversible reorganization following perturbation, a feature commonly associated with metabolic adaptability.

Within this perspective, states of reduced metabolic flexibility could be characterized by constrained signaling dynamics, attenuated responsiveness to nutritional challenges, and limited capacity for adaptive fuel switching, consistent with a more rigid network configuration [170]. Conversely, preserved flexibility might correspond to more reversible and coordinated signaling responses across interacting pathways. Importantly, such a construct would not be proposed as a diagnostic endpoint, but rather as a systems-oriented descriptor that could support hypothesis generation, phenotypic stratification, and mechanistic interpretation in metabolic research.

At present, the translational relevance of a systems-based assessment of this kind would remain largely theoretical and would require rigorous validation across diverse populations, intervention paradigms, and healthcare settings [171]. Nevertheless, simplified implementations might be envisioned, particularly in resource-limited contexts, by leveraging reduced biomarker panels or surrogate functional readouts while preserving the underlying network-based rationale. Iterative refinement and methodological harmonization could, over time, support the development of standardized approaches for evaluating metabolic adaptability across heterogeneous research and clinical settings.

By emphasizing network dynamics rather than isolated metabolic endpoints, such a framework would align with emerging principles in systems medicine and network physiology, which increasingly conceptualize health and disease as properties of adaptive, multiscale biological networks rather than the output of individual pathways [172].

9. Conclusions

Metabolic inflexibility should not be interpreted as a linear phenomenon attributable solely to caloric excess or physical inactivity; rather, it should be understood as the pathological emergence of a dysregulated complex biological network in which the dynamic interactions among nutritional, hormonal, microbial, and genetic signals are progressively disrupted.

From a network medicine perspective, metabolic flexibility represents an emergent property of the system, arising from the ability of metabolic and signaling networks to dynamically reconfigure in response to environmental perturbations [173]. The loss of this property reflects a gradual fragmentation of network architecture, characterized by impaired functional connectivity among key nodes, including receptors, kinases, phosphatases, transcription factors, and energy-regulating organelles, most notably the mitochondrion.

At the molecular level, metabolic rigidity is associated with a maladaptive reorganization of intracellular signaling networks, in which central pathways—such as insulin/IRS–PI3K–AKT, AMPK, mTOR, and PPAR signaling—cease to function as interconnected and plastically regulated modules and instead adopt rigid, self-sustaining configurations. In this context, reversible protein phosphorylation loses its role as a finely tuned mechanism for signal integration and becomes a state

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of chronic activation (e.g., mTORC1) or persistent inhibition (e.g., AMPK via PTP1B) of specific network nodes. This signaling misalignment compromises the system's ability to appropriately allocate energetic substrates and promotes convergence toward shared pathological phenotypes, including insulin resistance, ectopic lipid accumulation, oxidative stress, and chronic low-grade inflammation.

Within this framework, genomics is not viewed as an isolated causal determinant but as a structural component defining the topology of the individual metabolic network. Genetic variants, particularly single nucleotide polymorphisms in genes like PRKAA1, MTOR, and PTPN1, influence node robustness and edge resilience, thereby modulating the likelihood that specific environmental perturbations will drive transitions toward stable pathological states. In other words, the genotype delineates the boundaries of the dynamic landscape within which metabolic adaptation occurs, without uniquely determining its trajectory.

The gut microbiota integrates into this network as a highly dynamic and environmentally responsive subsystem capable of modulating host metabolic networks in real time. Microbial-derived metabolites act as both short- and long-range network signals ("kinomic interference"), influencing nuclear receptors, G protein–coupled receptors, and cellular energy sensors, while reshaping connectivity between seemingly distant pathways. From a network medicine perspective, dysbiosis should therefore be interpreted not merely as a compositional shift, but as a functional reconfiguration of the extended host–microbiota metabolic network, with systemic consequences for insulin signaling, lipid metabolism, and inflammatory tone.

The clinical implications of this model are substantial. Major metabolic disorders—including obesity, type 2 diabetes, non-alcoholic fatty liver disease, and metabolic syndrome—emerge as stable yet maladaptive network states maintained by dysfunctional feedback circuits [174]. In this context, standardized nutritional interventions often act as weak and nonspecific perturbations, insufficient to shift the system toward a healthier metabolic state. In contrast, personalized strategies that identify and target critical nodes and altered connections within the individual network hold the potential to restore metabolic flexibility by selectively intervening at points of maximal network vulnerability.

Future personalized and precision nutrition approaches must therefore evolve toward an integrated, multi-omic framework capable of combining genomic, metagenomic, and functional data with dynamic measurements of cellular signaling. Within this paradigm, phosphoproteomics plays a central role as a functional tool for mapping the operational state of signaling networks, enabling the distinction between potentially altered pathways and those that are effectively dysfunctional. The integration of these data supports the design of nutritional and therapeutic interventions aimed not at single targets, but at the coordinated reconfiguration of the metabolic network as a whole.

In conclusion, the adoption of a network-based personalized medicine paradigm applied to nutrition represents a critical step beyond reductionist and "one-size-fits-all" models [175]. Only through an improved understanding of the non-linear interactions among genotype, microbiota, nutritional inputs, and intracellular signaling networks will it be possible to develop effective strategies to restore metabolic flexibility—conceived not as the mere normalization of biochemical parameters, but as the recovery of the adaptive capacity of the biological system as an integrated whole.

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References

1. Ordovas, J. M., et al. (2018). "Personalised nutrition and health." BMJ, 361: k2173.
2. Berry, S. E., et al. (2020). "Human postprandial responses to food and potential for precision nutrition." Nature Medicine, 26(6), 964-973.
3. Zeevi, D., et al. (2015). "Personalized nutrition by prediction of glycemic responses." Cell, 163(5), 1079-1094.
4. Goodpaster, B. H., & Sparks, L. M. (2017). "Metabolic Flexibility in Health and Disease." Cell Metabolism, 25(5), 1027-1036.
5. Smith, R. L., et al. (2018). "Metabolic Flexibility as an Adaptation to Energy Resources and Requirements in Health and Disease." Endocrine Reviews, 39(4), 489-517.
6. Kelley, D. E., & Mandarino, L. J. (2000). "Fuel selection in human skeletal muscle in insulin resistance: a reexamination." Diabetes, 49(5), 677-683.
7. Muoio, D. M. (2014). "Metabolic inflexibility: when mitochondrial indecision leads to metabolic gridlock." Cell, 159(6), 1253-1262.
8. Gross, B., Pawlak, M., & Lefebvre, P. (2017). "PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD." Nature Reviews Endocrinology, 13(1), 36-49.
9. Galgani, J. E., et al. (2008). "Metabolic flexibility and insulin resistance." American Journal of Physiology-Endocrinology and Metabolism, 295(5), E1009-E1017.
10. Rynders, C. A., et al. (2018). "Metabolic flexibility as a determinant of weight management." International Journal of Obesity, 42, 793-794.
11. Faerch, K., et al. (2016). "Pathophysiology of type 2 diabetes: retention of the metabolic flexibility concept." The Lancet Diabetes & Endocrinology, 4(6), 478-479.
12. Crofts, C., et al. (2016). "Identifying hyperinsulinaemia in the absence of impaired glucose tolerance: An examination of the Kraft database." Diabetes Research and Clinical Practice, 118, 50-57.
13. Muoio, D. M., & Neufer, P. D. (2012). "Lipid-induced mitochondrial stress and insulin action." Cell Metabolism, 15(5), 595-605.
14. Samuel, V. T., & Shulman, G. I. (2012). "Mechanisms for insulin resistance: common threads and missing links." Cell, 148(5), 852-871.
15. Samuel, V. T., & Shulman, G. I. (2016). "The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux." Journal of Clinical Investigation, 126(1), 12-22.
16. Hotamisligil, G. S. (2017). "Inflammation, metaflammation and immunometabolic disorders." Nature, 542(7640), 177-185.
17. Boucher, J., Kleinridders, A., & Kahn, C. R. (2014). "Insulin receptor signaling in normal and insulin-resistant states." Cold Spring Harbor Perspectives in Biology, 6(1), a009191.
18. Freese, J., et al. (2017). "The sedentary (r)evolution: Have we lost our metabolic flexibility?" F1000Research, 6, 1787.
19. Manning, G., et al. (2002). "The protein kinase complement of the human genome." Science, 298(5600), 1912-1934.
20. Hunter, T. (2000). "Signaling—2000 and beyond." Cell, 100(1), 113-127.

 doi:10.20944/preprints202603.0608.v1

21. Bridges, D., et al. (2017). "Phosphoproteomics: A new frontier in the biology of insulin action." Cell Metabolism, 25(3), 541-542.
22. Hardie, D. G., Ross, F. A., & Hawley, S. A. (2012). "AMPK: a nutrient and energy sensor that maintains energy homeostasis." Nature Reviews Molecular Cell Biology, 13(4), 251-262.
23. Laplante, M., & Sabatini, D. M. (2012). "mTOR signaling in growth control and disease." Cell, 149(2), 274-293.
24. Saxton, R. A., & Sabatini, D. M. (2017). "mTOR signaling in growth, metabolism, and disease." Cell, 168(6), 960-976.
25. Schroeder, B. O., & Bäckhed, F. (2016). "Signals from the gut microbiota to distant organs in health and disease." Nature Medicine, 22(10), 1079-1089.
26. Koh, A., et al. (2016). "From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites." Cell, 165(6), 1332-1345.
27. Canfora, E. E., Meijer, K., & Blaak, E. E. (2015). "Dietary fibers and their fermentation products for glucose metabolism." Nature Reviews Endocrinology, 11(8), 465-475.
28. Molan, A. L., et al. (2021). "The role of gut microbiota-derived short-chain fatty acids in metabolic health." Signal Transduction and Targeted Therapy, 6, 142.
29. Gurzov, E. N., & Eizirik, D. L. (2011). "Bcl-2 proteins in diabetes: mitochondrial pathways of β-cell death and dysfunction." Trends in Cell Biology, 21(7), 424-431.
30. Vrieze, A., et al. (2012). "Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome." Gastroenterology, 143(4), 913-916.
31. Rühlemann, M. C., et al. (2021). "Genome-wide association study in 8,956 German individuals identifies influence of ABO histo-blood groups on gut microbiome." Nature Genetics, 53(2), 147-155.
32. Sonnenburg, J. L., & Bäckhed, F. (2016). "Diet–microbiota interactions as moderators of human metabolism." Nature, 535(7610), 56-64.
33. Donohoe, D. R., et al. (2012). "The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon." Cell Metabolism, 13(5), 517-526.
34. Humphrey, S. J., James, D. E., & Mann, M. (2015). "Protein phosphorylation: a major switch mechanism for metabolic regulation." Trends in Endocrinology & Metabolism, 26(12), 676-687.
35. Goodpaster, B. H., & Sparks, L. M. (2017). "Metabolic Flexibility in Health and Disease." Cell Metabolism, 25(5), 1027-1036.
36. Kelley, D. E., et al. (1999). "Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss." American Journal of Physiology, 277, E1130-E1141.
37. Muoio, D. M. (2014). "Metabolic inflexibility: when mitochondrial indecision leads to metabolic gridlock." Cell, 159(6), 1253-1262.
38. Smith, R. L., et al. (2018). "Metabolic Flexibility as an Adaptation to Energy Resources and Requirements in Health and Disease." Endocrine Reviews, 39(4), 489-517.
39. Corpeleijn, E., Saris, W. H., & Blaak, E. E. (2009). "Metabolic flexibility in the development of insulin resistance and type 2 diabetes: effects of lifestyle." Obesity Reviews, 10(2), 178-193.
40. Galgani, J. E., et al. (2008). "Metabolic flexibility and insulin resistance." American Journal of Physiology-Endocrinology and Metabolism, 295(5), E1009-E1017.
41. Petersen, M. C., & Shulman, G. I. (2018). "Mechanisms of Insulin Action and Insulin Resistance." Physiological Reviews, 98(4), 2133-2223.
42. Steinberg, G. R., & Kemp, B. E. (2009). "AMPK in Health and Disease." Physiological Reviews, 89(3), 1025-1078.
43. Kim, J., Kundu, M., Viollet, B., & Guan, K. L. (2011). "AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1." Nature Cell Biology, 13(2), 132-141.
44. Hardie, D. G., Ross, F. A., & Hawley, S. A. (2012). "AMPK: a nutrient and energy sensor that maintains energy homeostasis." Nature Reviews Molecular Cell Biology, 13(4), 251-262.
45. Gowans, G. J., & Hardie, D. G. (2014). "AMPK: a cellular energy sensor switching on catabolism and switching off anabolism." Biochemical Society Transactions, 42(1), 71-75.

 doi:10.20944/preprints202603.0608.v1

46. Fullerton, M. D., et al. (2013). "Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin." Nature Medicine, 19(12), 1649-1654.
47. Samuel, V. T., & Shulman, G. I. (2012). "Mechanisms for insulin resistance: common threads and missing links." Cell, 148(5), 852-871.
48. Jäger, S., Handschin, C., St-Pierre, J., & Spiegelman, B. M. (2007). "AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1α." Proceedings of the National Academy of Sciences, 104(29), 12017-12022.
49. Cantó, C., & Auwerx, J. (2009). "PGC-1alpha, SIRT1 and AMPK, an energy sensing network that controls energy expenditure." Current Opinion in Lipidology, 20(2), 98-105.
50. Ritov, V. B., et al. (2005). "Deficiency of subsarcolemmal mitochondria in obesity and type 2 diabetes." Diabetes, 54(1), 8-14.
51. Herzig, S., & Shaw, R. J. (2018). "AMPK: guardian of metabolism and mitochondrial homeostasis." Nature Reviews Molecular Cell Biology, 19(2), 121-135.
52. Coughlan, K. A., et al. (2014). "Nutrient excess in skeletal muscle causes mitochondrial accumulation of fatty acids and alters mitochondrial protein acetylation." Diabetes, 63(8), 2693-2704.
53. Saxton, R. A., & Sabatini, D. M. (2017). "mTOR signaling in growth, metabolism, and disease." Cell, 168(6), 960-976.
54. Laplante, M., & Sabatini, D. M. (2012). "mTOR signaling in growth control and disease." Cell, 149(2), 274-293.
55. Inoki, K., Li, Y., Zhu, T., Wu, J., & Guan, K. L. (2002). "TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling." Nature Cell Biology, 4(9), 648-657.
56. Newgard, C. B. (2017). "Metabolism: Anabolism and catabolism collide." Nature, 542(7642), 419-420.
57. Um, S. H., et al. (2004). "Absence of S6K1 protects against age-and diet-induced obesity while enhancing insulin sensitivity." Nature, 431(7005), 200-205.
58. Tremblay, F., et al. (2007). "Identification of IRS-1 Ser-1101 as a target of S6K1 in nutrient-and obesity-induced insulin resistance." Proceedings of the National Academy of Sciences, 104(35), 14056-14061.
59. Shimobayashi, M., & Hall, M. N. (2014). "Making new contacts: the mTOR network in metabolism and signalling crosstalk." Nature Reviews Molecular Cell Biology, 15(3), 155-162.
60. Gwinn, D. M., et al. (2008). "AMPK phosphorylation of raptor mediates a metabolic checkpoint." Molecular Cell, 30(2), 214-226.
61. Sontag, E., et al. (2007). "Regulation of the phosphorylation state and function of the tuberous sclerosis complex (TSC2) by PP2A." Biochemical Journal, 407(Pt 3), 425.
62. Rodgers, J. T., et al. (2014). "mTORC1 controls the adaptive transition to fasting." Cell Metabolism, 19(4), 682-693.
63. Koves, T. R., et al. (2008). "Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance." Cell Metabolism, 7(1), 45-56.
64. Vorolyova, N., et al. (2022). "The Role of Protein Phosphatase 2A (PP2A) in the Regulation of Autophagy." International Journal of Molecular Sciences, 23(19), 11822.
65. Tiganis, T. (2011). "Reactive oxygen species and insulin resistance: the good, the bad and the ugly." Trends in Pharmacological Sciences, 32(2), 82-89.
66. Elchebly, M., et al. (1999). "Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene." Science, 283(5407), 1544-1548.
67. Tonks, N. K. (2006). "Protein tyrosine phosphatases: from genes, to function, to disease." Nature Reviews Molecular Cell Biology, 7(11), 833-846.
68. Zabolotny, J. M., et al. (2008). "PTP1B regulates leptin signal transduction in vivo." Developmental Cell, 2(4), 489-495.
69. Bence, K. K., et al. (2006). "Neuronal PTP1B regulates body weight, adiposity and leptin action." Nature Medicine, 12(8), 917-924.
70. Yip, S. C., Saha, S., & Chernoff, J. (2010). "PTP1B: a double agent in metabolism and oncogenesis." Trends in Biochemical Sciences, 35(8), 442-449.

 doi:10.20944/preprints202603.0608.v1

71. Salmeen, A., et al. (2003). "Redox regulation of protein tyrosine phosphatase 1B involves a sulphenyl-amide intermediate." Nature, 423(6941), 769-773.
72. Bettaieb, A., et al. (2011). "Endoplasmic reticulum stress suppresses insulin signaling through c-Jun N-terminal kinase-dependent phosphorylation of insulin receptor substrate-1." Diabetes, 60(2), 391-400.
73. Delibegovic, M., et al. (2009). "Liver-specific deletion of protein tyrosine phosphatase 1B (PTP1B) improves metabolic syndrome in mice." Molecular and Cellular Biology, 29(15), 4195-4207.
74. Maehama, T., & Dixon, J. E. (1998). "The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate." Journal of Biological Chemistry, 273(22), 13375-13378.
75. Wijesekara, N., et al. (2005). "Muscle-specific Pten deletion protects against insulin resistance and diabetes." Molecular and Cellular Biology, 25(3), 1135-1145.
76. Song, M. S., Salmena, L., & Pandolfi, P. P. (2012). "The functions and regulation of the PTEN tumour suppressor." Nature Reviews Molecular Cell Biology, 13(5), 283-296.
77. Kurlawala, Z., et al. (2010). "The role of PTEN in skeletal muscle insulin signaling and glucose homeostasis." Journal of Biological Chemistry, 285, 3965-3975.
78. Bultman, S. J. (2014). "Molecular pathways: probable mechanisms of colon cancer prevention by dietary fiber and butyrate." Clinical Cancer Research, 20(4), 799-803.
79. Steinberg, G. R., & Carling, D. (2019). "AMP-activated protein kinase: the current landscape for drug development." Nature Reviews Drug Discovery, 18(7), 527-551.
80. Mihaylova, M. M., & Shaw, R. J. (2011). "The AMPK signalling pathway coordinates cell growth, autophagy and metabolism." Nature Cell Biology, 13(9), 1016-1023.
81. Kahn, B. B., & Alquier, T. (2017). "Obesity and insulin resistance: an energetic puzzle." Science, 355(6321), eaaf7754.
82. Cantini, G., et al. (2016). "Glucagon-like peptide 1 signals through AMPK to activate pathways of cellular clearance and autophagy." Scientific Reports, 6, 36473.
83. Watanabe, M., et al. (2006). "Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation." Nature, 439(7075), 484-489.
84. Canfora, E. E., Meijer, K., & Blaak, E. E. (2015). "Dietary fibers and their fermentation products for glucose metabolism." Nature Reviews Endocrinology, 11(8), 465-475.
85. Drucker, D. J. (2018). "Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1." Cell Metabolism, 27(4), 740-756.
86. Ordovas, J. M., & Corella, D. (2004). "Nutritional genomics." Annual Review of Genomics and Human Genetics, 5, 71-118.
87. Phillips, C. M. (2013). "Nutrigenetics and metabolic disease: current status and implications for personalised nutrition." Nutrients, 5(1), 32-57.
88. Horikoshi, M., et al. (2016). "Transancestral fine-mapping of four type 2 diabetes susceptibility loci highlights potential causal regulatory mechanisms." Human Molecular Genetics, 25(10), 2070-2081.
89. Corella, D., et al. (2009). "APOA2, dietary fat, and the genetic architecture of obesity." Archives of Medical Research, 40(8), 690-696.
90. Ferguson, L. R., et al. (2016). "Nutrigenomics and gut health in a clinical setting: what is the evidence?" Current Opinion in Clinical Nutrition and Metabolic Care, 19(6), 441-447.
91. Nott, A., et al. (2019). "Brain cell type–specific enhancer–promoter interactome maps and disease-risk association." Science, 366(6469), 1134-1139.
92. Viollet, B., et al. (2009). "AMPK: Lessons from transgenic and knockout animals." Frontiers in Bioscience, 14, 19-44.
93. Laplante, M., & Sabatini, D. M. (2012). "mTOR signaling in growth control and disease." Cell, 149(2), 274-293.
94. Moore, H. C., et al. (2004). "The effect of genetic variants in the mTOR pathway on the risk of breast cancer." Carcinogenesis, 25, 1-7.
95. Udler, M. S., et al. (2018). "Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis." PLOS Medicine, 15(9), e1002654.

 doi:10.20944/preprints202603.0608.v1

96. Longo, V. D., & Panda, S. (2016). "Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan." Cell Metabolism, 23(6), 1048-1059.
97. Bento, J. L., et al. (2004). "The PTPN1 promoter polymorphism is associated with type 2 diabetes and insulin resistance." Diabetes, 53(11), 3007-3012.
98. Cheyssac, C., et al. (2006). "Analysis of the PTPN1 gene in type 2 diabetic patients." Diabetes & Metabolism, 32(3), 247-254.
99. Mattson, M. P., et al. (2014). "Intermittent fasting: dissociation of effects on healthspan and lifespan." Cell Metabolism, 19, 1-9.
100. Cicero, A. F. G., & Baggiki, A. (2016). "Berberine and its role in chronic disease." Advances in Experimental Medicine and Biology, 929, 27-45.
101. Nicholson, J. K., et al. (2012). "Host-gut microbiota metabolic interactions." Science, 336(6086), 1262-1267.
102. Koh, A., et al. (2016). "From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites." Cell, 165(6), 1332-1345.
103. Canfora, E. E., Meijer, K., & Blaak, E. E. (2015). "Dietary fibers and their fermentation products for glucose metabolism." Nature Reviews Endocrinology, 11(8), 465-475.
104. Morrison, D. J., & Preston, T. (2016). "Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism." Gut Microbes, 7(3), 189-200.
105. Donohoe, D. R., et al. (2012). "The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon." Cell Metabolism, 13(5), 517-526.
106. Bultman, S. J. (2014). "Molecular pathways: probable mechanisms of colon cancer prevention by dietary fiber and butyrate." Clinical Cancer Research, 20(4), 799-803.
107. Kurlawala, Z., et al. (2010). "The role of PTEN in skeletal muscle insulin signaling and glucose homeostasis." Journal of Biological Chemistry, 285, 3965-3975.
108. Pal, A., et al. (2012). "PTEN: a potential target for the treatment of type 2 diabetes?" Expert Opinion on Therapeutic Targets, 16(11), 1079-1081.
109. Hardie, D. G. (2015). "AMPK: positive and negative regulation, and its role in whole-body energy homeostasis." Current Opinion in Cell Biology, 33, 1-7.
110. Tolhurst, G., et al. (2012). "Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2." Diabetes, 61(2), 364-371.
111. Den Besten, G., et al. (2013). "The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism." Journal of Lipid Research, 54(9), 2325-2340.
112. Gao, Z., et al. (2009). "Butyrate improves insulin sensitivity and increases energy expenditure in mice." Diabetes, 58(7), 1509-1517.
113. Byrne, C. S., et al. (2015). "The role of short-chain fatty acids in appetite regulation and energy homeostasis." International Journal of Obesity, 39(9), 1331-1338.
114. Ridlon, J. M., Kang, D. J., & Hylemon, P. B. (2006). "Bile salt biotransformations by human intestinal bacteria." Journal of Lipid Research, 47(2), 241-259.
115. Watanabe, M., et al. (2006). "Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation." Nature, 439(7075), 484-489.
116. Thomas, C., et al. (2009). "TGR5-mediated bile acid sensing controls glucose homeostasis." Cell Metabolism, 10(3), 167-177.
117. Inagaki, T., et al. (2005). "Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis." Cell Metabolism, 2(4), 217-225.
118. Kliewer, S. A., & Mangelsdorf, D. J. (2015). "Bile acids as hormones: the FXR-FGF15/19 pathway." Digestive Diseases, 33(3), 327-331.
119. Parséus, A., et al. (2017). "Microbiota-induced obesity requires farnesoid X receptor." Gut, 66(3), 429-437.
120. Roager, H. M., & Licht, T. R. (2018). "Microbial tryptophan catabolites in health and disease." Nature Communications, 9(1), 3294.
121. Rothhammer, V., & Quintana, F. J. (2019). "The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease." Nature Reviews Immunology, 19(3), 184-197.

 doi:10.20944/preprints202603.0608.v1

122. Cani, P. D., et al. (2007). "Metabolic endotoxemia initiates obesity and insulin resistance." Diabetes, 56(7), 1761-1772.
123. Hotamisligil, G. S. (2010). "Endoplasmic reticulum stress and the inflammatory basis of metabolic disease." Cell, 140(6), 900-917.
124. Zelante, T., et al. (2013). "Tryptophan catabolites from microbiota engage AhR and balance mucosal reactivity via IL-22." Immunity, 39(2), 372-385.
125. Chen, R., et al. (2012). "Personal omics profiling reveals dynamic molecular and medical phenotypes." Cell, 148(6), 1293-1307.
126. Needham, E. J., et al. (2019). "Phosphoproteomics reveals the systems-level response to insulin signaling." Molecular Systems Biology, 15(1), e8603.
127. Zeevi, D., et al. (2015). "Personalized nutrition by prediction of glycemic responses." Cell, 163(5), 1079-1094.
128. Hoffman, N. J., et al. (2015). "Global phosphoproteomic analysis of human skeletal muscle reveals a network of exercise-regulated kinases and AMPK substrates." Cell Metabolism, 22(5), 922-935.
129. Humphrey, S. J., et al. (2013). "Dynamic adipocyte phosphoproteome reveals that Akt directly regulates mTORC2." Cell Metabolism, 17(6), 1009-1020.
130. Ling, N. X. Y., et al. (2020). "mTORC1 directly inhibits AMPK to promote cell proliferation under nutrient stress." Nature Metabolism, 2(1), 41-49.
131. Copps, K. D., & White, M. F. (2012). "Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2." Diabetologia, 55(10), 2565-2582.
132. Fazakerley, D. J., et al. (2023). "Phosphoproteomics reveals rewiring of the insulin signaling network and multi-nodal defects in insulin resistance." Nature Communications, 14, 923.
133. Ordovas, J. M., et al. (2018). "Personalised nutrition and health." BMJ, 361:k2173.
134. Mills, S., et al. (2019). "Precision nutrition and the microbiome, part I: current state of the science." Nutrients, 11(2), 386.
135. Loscalzo, J. (2019). "Network medicine: a system-wide approach to human disease." Nature Reviews Genetics, 21, 57-58.
136. Berry, S. E., et al. (2020). "Human postprandial responses to food and potential for precision nutrition." Nature Medicine, 26(6), 964-973.
137. Vreeken, R. J., et al. (2015). "Mass spectrometry-based proteomics and metabolomics for the discovery of biomarkers in diabetes." Proteomics - Clinical Applications, 9(3-4), 312-327.
138. Stomby, A., et al. (2019). "Diet-induced weight loss has chronic tissue-specific effects on the insulin signaling pathway in humans." Diabetes, 68(11), 2081-2093.
139. Semple, R. K., Savage, D. B., & O'Rahilly, S. (2011). "Severe insulin resistance: genotypes, phenotypes and therapeutic implications." Nature Reviews Endocrinology, 7(12), 735-749.
140. Zhang, Y., et al. (2015). "Natural products as protein tyrosine phosphatase 1B (PTP1B) inhibitors." European Journal of Medicinal Chemistry, 106, 11-25.
141. Boucher, J., Kleinridders, A., & Kahn, C. R. (2014). "Insulin receptor signaling in normal and insulin-resistant states." Cold Spring Harbor Perspectives in Biology, 6(1), a009191.
142. Koren, S., & Fantus, I. G. (2007). "Inhibition of the protein tyrosine phosphatase PTP1B: potential therapy for obesity, insulin resistance and type-2 diabetes mellitus." Best Practice & Research Clinical Endocrinology & Metabolism, 21(4), 621-640.
143. Jiang, S., et al. (2012). "Curcumin as a potential protein tyrosine phosphatase 1B inhibitor." Bioorganic & Medicinal Chemistry Letters, 22(11), 3751-3754.
144. Kim, J. H., et al. (2010). "Curcumin ameliorates insulin resistance by inhibiting the activation of the IKK/NF-κB pathway and reducing PTP1B protein expression in skeletal muscle of high-fat diet-induced obese rats." Nutrition Research and Practice, 4(5), 362-369.
145. Na, L. X., et al. (2011). "Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial." Molecular Nutrition & Food Research, 55(10), 1456-1462.
146. Krishnan, N., et al. (2018). "Targeting the disordered C terminus of PTP1B with an allosteric inhibitor." Nature Chemical Biology, 14(6), 550-559.

 doi:10.20944/preprints202603.0608.v1

147. Chen, C., et al. (2010). "Berberine inhibits PTP1B activity and mimics insulin action." Biochemical and Biophysical Research Communications, 397(3), 543-547.
148. Cicero, A. F. G., & Baggiki, A. (2016). "Berberine and its role in chronic disease." Advances in Experimental Medicine and Biology, 929, 27-45.
149. Sonnenburg, J. L., & Bäckhed, F. (2016). "Diet–microbiota interactions as moderators of human metabolism." Nature, 535(7610), 56-64.
150. Louis, P., & Flint, H. J. (2017). "Formation of propionate and butyrate by the human colonic microbiota." Environmental Microbiology, 19(1), 29-41.
151. Molan, A. L., et al. (2021). "The role of gut microbiota-derived short-chain fatty acids in metabolic health." Signal Transduction and Targeted Therapy, 6, 142.
152. Wikoff, W. R., et al. (2009). "Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites." Proceedings of the National Academy of Sciences, 106(10), 3698-3703.
153. Veiga, P., et al. (2014). "Moving from probiotics to precision probiotics." Nature Microbiology, 5, 439-450.
154. Ferguson, L. R. (2014). "Nutrigenomics and nutrigenetics in functional foods and personalized nutrition." CRC Press.
155. Corella, D., et al. (2011). "Saturated fat intake and the association of the PRKAA1 gene with obesity in the general population." Journal of Molecular Medicine, 89(9), 929-937.
156. Paoli, A., et al. (2013). "Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets." European Journal of Clinical Nutrition, 67, 789-796.
157. Lamming, D. W. (2016). "Inhibition of the mechanistic target of rapamycin (mTOR)–rapamycin and beyond." Cold Spring Harbor Perspectives in Medicine, 6(5), a025924.
158. Fontana, L., & Partridge, L. (2015). "Promoting health and longevity through diet: from model organisms to humans." Cell, 161(1), 106-118.
159. Hood, L., & Flores, M. (2012). "A personal view on systems medicine and the emergence of P4 medicine: predictive, preventive, personalized and participatory." New Biotechnology, 29(6), 613-624.
160. Barabási, A. L., Gulbahce, N., & Loscalzo, J. (2011). "Network medicine: a network-based approach to human disease." Nature Reviews Genetics, 12(1), 56-68.
161. Wolkenhauer, O., et al. (2009). "Systems biology as a foundation for future medicine." IET Systems Biology, 3(5), 313.
162. Chen, R., et al. (2012). "Personal omics profiling reveals dynamic molecular and medical phenotypes." Cell, 148(6), 1293-1307.
163. Dorrestein, P. C., et al. (2014). "Finding the missing links among metabolites, microbes, and the host." Immunity, 40(6), 824-832.
164. Yaffe, M. B. (2019). "The scientific benefits of sharing data: a phosphoproteomics case study." Science Signaling, 12(579), eaax2093.
165. Hijazi, M., et al. (2020). "Mass spectrometry-based phosphoproteomics for biology and medicine." Biochemical Journal, 477(16), 2951-2969.
166. Vidal, M., Cusick, M. E., & Barabási, A. L. (2011). "Interactome networks and human disease." Cell, 144(6), 986-998.
167. Loscalzo, J. (2019). "Network medicine: a system-wide approach to human disease." Nature Reviews Genetics, 21, 57-58.
168. Smith, R. L., et al. (2018). "Metabolic Flexibility as an Adaptation to Energy Resources and Requirements in Health and Disease." Endocrine Reviews, 39(4), 489-517.
169. Nolan, C. J., & Prentki, M. (2019). "Insulin resistance and insulin hypersecretion in the metabolic syndrome and type 2 diabetes: Time for a conceptual framework shift." Diabetes and Vascular Disease Research, 16(2), 118-127.
170. Ivanov, P. C. (2021). "The new field of Network Physiology: Building the Human Physiolome." Frontiers in Network Physiology, 1, 711778.
171. Alyass, A., Turcotte, M., & Meyre, D. (2015). "From big data analysis to personalized medicine for all: challenges and opportunities." BMC Medical Genomics, 8, 33.

 doi:10.20944/preprints202603.0608.v1

172. Bartsch, R. P., et al. (2015). "Network physiology: how organ systems visit integrate physiological states." PLOS Computational Biology, 11(11), e1004571.
173. Chan, J. D., & Loscalzo, J. (2012). "The emerging paradigm of network medicine in the study of human disease." Circulation Research, 111(8), 959-964.
174. Huang, S. (2009). "Reprogramming cell fates: reconciling rarity with robustness." BioEssays, 31(5), 546-560.
175. Topol, E. J. (2019). "High-performance medicine: the convergence of human and artificial intelligence." Nature Medicine, 25, 44-56.