Review

Not peer-reviewed version

Systems-Level Coordination of Metabolism and Immunity in Health and Metabolic Disorders

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Posted Date: 23 December 2025

doi: 10.20944/preprints202512.2007.v1

Keywords: immune system; hormones; metabolism; microbiotia; organokine; human milk

 doi:10.20944/preprints202512.2007.v1

Review

Systems-Level Coordination of Metabolism and Immunity in Health and Metabolic Disorders

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Abstract

Immuno modulation and metabolism are crucial for survival, with host metabolites and microbiota influencing immune responses. This study explores the role of immune stimulation on insulin sensitivity, lipid management, and glucose regulation, highlighting tissue-specific effects in muscles, liver, adipose tissue, and the gut. It also examines human milk-derived bioactives on early metabolism and immunity, as well as how microbial substrates, postbiotics, and dysbiosis impact immune function and contribute to metabolic diseases, including obesity and inflammation. Prenatal immunometabolism changes significantly impact pregnancy outcomes and are linked to long-term metabolic issues. This review explores various factors, including the microbiome, autophagy, epigenetics, organokine signaling, and immunological dysfunction from undernutrition, along with advancements in metabolomics. It assesses therapeutic strategies aimed at restoring metabolic-immune balance, particularly focusing on anti-inflammatory and nutritional interventions such as IL-1β antagonism, omega-3 fatty acids, and intermittent fasting. The findings highlight the importance of understanding immune-metabolic interactions to improve health and develop personalized treatments for metabolic syndrome and related disorders.

Keywords: immune system; hormones; metabolism; microbiotia; organokine; human milk

Introduction

Multicellular organism's exhibit interconnected immunological and metabolic systems. In Drosophila, adipose and hematopoietic tissues integrate information, where stimulation of innate immunity can disrupt insulin regulation and energy conservation (Becker et al., 2010). Reduced glucose in adipose tissue leads to stress and decreased mTOR activity, influencing muscle function and related to cytokines and insulin inhibitors. Lifespan and genetics significantly affect immune responses (Franceschi & Campisi, 2014). Figure 1. Perceptive of integrated metabolic and immune Interactions. Systemic immune reactions may arise from oxidative damage and inflammation due to metabolic problems, with immune cells altering their metabolism in response to cytokines, linking immunological and metabolic processes via mechanisms such as mitochondrial dysfunction and chronic inflammation (O'Neill & Pearce, 2016). Dietary restrictions and intermittent fasting influence inflammasome activity and gut bacteria, potentially enhancing insulin sensitivity, reducing inflammation, and bolstering immune responses (Jordan et al., 2019). Custom dietary strategies, including probiotics and microbiome-targeted diets, may improve metabolic health by lowering blood sugar and inflammation. Barley-based diets are highlighted for promoting Prevotella-rich microbiomes that are positive for metabolic health (Franceschi & Campisi, 2014). The study advocates for a tailored approach that integrates pharmacological, dietary, and microbiome-based strategies to treat immunological and metabolic disorders, stressing the importance of sustained immune activation and individualized treatment plans considering immune interactions, microbial communities, and dietary factors (Tang et al., 2017).

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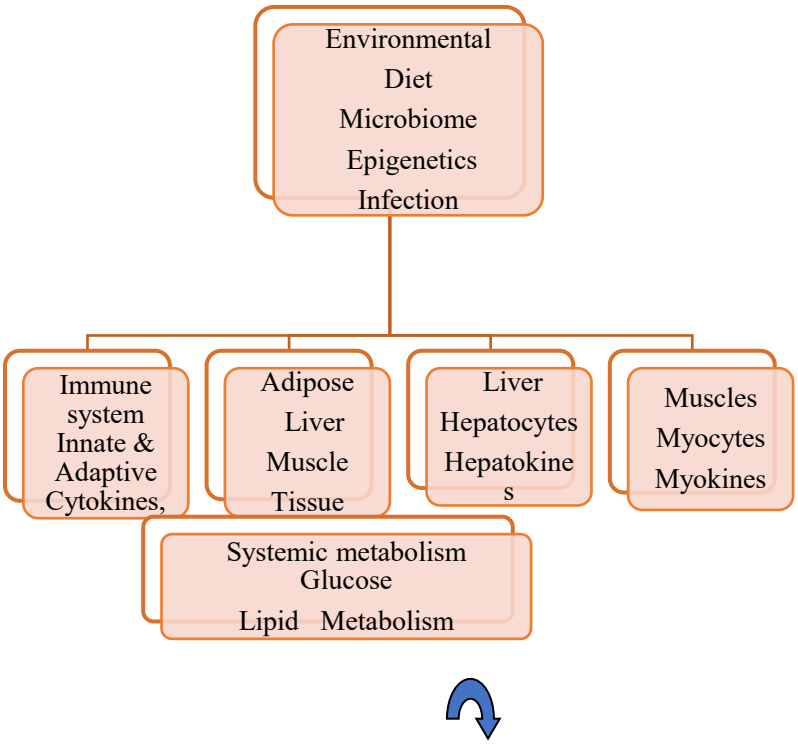

Figure 1. Perceptive of integrated metabolic and immune Interactions.

Metabolic–Immune Hemostasis

Organisms adjust to their environment in order to preserve vital metabolic balances. Immunological subgroups improve metabolic adaptability by modifying specific pathways in response to activation and environmental variables. Immune responses affect insulin sensitivity and glucose balance during exercise and hunger, as well as the metabolic processes in muscle, liver, and adipose tissue (Ryan & O'Neill, 2020). Pathogenic bacteria use metabolites as signaling molecules to influence immunity through metabolic processes including glycolysis and oxidative phosphorylation of DNA. Important biological processes associated with metabolism and immune impairment in Table 1. Immune interactions with microorganisms in muscle, liver, and adipose tissues are crucial for meeting the metabolic requirements of tissue-resident innate lymphoid cells. Blood glucose levels, lipid metabolism, and insulin tolerance are all impacted by these interactions. Immune responses and host metabolism are dramatically changed by microbial metabolites and postbiotics (Fang et al., 2025). Microbial components affect metabolic processes, and lymphocytes in the liver and adipose tissue are important in obesity and liver failure. Pro-inflammatory macrophages associated with obesity are linked to the development of hepatic steatosis because they impair insulin tolerance and interfere with lipid transport in adipose tissue (Alzaid et al., 2025). The gut microbiota plays a critical role in the molecular pathways that connect immunological responses to metabolic alterations and impact macrophage inflammation. The study highlights how aging affects metabolic and immunological responses through changes in organelles mediating these processes. It also looks at cytosolic function and molecular mechanisms of physiological resilience in health and immune-metabolic interactions (Rodríguez-Morales et al., 2023).

Table 1. Important biological processes associated with metabolism and immune impairment.

Mechanism	Molecular Players	Effect on Metabolism	References
Inflammasome Activation	NLRP3, IL-1β, caspase-1	Insulin resistance; lipid dysregulation	(Stienstra et al., 2011; Youm et al., 2013)

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TLR Signaling	LPS, TLR4, MyD88	Chronic inflammation impaired insulin signaling	(Shi et al., 2006; Vijay-Kumar et al., 2010)
Metabolic Reprogramming of Immune Cells	mTOR, HIF-1α, AMPK	Controls macrophage polarity, T-cell subsets	(O'Neill & Pearce, 2016; Buck et al., 2015)
SCFA-Mediated Signaling	Butyrate, GPR41/43	Improves glucose tolerance; enhances anti-inflammatory immunity	(Canfora et al., 2015; Koh et al., 2016)
Cytokine Regulation of Insulin Pathways	TNF-α, IL-6, IFN-γ	Inhibits IRS-1, decreases GLUT4 translocation	(Hotamisligil, 2006; Wensveen et al., 2019)
Mitochondrial ROS Generation	ROS, Unfolded protein respose , ER stress	Drives chronic low-grade inflammation	(Gregor & Hotamisligil, 2011; Ma et al., 2020)

Human Milk-Based Neonatal Metabolic- Immune Programming

Breastfeeding is vital to a baby's health because it provides nourishment and immunity passively. It additionally encourages immunological tolerance, gut growth, and infection prevention. It affects babies' immune and nutritional systems through glycoconjugates and microbial signals. Sialylated human milk oligosaccharides promote metabolism and weight gain, but lower glycans are linked to slower growth (Camacho-Morales et al., 2021). Furthermore, lacto N fucopentaose III in breast milk may reduce liver fat by boosting interleukin 10 production and lowering inflammation. Notably, polyamines—which are necessary for the development of immune cells—are present in lower amounts in the breast milk of obese women (Lokossou et al., 2022). Dietary counseling related to pregnancy can improve the mother's gut flora, which benefits the fetus's immunological and metabolic health and may help with future weight control. Breast milk is essential for the development of the immune system and the control of metabolism. Immune-metabolizing can be strengthened by adding immune-active compounds to breast milk or altering the gut flora of newborns with prebiotics and probiotics (Parrettini et al., 2020). Metabolic and immune effects of human milk components in Table 2. Compared to formula-treated infants, human milk-fed newborns show different pathways for metabolism and immune system cell expression. According to research, human milk increases interleukin signaling, which helps gut organoids maintain homeostasis and metabolize fatty acids. According to a study, children of obese mothers have delayed microbiome development and lower levels of human milk oligosaccharides (Carr et al., 2021). *Bifidobacterium* and 2′-fucosyllactose supplements enhance microbiome diversity and immunological responses. While supplemental feeding modifies gut flora and metabolic profiles, observational studies indicate that nursing increases intestinal glucose production (Shan et al., 2025). Human milk contains vital active components, including cytokines, immunoglobulins, and human milk oligosaccharides (HMOs), which are crucial for the development of immunological and metabolic systems. HMOs facilitate the growth of beneficial bacteria like *Bifidobacterium*, aiding in gut barrier formation, metabolic signaling, and the maturation of immune cells (Ballard et al., 2013). Cytokines, immunoglobulins, and human milk oligosaccharides (HMOs) are among the essential active ingredients found in human milk that are critical for the growth of immune and metabolic systems (Zhernakova et al., 2025)

Table 2. Metabolic and immune effects of human milk components.

Component	Immune Effects	Metabolic Effects	Function	References
IgA	Protects mucosal surfaces; prevents pathogen colonization	Indirect metabolic stability via reduced inflammation	Central in passive immunity	Brandtzaeg, 2013; Gopalakrishna & Hand, 2020

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Cytokines (e.g., IL-10–inducing factors)	Promotes anti-inflammatory environment	Reduces adipose inflammation, protects liver from fat accumulation	LNFP III promotes IL-10	Hennet & Borsig, 2016; Donovan & Comstock, 2016
HMOs (e.g., sialylated HMOs, 2′-FL, LNFP III)	Promote Bifidobacterium; enhance gut barrier; influence immune tolerance	Influence weight gain, tissue metabolism, musculoskeletal growth	Levels vary with maternal health	Bode, 2012; Wang et al., 2021
Polyamines	Support intestinal lymphocyte maturation	Essential for healthy gut development	Lower in milk from obese mothers	Canani et al., 2011; Carrasco et al., 2018
Glycoconjugates	Support gut wall maturation; defense	Influence metabolic development	Strong neonatal impact	Newburg & Walker, 2007; Gopal *et al*., 2008
Microbial modulators	Shape infant microbiota composition	Affect short chain fatty acid production, energy balance	Support early colonization	Arrieta et al., 2014; Bäckhed et al., 2015

Pregnancy Immunometabolic Outcomes

Significant metabolic and immunological changes, such as elevated insulin levels and modified maternal tolerance to the fetus, take place throughout pregnancy. CD68-positive macrophages and inflammatory indicators including interleukin-6 and C-reactive protein are more prevalent in overweight people (Parrettini et al., 2020). Future metabolic diseases may arise from low birth weight and nutritional deficiencies impacting glucocorticoid effects on T-cell modulation. Moreover, elevated fetal macrophage activity and inflammatory cytokines in obese pregnant women may lead to persistent inflammatory markers after birth (Nagano et al., 2025). Poor hepatic metabolism in newborns is linked to nonalcoholic fatty liver disease, with maternal high-fat diets contributing to steatosis. This condition is associated with heightened intestinal inflammation and autoimmune responses driven by activated Kupffer and NKT cells, along with elevated inflammatory cytokines such as IL-12 and IL-18 (McNelis et al., 2021).

The role of gut microbiota dysbiosis in inflammation and its potential to worsen insulin resistance during pregnancy needs further investigation (Mosca et al., 2020 Immunological tolerance is crucial for metabolic changes during pregnancy, particularly concerning CD4-regulatory T (Treg) cells that balance maternal-fetal immunity. Alterations in glucose metabolism and insulin resistance can lead to hyperglycemia, negatively affecting fetal growth and Treg functionality (Moldenhauer et al., 2022). Hormonal changes in the placenta may exacerbate these immunological and metabolic shifts, increasing disease risks like sepsis. This highlights the importance of proper metabolic adjustments and food assistance during pregnancy (Sharma et al., 2022).

Treg and innate immune cell production are altered by immunity remodeling in the uterus during pregnancy, with disruptions leading to preterm birth. Reduced Treg cell production due to maternal metabolic issues, such as obesity and insulin resistance, negatively affects immunological tolerance. Maintaining a healthy BMI and a balanced diet can enhance immunity and reduce pregnancy-related complications (Abu-Raya et al., 2020). Perinatal issues such as infections, early birth, and pregnancy-related diabetes are influenced by maternal obesity, which leads to chronic inflammation and innate immune system activation, affecting Treg cell proliferation and immunological tolerance. Furthermore, maternal obesity alters the diversity and composition of gut microbiota, impacting immunological and metabolic processes associated with diabetes during pregnancy, with short-chain fatty acids, insulin sensitivity, and inflammation serving as key mediators (Gerede et al., 2025).

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Study indicates that a mother's microbiome, marked by elevated lipopolysaccharide and reduced short-chain fatty acids, may heighten the risk of type 2 diabetes in offspring. Increased dietary fiber during pregnancy enhances insulin sensitivity and alters gut flora in obese pregnant sows. Additionally, microbial metabolites related to pregnancy, such as tryptophan metabolites and short-chain fatty acids, are crucial for regulating immune and metabolic functions (Sajdel-Sulkowska, 2023). Dysbiosis disrupts insulin signaling and promotes low-grade inflammation by elevating LPS levels, which activate TLR4 on immune cells. Dietary and obesity-related changes in a mother's microflora affect gut colonization, metabolic gene regulation, insulin resistance, metabolic risks, and fetal immunological development (Mehdi et al., 2023).

Aging-Related Immune–Metabolic Stress

Age-related physiological changes lead to "inflammaging," characterized by low-grade inflammation that heightens the risk of chronic conditions such as sarcopenia and dementia. This phenomenon is driven by a feedback loop of heightened cortisol and HPA axis activity stimulating anti-inflammatory responses. Figure 2. Immune metabolic pathway associated with ageing. Additionally, increased NF-κB activity disrupts metabolic processes, exacerbating diseases like memory impairment and metabolic syndrome by activating the NLRP3 inflammasome, thereby impairing insulin signaling and fat metabolism (Zheng et al., 2024). Alterations in immune cells affect metabolic processes, resulting in decreased NAD^+ and sirtuins, hindering mitochondrial repair and elevating oxidative stress. This shows the link between immunological and metabolic changes, as pro-inflammatory cytokines IL-1β and IL-18 from the NLRP3 inflammasome are regulated by lipid metabolism and mitochondrial reactive oxygen species (Li et al., 2023). Aging-related metabolic alterations and endoplasmic reticulum stress lead to macrophage "inflammaging," which negatively affects T-cell activity by lowering important metabolites such αKG, NAD^+, and SAM (Guimarães et al., 2021). This behavior is associated with inflammatory conditions that are characterized by insulin resistance, such as arthritis and heart disease. NLRP3 and IL-1β are linked to metabolic syndrome in older adults, and immunological aging and mitochondrial dysfunction exacerbate neurological conditions, increasing insulin resistance and dementia through elevated reactive oxygen species and mitochondrial DNA, activating the NLRP3 inflammasome, and triggering pro-inflammatory cytokines (Matsushima et al., 2025).

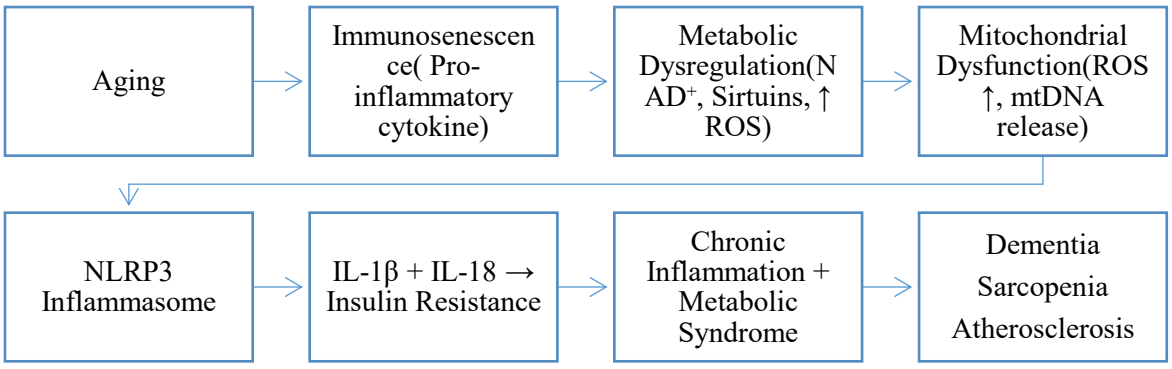

Figure 2. Immune metabolic pathway associated with ageing.

Microbiota–Autophagy Dynamics

Spermidine supplementation in mice has been shown to enhance longevity, reverse nutritional metabolic dysfunction, and restore phagocytosis (Zheng et al., 2024). Reduced autophagic activity correlates with lower spermidine levels, potentially worsening age-related disorders. The buildup of reactive oxygen species and damaged organelles due to aging leads to inflammation. (Hofer et al., 2025). Table 3. Integrated effect of aging on autophagy, microbiome and inflammagation. The aging

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process negatively affects the intestinal barrier and gut microbiota, leading to microb-aging, marked by persistent low-grade inflammation. This condition is associated with an increase in Gram-negative bacteria and a decrease in antimicrobial peptides, resulting in dysbiosis and immune activation. Heightened gut permeability allows bacterial toxins like lipopolysaccharides (LPS) to enter the bloodstream, potentially causing metabolic issues such as weight gain, insulin resistance, and chronic inflammation. Enhancing microbiota health may improve metabolic function, reduce inflammation, and restore intestinal barrier integrity (Le Cosquer et al., 2024). Gut microbiota is influenced by diet and environment, significantly affecting immune signaling and metabolism. Diets high in saturated fat worsen insulin resistance, while vitamin D and omega-3 fatty acids promote intestinal barrier function and reduce inflammation. Cruciferous vegetables enhance metabolic health through dietary fiber, and probiotics, prebiotics, and spermidine contribute to gut health and phagocytosis, supporting metabolic balance and healthy aging (Yoo et al., 2020).

Table 3. Integrated effect of aging on autophagy, microbiome and inflammagation.

Aging Change	Mechanism	Main Effect	Disease Connection	References
↓ Autophagy	ROS ↑ → NLRP3 inflammasome activation	IL-1β / IL-18 ↑	Metabolic syndrome; inflammaging	(Franceschi et al., 2018; Salminen et al., 2012)
Hypothalamic autophagy loss	IKKβ activation → inflammatory signaling	Insulin resistance	Obesity; type 2 diabetes	(Zhang et al., 2021; Meng & Cai, 2011)
↓ Spermidine	↓ Autophagy → ROS accumulation	Increased cellular stress	Accelerated aging	(Eisenberg et al., 2016; Madeo *et al*., 2018)
Gut dysbiosis	↓ *Faecalibacterium prausnitzii*, ↓ *Bifidobacterium*	Pro-inflammatory cytokines ↑	Hypertension; chronic inflammation	(O'Toole & Jeffery, 2015; Kim et al., 2018)
Leaky gut	LPS translocation into circulation	Systemic inflammation ↑	Inflammaging; frailty	(Thevaranjan *et al*., 2017; Man et al., 2015)

Genomic–Epigenetic Immunometabolism

Genetic diversity impacts homeostasis and disease development by affecting the relationship between immune function and metabolism. Genes like CD44 are associated with long-term metabolic diseases such as type 2 diabetes through immune cell migration and adipose inflammation. Furthermore, metabolic characteristics such as insulin levels and HDL cholesterol correlate with single nucleotide polymorphisms in cytokine and acute-phase genes, including IL6, TNFA, and CRP. These findings highlight the role of immune regulation in metabolic health and suggest potential genetic biomarkers for early detection and management of metabolic disorders (Nguyen et al., 2025). Figure 3 illustrates a mechanistic pathway connecting environmental factors, gut syndrome and metabolic dysfunction.

It highlights the relationship between obesity and DNA methylation changes in immune-related genes due to microbial abnormalities. Elevated methylation in inflammatory genes is potentially driven by high blood sugar and histone modifications. This immune cell methylation correlates with obesity and insulin resistance, although the exact causes remain unclear. Additionally, adipose tissue monocytes produce more DNMT3b in response to increased fatty acids, thereby exacerbating inflammation (de la Calle-Fabregat et al., 2020). Gut microbiota influences immune gene expression and epigenetic changes, impacting metabolic outcomes in infants at maternal risk. In type 2 diabetes and obesity, alterations in immune cell methylation are linked to insulin resistance, demonstrating the relationship between gut microbiota and immune gene regulation in children (Ramos-Lopez, O., Milagro et al., 2021).

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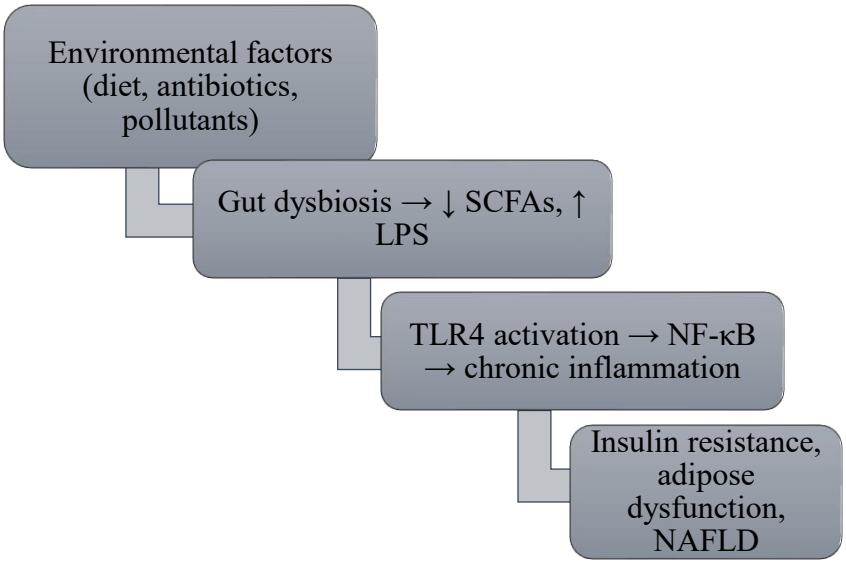

Figure 3. Mechanistic pathway connecting environmental factors gut syndrome, and metabolic dysfunction.

Immunometabolic Adipose Stress

Metabolic syndrome is characterized by obesity, type 2 diabetes, dyslipidemia, and nonalcoholic fatty liver disease, all linked to low-grade inflammation stemming from fat tissue. This condition exhibits a shift in the immunological profile from M2/Treg to M1/Th1/Th17, evidenced by increased pro-inflammatory macrophages, and cytokines such as IL-1β, IL-6, TNF-α, and MCP-1. There is a significant correlation between the systemic immune-inflammation index and adult metabolic syndrome risk (Dhondge et al., 2024). Table 4. Metabolic consequences of Adipose inflammation. An important aspect of immune cell interactions with parenchymal cells involves the release of chemokines and adipokines by stressed adipocytes, which attract macrophages and promote inflammation. Immune receptors like TLR4 and Mincle detect these stress signals, triggering inflammatory responses that hinder insulin delivery. Additionally, food sensing, mitochondrial stress, and immune-metabolic dysfunction interact to show how metabolic reprogramming can influence immune cell behavior (Fantuzzi, 2025). Chemokines from insulin-resistant adipocytes demonstrate a cycle linking inflammation and insulin resistance. The scarcity of clinical studies on immune-metabolic interactions highlights to identify dysfunctional markers and assess muscle and liver tissues concerning immunological management and host defense (Makki et al., 2013).

Table 4. Metabolic consequences of adipose inflammation.

Tissue	Inflammatory Mechanism	Outcome	References
Adipose	M1 macrophages; TNF-α	↑ Lipolysis; ↑ Free fatty acids	(Hotamisligil, 2006; Lumeng & Saltiel, 2011)
Liver	Kupffer cell activation	NAFLD; ↑ VLDL secretion	(Baffy, 2009; Kazankov *et al.*, 2019)
Muscle	NF-κB; JNK signaling	↓ Glucose uptake	(Hirosumi et al., 2002; Bindra et al., 2013)
Pancreas	IL-1β–mediated β-cell dysfunction	↓ Insulin secretion	(Maedler et al., 2002; Donath, 2014)

Organs' Endocrine Interaction in Metabolic Syndrome

Adipocytes secrete adipokines like leptin and adiponectin, acting as endocrine regulators that link insulin resistance, inflammation, and obesity. While adiponectin mitigates insulin resistance and

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low levels elevate TNF α, leptin influences hunger and T cell maturation. Hepatocytes produce hepatokines such as hepatocyte growth factor and macrophage stimulating protein (MSP), enhancing insulin sensitivity and reducing inflammation, respectively (Greenberg et al., 2006). Other hepatokines like fetuin A and MCP 1 also impact metabolism and inflammation. Adipokines, hepatokines, and myokines interact to modulate metabolism, tissue homeostasis, insulin sensitivity, and inflammation. Adipose tissue produces adipokines like leptin and adiponectin, vital for immune responses and metabolic processes (Stern et al., 2016). Figure 4. Integrated organokine model in metabolic syndrome. Adiponectin reduces insulin resistance, while leptin triggers the release of pro-inflammatory cytokines, creating adipokine imbalances that affect vascular function and are associated with metabolic syndrome. Hepatokines from the liver also influence immune responses and metabolic stability. Individuals with poor glycemic control and metabolic dysfunction-related steatotic liver disease exhibit higher levels of the hepatokine LECT2, which is linked to increased insulin levels. Animal studies indicate that LECT2 deletion leads to greater macrophage entry and worsens steatosis, possibly regulating inflammation through p38/STAT-1 signaling (Liu & Li, 2025). Type 2 diabetes and obesity correlate with hepatokines like Fetuin A and FGF21, while liver disease may be indicated by LECT2. Dysregulated hepatokine production can lead to inflammation and insulin resistance. Organokines affect cardiometabolic disorders through immune-metabolic interactions in tissues like muscle and fat. Weight loss surgery can enhance metabolic outcomes by altering hormone release, highlighting interconnected organ issues and the necessity for multi-target treatment (Meex & Watt, 2017).

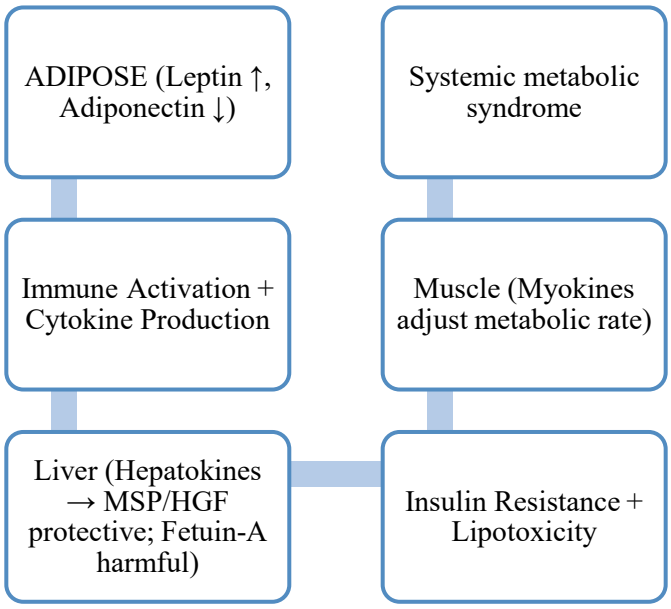

Figure 4. Integrated organokine model in metabolic syndrome.

Childhood Cachexia and Immune Impact

Undernutrition is responsible for the deaths of 149 million children under five, especially in low- and middle-income regions of Asia and Africa. It causes immunological reactions and intestinal dysfunction, but nutritional supplements may help restore gut integrity due to a malnourished microbiota in these children. Addressing both dietary and immunological factors is crucial for enhancing health and alleviating growth and neurodevelopmental challenges in underweight populations (Vassilakou, 2021). Figure 5. Integrated model of mal nutrition. Cachexia and protein deficiencies increase metabolic rates and muscle breakdown, while hunger reduces metabolic rates. Environmental enteric dysfunction (EED), prevalent in underdeveloped countries, is associated with chronic undernutrition, leading to mucosal inflammation and developmental delays. Treating EED requires a comprehensive approach targeting both immunological dysfunction and gastrointestinal

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health, as nutritional supplements alone are insufficient (Hu et al., 2024). Cachexia and protein deficiency increase metabolic rates and muscle breakdown, while hunger reduces them to conserve energy. Environmental enteric dysfunction (EED), resulting from chronic undernutrition, leads to growth retardation and mucosal inflammation, particularly in children in developing regions. Effective treatment for EED requires a combined approach targeting both immune and gastrointestinal health. Malnutrition impairs both innate and adaptive immunity by inhibiting cytokine responses and the growth of immune cells. Cachexia, often linked to cancer, is marked by central inflammation, insulin resistance, heightened metabolic rates, and the breakdown of proteins and lipids, mainly driven by immune dysfunction (Amin & Mercer, 2016).

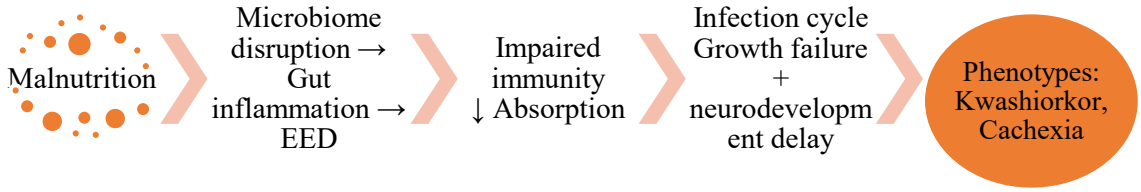

Figure 5. Integrated model of malnutrition.

Precision Metabolomics in Malnutrition

Recent metabolomics research has identified eight metabolic pathways and 27 metabolites as indicators of malnutrition in stomach cancer patients. These pathways involve immune-metabolic signaling, oxidative stress, mitochondrial dysfunction, and nutritional sensing. Additionally, issues with intestinal permeability are associated with growth failure, highlighting the need for nutritional therapy alongside treatments for immune and gastrointestinal conditions (Kumar et al., 2022). Immunonutrition combined with immunomodulation may enhance cachexia outcomes before surgery. Further research is needed on innovative therapies for gut function repair, precision biomarkers for targeted treatment of malnutrition and cachexia, and longitudinal studies examining the link between nutrient insufficiency and immune/metabolic shifts, incorporating metabolomics, immunological phenotyping, and microbiome data to deepen understanding of malnutrition-related dysregulation (You et al., 2023). Intermittent fasting (IF) promotes metabolic health and may prolong lifespan by periodic energy restriction. It lowers fasting insulin, improves insulin sensitivity, reduces blood pressure, and enhances lipid profiles. Additionally, IF decreases systemic inflammation, supports immune adaptations, delays immunosenescence, and alters inflammatory markers while increasing beneficial gut bacteria that facilitate metabolic processes through ketogenesis (Ciastek et al., 2025).

Translating Anti-Inflammatory Strategies into Therapy

Anti-inflammatory therapies may alleviate insulin resistance and metabolic disorders by reducing inflammation's impact on metabolism. Key research focuses on inhibiting pro-inflammatory cytokines, specifically TNF α and IL 1β. Inhibition of IL 1β has been shown to enhance glucose homeostasis and insulin production, resulting in lower fasting glucose and HbA1c levels. In contrast, TNF α blockage only mildly reduced blood glucose without significantly improving insulin sensitivity in obese patients. Historically, salicylates have reduced blood glucose in diabetics by inhibiting the IKKβ/NF κB pathway, though individual responses can vary. Thiazolidinediones enhance lipid metabolism, decrease insulin resistance and HbA1c, and reduce adipose inflammation, attributed to their activation of PPARγ (Yen et al., 2025).

Omega-3 fatty acids activate GPR120, providing anti-inflammatory effects that enhance glucose tolerance and insulin sensitivity, while decreasing macrophage chemotaxis. Further research is needed to determine their efficacy and optimal dosage for metabolic diseases. Intermittent fasting (IF) aids in weight control without starvation, improves lipid profiles, normalizes blood pressure,

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and enhances insulin sensitivity, thereby promoting metabolic and immunological health. IF also delays immunosenescence and reduces inflammation, indicating potential benefits for longevity through various metabolic changes (Oh et al., 2010). Table 5. Translating anti-inflammatory strategies into metabolic therapy targeting inflammation to improve metabolic health.

Intermittent fasting (IF) exerts anti-inflammatory effects by elevating IL-10 levels and reducing pro-inflammatory cytokines such as IL-6. It enhances β-hydroxybutyrate production, promoting ketogenesis and suppressing the NLRP3 inflammasome, leading to improved immune modulation. Moreover, IF activates the hypothalamic-pituitary-adrenal axis, potentially enhancing stress tolerance during inflammation, and improves gut flora, contributing to better immunological and metabolic health. Overall, IF balances energy efficiency with inflammation reduction (Khalafi et al., 2025). According to recent studies, unique immune responses and metabolic characteristics make treatments for metabolic syndrome frequently inefficient. Personalized diagnosis and therapy are therefore essential. Probiotic supplements and certain dietary changes have the potential to improve immune system performance and address metabolic issues. For example, barley bread may help people with *Prevotella*-rich microbiomes metabolize glucose, but eggs and beef may raise TMAO levels in people with less diverse microbial communities, thus increasing the risk of arteries. This emphasizes the necessity of customized approaches to the management of the metabolic disorder (Hu et al., 2022).The gut microbiota influences metabolic-immune interactions, indicating the need for targeted probiotics and dietary strategies to restore balance. Low microbial diversity linked to animal based diets may increase atherosclerosis risk, whereas barley-rich diets could enhance microbiome profiles. Personalized treatment for metabolic diseases and inflammation should account for individual variations. The development of precision medicines for metabolic syndrome can be enhanced by integrating multi-omics data with computational modeling, facilitating better predictions of individual responses (Najjar, 2023).

Table 5. Translating anti-inflammatory strategies into metabolic therapy targeting inflammation to improve metabolic health.

Strategy	Molecular Target	Mechanistic Action	Clinical Outcome	Limitations	References
TNF-α Blockade	TNF-α → TNFR1/2	↓ NF-κB activation; ↓ macrophage inflammation	Minimal improvement in insulin sensitivity; slight glucose reduction	Weak metabolic effect; heterogeneity in response	Ofei et al. (1996); Ferrannini *et* al., 2007)
IL-1β Antagonism	IL-1β → IL-1R	↓ β-cell apoptosis; ↑ insulin secretion; ↓ systemic inflammation	Improved glucose homeostasis; moderate HbA1c & fasting glucose reduction	Cost; variable long-term benefits	Larsen *et al*. 2007; Cavelti-Weder *et al*. 2012.
Salicylates (e.g., high-dose aspirin)	IKKβ/NF-κB pathway	Blocks inflammatory signaling; ↓ hepatic glucose output	HbA1c reduction in T2D; ↓ systemic inflammation	Benefits limited to specific patient subgroups	Yuan *et al*., 2001; Goldfine et al., 2008)
Thiazolidinediones (TZDs)	PPAR-γ (nuclear receptor)	↑ adiponectin; ↓ macrophage infiltration; ↑	Markedly improved insulin sensitivity; ↓	Weight gain, edema, variable	Yki-Järvinen 2004: Haffner et al. (2002)

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		Treg cells; ↑ FGF21	adipose inflammation	patient response	
Omega-3 (EPA/DHA)	GPR120 (anti-inflammatory receptor)	↓ macrophage chemotaxis; ↓ cytokines; ↑ insulin signaling	Improved insulin sensitivity; better glucose tolerance	Dose-dependent; inconsistent trial outcomes	Oh et al. 2010); Kalupahana et al. (2011)

Key Insights and Emerging Directions

For physiological stability, effective communication between immune and metabolic systems is crucial. Disruptions from microbial dysbiosis and chronic inflammation can lead to metabolic diseases such as insulin resistance and obesity. Factors such as immune cell metabolism and organ-specific interactions are influenced by early life events and aging, which exacerbate metabolic dysfunction. Potential therapeutic strategies include intermittent fasting, omega-3 fatty acids, PPARγ agonists, and IL-1β blocking to manage inflammation. Utilizing multi-omics technologies like metabolomics and microbiome profiling is vital for developing personalized therapies and predicting biomarkers. Restoring the immune-metabolic balance is essential for resilience and maintaining health.

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