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Immunometabolic Remodeling in Diabetes: Impacts on Organ Toxicity and Disease Progression

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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia and disturbances in carbohydrate, lipid, and protein metabolism. Beyond classical metabolic derangements, diabetes induces profound immunometabolic remodeling that reshapes cellular energy utilization, immune functions, and tissue homeostasis. This remodeling plays a central role in the initiation and progression of diabetic complications, including cardiovascular disease, nephropathy, neuropathy, retinopathy, and nonalcoholic fatty liver disease (NAFLD). Immunometabolic changes involve chronic low-grade inflammation, immune cell dysregulation, increased production of reactive oxygen species (ROS), and alterations in nutrient-sensing pathways such as AMP-activated protein kinase (AMPK), mechanistic target of rapamycin (mTOR), and nuclear factor kappa B (NF-κB). These pathways intersect with metabolic signaling to drive organ-specific toxicity and accelerate disease progression. This comprehensive review synthesizes current knowledge on immunometabolic interactions in diabetes, highlights mechanisms linking metabolic dysfunction and immune responses, and discusses the impact of immunometabolic remodeling on organ damage. We also evaluate emerging biomarkers and therapeutic strategies that modulate immunometabolic pathways to prevent or attenuate diabetic complications. A deeper understanding of immunometabolic remodeling offers new avenues for precision medicine in diabetes management.

Keywords: Immunometabolism, diabetes complications, inflammation, metabolic signaling, organ toxicity

INTRODUCTION

Diabetes mellitus is a major global public health challenge, affecting hundreds of millions of individuals and accounting for substantial morbidity and mortality due to its chronic and progressive complications [1-5]. Traditionally, the pathophysiology of diabetes has been understood primarily in metabolic terms, with emphasis on hyperglycemia, insulin resistance, impaired insulin secretion, and dyslipidemia [6-8]. While these factors remain central, growing evidence indicates that metabolic disturbances in diabetes are inseparably linked to immune system activation and dysfunction. This recognition has given rise to the field of immunometabolism, which explores how metabolic pathways regulate immune cell behavior and how immune responses, in turn, influence metabolic homeostasis [9-10]. Immunometabolic remodeling refers to sustained alterations in cellular metabolism that occur within immune cells and insulin-sensitive tissues under diabetic conditions [11-15]. Chronic hyperglycemia, excess lipid availability, and advanced glycation end products drive shifts in energy utilization, mitochondrial function, and nutrient-sensing pathways [16-20]. These changes promote a proinflammatory immune phenotype characterized by persistent cytokine production and oxidative stress. Rather

than serving an adaptive role, such remodeling becomes maladaptive over time, reinforcing inflammation and accelerating tissue injury [21-26].

The dynamic interplay between metabolic stress and immune activation affects multiple organ systems, including the vasculature, kidneys, nerves, liver, and retina [27-32]. Disruption of key signaling pathways that regulate energy balance and inflammatory responses underlies many of the long-term complications of diabetes [33-37]. Understanding immunometabolic remodeling, therefore, provides a unifying framework for explaining disease progression and offers new opportunities for targeted therapeutic intervention.

2. Foundations of Immunometabolic Remodeling and Links to Organ Toxicity

2.1 Metabolic Disturbances in Diabetes

Diabetes mellitus is characterized by profound metabolic disturbances that extend beyond elevated blood glucose levels. In type 1 diabetes, autoimmune destruction of pancreatic beta cells results in absolute insulin deficiency, whereas type 2 diabetes is driven by insulin resistance combined with relative insulin insufficiency [38-45]. Despite these differences, both forms of diabetes share common metabolic consequences, including impaired glucose uptake, increased hepatic glucose production, elevated circulating free fatty acids, and ectopic lipid accumulation in non-adipose tissues [46-50]. These abnormalities impose sustained metabolic stress on cells and disrupt intracellular signaling networks that regulate energy homeostasis [51-56]. Central to this disruption are nutrient-sensing pathways such as AMP-activated protein kinase, mechanistic target of rapamycin, and insulin signaling cascades. Reduced insulin action and excess nutrient availability suppress protective AMPK signaling while promoting mTOR activation, favoring anabolic processes even in the presence of cellular stress [57-63]. These alterations not only impair metabolic flexibility but also create a permissive environment for inflammatory signaling, laying the groundwork for immunometabolic remodeling [64-68].

2.2 Immune Cell Metabolism and Function

Immune cell behavior is closely governed by metabolic programming. Under resting conditions, most immune cells rely on oxidative phosphorylation to meet their energy demands [68-70]. Upon activation, however, they undergo a metabolic shift toward aerobic glycolysis, enabling rapid ATP generation and biosynthesis required for effector functions [1-7]. In diabetes, chronic exposure to hyperglycemia, lipid metabolites, and advanced glycation end products drives persistent immune activation and maladaptive metabolic reprogramming [8-11]. Macrophages increasingly adopt a proinflammatory phenotype characterized by enhanced glycolysis and production of cytokines such as tumor necrosis factor alpha and interleukin-6. Similarly, T lymphocytes are skewed toward proinflammatory Th1 and Th17 subsets, while anti-inflammatory regulatory T cells are functionally impaired [12-17]. These immune alterations reinforce systemic inflammation and contribute to insulin resistance, creating a self-perpetuating cycle between metabolic dysfunction and immune activation [18].

2.3 Nutrient-Sensing Pathways, Inflammation, and Organ Toxicity

Nutrient-sensing pathways act as critical interfaces between metabolism and immunity. Reduced AMPK activity diminishes anti-inflammatory signaling and mitochondrial health, whereas sustained mTOR activation promotes immune cell proliferation and inflammatory cytokine production [19]. Metabolic stress also activates nuclear factor kappa B through oxidative stress and receptor-mediated pathways involving advanced glycation end products. This signaling convergence drives chronic low-grade inflammation and excessive reactive oxygen species generation [20]. The downstream consequence of these processes is organ toxicity. Persistent inflammation and oxidative stress damage endothelial cells, impair tissue perfusion, and disrupt cellular metabolism [21]. In parenchymal tissues, chronic nutrient overload and immune-mediated injury overwhelm adaptive responses. Renal cells develop mitochondrial dysfunction and fibrotic changes, hepatocytes accumulate toxic lipids and inflammatory infiltrates, and neurons experience oxidative damage and energy failure [22]. Together, these mechanisms explain how immunometabolic remodeling serves as a unifying driver of progressive organ injury and disease advancement in diabetes [23].

3. Organ-Specific Impacts of Immunometabolic Remodeling

Immunometabolic remodeling in diabetes affects multiple organ systems, with chronic metabolic stress and immune activation converging to drive progressive tissue injury. The nature and severity of damage vary by organ, reflecting differences in metabolic demand, vascular supply, and immune susceptibility.

3.1 Cardiovascular System

Cardiovascular disease remains the leading cause of morbidity and mortality in individuals with diabetes. Persistent hyperglycemia and dyslipidemia induce endothelial dysfunction by impairing nitric oxide bioavailability and increasing oxidative stress [24]. Endothelial cells exposed to inflammatory cytokines upregulate adhesion molecules, promoting leukocyte attachment and vascular inflammation [25]. At the same time, macrophages

undergo metabolic reprogramming that enhances lipid uptake and glycolytic flux, facilitating foam cell formation and accelerating atherosclerotic plaque development. Insulin resistance within cardiomyocytes shifts substrate utilization toward fatty acid oxidation, which is less energy efficient and increases mitochondrial stress [26]. These combined immunometabolic changes heighten vulnerability to ischemia, heart failure, and arrhythmias.

3.2 Renal Complications

The kidney is particularly sensitive to immunometabolic stress. Diabetic nephropathy develops through a combination of glomerular hyperfiltration, inflammation, and fibrotic remodeling [27]. Hyperglycemia promotes mesangial cell activation and excessive extracellular matrix deposition, leading to glomerulosclerosis [28]. Chemokine-driven infiltration of immune cells disrupts normal renal metabolism and amplifies inflammatory signaling. Tubular epithelial cells experience mitochondrial dysfunction and oxidative injury, impairing reabsorption processes and accelerating loss of renal function.

3.3 Nervous System

Diabetic neuropathy arises from the intersection of vascular insufficiency, immune-mediated inflammation, and metabolic dysfunction [29]. Reduced blood flow limits nutrient delivery to nerves, while inflammatory cytokines and oxidative stress damage neuronal and Schwann cell structures. Impaired glucose utilization diminishes ATP production, compromising axonal transport and nerve conduction. These changes manifest clinically as sensory loss, pain, and autonomic dysfunction.

3.4 Liver, Muscle, and Retina

In the liver, insulin resistance and adipose-derived inflammation promote lipid accumulation and activation of resident immune cells, driving steatosis, inflammation, and fibrosis [30]. Skeletal muscle develops metabolic inflexibility, reducing glucose uptake and worsening systemic insulin resistance. In the retina, microvascular injury, immune cell infiltration, and oxidative stress disrupt vascular integrity, leading to pathological neovascularization and progressive vision loss.

4. Biomarkers of Immunometabolic Remodeling

Early detection and monitoring of diabetic complications require biomarkers that capture both metabolic dysfunction and immune dysregulation. Traditional markers, such as fasting glucose and hemoglobin A1c, reflect glycemic control but fail to provide insight into underlying immunometabolic stress [31]. Emerging biomarkers offer a more integrated perspective. Proinflammatory cytokines, including interleukin-6 and tumor necrosis factor-alpha, indicate systemic inflammatory burden and correlate with insulin resistance and cardiovascular risk [32]. Metabolic intermediates such as lactate, free fatty acids, and acylcarnitines reveal shifts in energy utilization and mitochondrial function. Advanced glycation end products accumulate in tissues under chronic hyperglycemia, engaging receptors that amplify oxidative stress and inflammation [33]. Oxidative stress markers, including 8-isoprostane and malondialdehyde, provide evidence of lipid peroxidation and cellular damage. Recent advances in multiomic profiling, combining metabolomics, transcriptomics, and proteomics, enable the detection of cell-specific immunometabolic signatures [34]. Single-cell transcriptomic analyses of immune populations, for example, can identify proinflammatory macrophage or T-cell subsets that contribute to organ-specific injury. Integration of these biomarkers with clinical parameters may improve risk stratification, guide early interventions, and monitor therapeutic responses [35]. Development of standardized panels reflecting both metabolic and immune activity holds promise for precision medicine in diabetes.

5. Therapeutic Strategies Targeting Immunometabolic Pathways

Targeting immunometabolic pathways requires a multifaceted approach that addresses both glycemic control and inflammatory signaling. Optimal glucose management remains foundational, with agents such as metformin offering dual benefits: reduction of hyperglycemia and activation of AMPK, which exerts anti-inflammatory and cytoprotective effects [36]. Glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors improve glycemic control while reducing oxidative stress and lowering cardiovascular risk. Direct anti-inflammatory and immunomodulatory therapies provide additional benefits [37]. Salicylates, TNF inhibitors, and IL-1 antagonists have shown potential in reducing inflammation-driven tissue damage, while experimental modulators of mTOR and NF-κB aim to recalibrate metabolic-immune crosstalk. Antioxidative strategies, including exogenous vitamins and novel reactive oxygen species scavengers, target oxidative injury directly[38]. Activating endogenous pathways such as Nrf2 further enhances cellular resilience against oxidative stress. Lifestyle interventions remain a cornerstone of immunometabolic modulation. Caloric restriction, balanced macronutrient intake, regular physical activity, and weight management influence AMPK/mTOR signaling, reduce chronic inflammation, and improve metabolic flexibility. Integrating pharmacologic and lifestyle

interventions provides a synergistic framework for mitigating diabetic complications and slowing disease progression.

6. Future Directions

Emerging research priorities in diabetes focus on a deeper understanding of immunometabolic remodeling at the cellular and tissue levels. Investigating cell-specific metabolic and immune pathways will clarify how different immune and parenchymal cell types contribute to organ-specific injury [39]. Refining biomarkers through multiomic approaches, including metabolomics, transcriptomics, and proteomics, will support precision medicine by enabling early detection, risk stratification, and monitoring of therapeutic response [40]. Concurrently, development of novel therapies that simultaneously modulate metabolic pathways and immune function offers the potential to halt or reverse disease progression. Integrating systems biology, single-cell omics, and detailed clinical phenotyping will accelerate translation of mechanistic insights into personalized interventions and improved patient outcomes across diverse diabetic populations.

CONCLUSION

Immunometabolic remodeling in diabetes represents a fundamental link between metabolic dysfunction and immune activation that drives organ toxicity and disease progression. Chronic inflammation, oxidative stress, and dysregulated nutrient sensing converge to damage tissues across multiple organ systems. Addressing both metabolic and immune pathways offers a more comprehensive strategy for preventing and treating diabetic complications. A nuanced understanding of immunometabolism will be pivotal in shaping future therapeutic paradigms in diabetes care.

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