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The immunometabolic interface in chronic disease: An integrated view beyond inflammasomes

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Dear Editor

The intricate interplay between the immune system and metabolic processes -commonly termed immunometabolism- has emerged as a central concept in understanding chronic diseases. Historically, research has emphasized inflammasomes, particularly NLRP3, as key mediators of inflammation in metabolic dysfunction. While inflammasomes undoubtedly contribute to the pathogenesis of conditions such as obesity, type 2 diabetes, and cardiovascular disease, focusing exclusively on these complexes risks oversimplifying a highly dynamic and multifactorial network. Beyond canonical inflammasome pathways, immunometabolic interactions extend across broader cellular and systemic circuits, encompassing nutrient sensing, energy flux, and hormonal regulation, all of which collectively shape disease trajectories.[1,2]

Chronic low-grade inflammation, often referred to as metaflammation, exemplifies the bidirectional crosstalk between metabolic tissues and immune signaling. In obesity, adipose tissue undergoes profound remodeling, characterized by macrophage infiltration, altered cytokine profiles, and dysregulated lipid metabolism. These changes are not confined to local tissue stress but propagate systemic metabolic disturbances, contributing to insulin resistance, hepatic steatosis, and vascular dysfunction.[3,4] Similarly, in heart failure, immunometabolic dysregulation manifests as impaired mitochondrial function in immune cells, aberrant substrate utilization, and persistent activation of inflammatory pathways, indicating that immune dysfunction both drives and results from metabolic stress.[5] Collectively, these observations underscore the necessity of moving beyond single-pathway models toward an integrated, systems-level perspective.

A critical component of this integrated view involves the influence of nutrient sensing and energy status on immune cell function. Immune cells are metabolically plastic, adapting their bioenergetic pathways to meet functional demands. For example, activated macrophages predominantly rely on glycolysis to support rapid cytokine production, whereas regulatory T cells preferentially utilize oxidative phosphorylation and fatty acid oxidation to maintain tolerance.[2] Dysregulation of these pathways -whether through nutrient excess, mitochondrial dysfunction, or chronic stress signaling- can shift the balance toward pro-inflammatory states, amplifying tissue damage. Notably, such metabolic rewiring is not limited to classical immune cells; stromal and parenchymal cells also participate in immunometabolic crosstalk, further integrating tissue function with systemic homeostasis.[6]

The endocrine system constitutes another crucial interface linking metabolism and immunity. Adipokines, myokines, and hepatokines serve as systemic mediators that translate metabolic status into immune responses. Leptin, for instance, not only regulates appetite and energy expenditure but also modulates T cell proliferation and macrophage activation. Conversely, adiponectin exerts anti-inflammatory effects, promoting regulatory immune circuits and enhancing insulin sensitivity.[7] Disruption of these signaling axes -whether due to obesity, aging, or chronic stress- contributes to the persistent low-grade inflammation characteristic of many chronic diseases. Emerging evidence further suggests that gut-derived metabolites and the microbiome refine these immune-

metabolic interactions, adding additional complexity to disease pathogenesis.[8]

Although inflammasomes, particularly NLRP3, have garnered considerable attention as therapeutic targets, an integrated immunometabolic perspective encourages broader intervention strategies. Approaches such as targeting metabolic checkpoints within immune cells, modulating systemic nutrient and hormonal signaling, and restoring mitochondrial function offer potential beyond direct inflammasome inhibition.[9] Polyphenols, for example, exert immunometabolic effects by modulating oxidative stress, mitochondrial activity, and cytokine production, illustrating the potential of dietary interventions to recalibrate immune-metabolic networks in chronic disease.[8] Similarly, pharmacologic modulation of glycolytic or oxidative pathways in immune cells has demonstrated preclinical promise in conditions ranging from metabolic syndrome to cardiac dysfunction.[10]

Age-related immunometabolic alterations further underscore the value of this integrated perspective. The concept of "inflammaging" describes a chronic, low-grade pro-inflammatory state resulting from cumulative metabolic, mitochondrial, and immune stress over the lifespan.[11] Inflammaging is associated with impaired autophagy, senescent cell accumulation, and dysregulated nutrient sensing, collectively predisposing individuals to metabolic, cardiovascular, and neurodegenerative diseases. Addressing these intersecting pathways necessitates strategies that extend beyond inflammasome inhibition, emphasizing interventions that restore metabolic flexibility and immune homeostasis.[12]

Chronic diseases often exhibit tissue-specific immunometabolic signatures. In the liver, non-alcoholic fatty liver disease involves crosstalk among hepatocytes, Kupffer cells, and hepatic stellate cells, creating a self-perpetuating cycle of metabolic stress and immune activation that drives fibrosis and systemic inflammation.[13] In skeletal muscle, obesity-induced infiltration of pro-inflammatory immune cells disrupts local insulin signaling, contributing to systemic insulin resistance. These findings highlight the need for therapeutic strategies tailored to tissue-specific immunometabolic profiles rather than relying solely on systemic inflammasome modulation.[3]

An integrated approach to immunometabolism also emphasizes the interplay of lifestyle, nutrition, and pharmacology in managing chronic disease. Caloric restriction, exercise, and targeted nutrient interventions can recalibrate immune cell metabolism, reduce metaflammation, and improve systemic metabolic health. Pharmacologic agents that restore mitochondrial function, enhance regulatory immune circuits, or modulate metabolic fluxes in immune cells offer complementary strategies. Viewing chronic disease through the lens of integrated immunometabolism enables precision interventions that address the root causes of inflammation and metabolic dysfunction rather than merely managing downstream symptoms.

In conclusion, while inflammasomes remain pivotal mediators of chronic disease, they represent only one node within a complex immunometabolic network. A broader, integrated perspective recognizes that metabolic substrates, nutrient-sensing pathways, endocrine mediators, and tissue-specific immune circuits collectively influence disease progression and therapeutic response. Targeting these interconnected pathways holds potential to redefine prevention and treatment strategies across a wide spectrum of chronic conditions, from obesity and type 2 diabetes to cardiovascular and age-related diseases. Embracing this holistic view will facilitate the development of interventions that not only attenuate inflammation but also restore metabolic homeostasis and systemic resilience. Future research must continue to map these intricate networks, elucidate tissue-specific dynamics, and translate mechanistic insights into clinically actionable strategies that transcend traditional inflammasome-centric paradigms.

Practical points in Biochemistry/Nutrition:

► Immunometabolism reveals that immune cell function is dictated by their metabolic state, with pro-inflammatory cells relying on glycolysis and anti-inflammatory cells using oxidative phosphorylation; this interplay is critically shaped by nutrients, hormones like leptin and adiponectin, and systemic energy status, meaning dietary and therapeutic strategies must target these underlying metabolic circuits -not just inflammation- to effectively address chronic diseases.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

Acknowledgment

None.

Competing interests

None.

Abbreviations

NLRP3: NOD-, LRR- and pyrin domain-containing protein 3.

Authors' contributions

The authors read and approved the final manuscript. They take responsibility for the integrity and accuracy of the data.

Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

None.

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