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Editorial

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Harnessing immunometabolism for cardiovascular health and cancer therapy

Angela Markovska[1], Henk S. Schipper[1,2] and Marianne Boes[1,3,*,]

[1]Center for Translational Immunology, University Medical Centre Utrecht, Utrecht, the Netherlands, [2]Department of Pediatric Cardiology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands and [3]Department of Pediatric Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands

*Correspondence: Marianne Boes, Center for Translational Immunology, University Medical Centre Utrecht, Utrecht, the Netherlands. Email: m.l.boes@umcutrecht.nl

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Introduction

An interesting paradox in healthcare is that while health literacy increased in the last decade, expected improvements in health prospects are lagging. Due to global trends such as the obesity epidemic, an aging population, and an increasingly sedentary lifestyle, cases of metabolic syndrome continue to rise. Characteristic to the syndrome are visceral obesity, insulin resistance, dyslipidemia, and hypertension, and it carries a significantly increased risk for the development of cardiovascular disease, type II diabetes, and certain cancers [1]. Research over the last decade now shows how glucose and lipid metabolism are intricately linked to inflammation, both on a systemic and cellular level. We here discuss developments in the field of translational immunometabolism, where we focus on cardiovascular disease and cancer.

Metabolic syndrome: from overnutrition to an immunometabolic disease

Historically, metabolic syndrome was primarily considered a lipid storage disease caused by overnutrition. An overabundance of circulating glucose and lipids was deemed responsible for the impaired insulin signaling, also termed insulin resistance, and the ensuing effects on vascular endothelium and atherosclerosis development [2]. More recently, intricate links between energy metabolism and inflammation emerged. Visceral obesity coincides with adipose tissue inflammation and low-grade systemic inflammation, which impairs insulin signaling, enhances circulating glucose and lipid levels, and thus promotes the development of type 2 diabetes and atherosclerosis. Adipose tissue secreted inflammatory factors, called adipokines, pivot local and systemic inflammation [3]. One of the proposed evolutionary models is the 'energy-on-demand' model, which assumes that adipose tissue has partly evolved to fulfill the energetic demands for an effective immune response against pathogens. Hence the intricate links between adipose tissue and inflammation are considered an adaptive strategy, enabling adipose tissue to release nutrients under inflammatory conditions [3, 4]. As such, glucose and lipid metabolism modulate immune responses and, vice versa, could also provide therapeutic targets for metabolic syndrome, cardiovascular disease, and cancer. What exactly are the up-and-coming new themes in this new discipline of immunometabolism that go beyond metabolic syndrome? We will focus on recently identified interactions

between metabolism, and innate and adaptive immune cell function.

Immunometabolism as a novel strategy to treat disease: recent progress

In the context of a viral infection such as COVID-19, immune cells undergo metabolic reprogramming to elicit hyper-inflammatory immune responses [5]. But also in chronic disease settings, immune cells shift toward different metabolic states to meet their energetic demands. Resting leukocytes generate sufficient ATP for cell maintenance through mitochondrial tricarboxylic cycle (TCA) and oxidative phosphorylation (OXPHOS). Upon activation and proliferation, the increased demand for macromolecular building blocks in leukocytes is met by a shift toward aerobic glycolysis [6]. Metabolic reprogramming of immune cells is not only intrinsically tied to their activation state, but can also direct their phenotype. As an example, blocking glycolysis redirects T-helper cells from effector end-stage cells toward a regulatory phenotype [7]. This plasticity opens novel therapeutic avenues to alter immune cells from inflammatory to immunomodulatory and vice versa, depending on the clinical needs. In this regard, Lübbers *et al.* have introduced the α2-3sia-Siglec9 axis on dendritic cells (DCs) as a target to induce immune tolerance [8]. Binding of the self-associated α2-3 linked sialic acid (α2-3sia) to the inhibitory Siglec-9 receptor on monocyte-derived DCs (moDCs) correlated with increased glycolysis and OXPHOS in the moDCs. The altered metabolic pathways were associated with reduced production of inflammatory cytokines, decreased effector T-cell proliferation, and increased regulatory T-cell differentiation.

In addition to glycolysis and OXPHOS, cholesterol metabolism also plays a pivotal role in immune cell function. Indeed, cholesterol is critical for T-cell activation and proliferation, one reason for which are the cholesterol-enriched lipid microdomains within the cell membrane, needed for oligomerization of signaling receptor complexes [9]. Via different mechanisms, intracellular cholesterol accumulation as well as circulating cholesterol and lipoproteins also affect innate immune cells. Intracellular cholesterol accumulation in innate immune cells, and particularly macrophages, has been linked to inflammatory responses, which can be beneficial in fighting against tumors and pathogens, but can also be associated with atherosclerosis development. Intriguingly, lipids are amongst the key mediators in the phenomenon of 'trained immunity', during which innate immune cells build immunological memory. Transcriptome studies have revealed increased cholesterol and fatty acid synthesis pathways within 'trained' macrophages. In support, pharmacological inhibition of cholesterol biosynthesis using statins hinders trained immunity *in vitro* and *in vivo* in mouse models [10]. The clinical impact of 'trained immunity' is seen in patients with cardiovascular risk due to elevated circulating low-density lipoprotein cholesterol levels. Myeloid cells of such patients retain the increased capacity for cytokine production despite 3-month treatment with lipid-lowering drugs [11].

In line with the need of cholesterol for T-cell activation and proliferation, recent research shows that cancer models in obese settings can have a better response to immune checkpoint inhibition compared to lean models [12]. Accordingly, the metabolic rewiring of T-cells in obesity might be exploited as a potential cancer treatment. The tumor-derived metabolites and waste products, together with the competition for nutrients between the immune and tumor cells make the tumor microenvironment metabolically hostile for protective immune cell responses. These aspects are elucidated by Pallett *et al.*, who discuss how the tumor and immune cells compete with each other for the availability of glutamine, the most abundant amino acid in the body [13]. They further discuss the recent progress made in clinical trials with glutamine inhibitors. As glutamine is critical for the proliferation and function of most cells, unwanted side effects are a likely outcome of systemic glutamine targeting. As such, Pallett *et al.* describe tumor-selective blockade of glutamine as a promising strategy to fight cancer, by simultaneously improving the immune cell killing responses while targeting the tumor cell's growth. Even though studies using targeted inhibitors of glutamine transporters have proven promising in preclinical studies, their ultimate benefit in the clinic is yet to be elucidated.

Besides systemic metabolism affecting immunity, metabolic tissues can also influence immune cell function. In this issue, Lenehan *et al.* shed light on the critical role of adipose tissue in regard to immune cell function, while providing a framework for future cancer therapy research [14]. They show the absence of a shift toward Th1 and Th17 inflammation and a maintained regulatory type-2 immunity in the adipose tissue of mice with cachexia. Indeed, cachexia is characterized by adipose tissue wasting, mainly observed during cancer and chronic disease. Obesity, which on the other hand is characterized by adipose tissue excess, is associated with increased Th1/17-like immunity and decreased Th2-like immunity. Future research, possibly making use of recent progress

in metabolomics, proteomics, and single-cell sequencing, can help to re-evaluate why cachexia and obesity are both accompanied by inflammation, insulin resistance, and enhanced cardiovascular risk.

Bringing immunometabolism to the clinic: where research should be headed

The increasing prevalence of metabolic syndrome has led to considerable interest in the crosstalk between immune cells and metabolism. Indeed, recent progress highlights immunometabolism as the next frontier in the management of cardiovascular diseases and cancer. As our understanding of systemic and cellular metabolic processes increases, so is our appreciation of their inherent complexity. As immunometabolism is involved in a vast array of biological processes, its impact is far broader than the cardiovascular diseases and cancer described here. One example, reviewed by Preston *et al.*, is the recent evidence of iron availability as a key regulator of adaptive immune response to infection and immunization [15].

To further develop the immunometabolism field and application of such knowledge in the clinic, a deeper understanding is required of the interplay between metabolism and immunity. For this purpose, joint research efforts that bring together diverse experts, including immunologists, endocrinologists, and lipidologists, are necessary. Thus far, immunometabolic research has mainly focused on glucose and energy metabolism but less on lipid and lipoprotein metabolism. Identification of immunometabolic checkpoints that control the immune cell response to cholesterol and lipoproteins will open new avenues for therapeutic discovery. Future studies should explore the availability of patients bearing mutations in genes predisposing to dyslipidemia and use these mutations as a tool to study the impact of metabolic alteration on immune cells. While the majority of these genetic disorders, including familial hypercholesterolemia and Niemann–Pick type C disease, do not present with an apparent immune dysregulation, immune cells are yet to be extensively studied in these settings.

In addition to identifying new therapeutic targets, further investigations should be performed on the immune effects of metabolic drugs currently used in the clinic. In particular, statins have long been used for lipid-lowering purposes, but it remains to be addressed whether the beneficial effects of statins are a consequence of systemic reduction of cholesterol levels, a direct metabolic effect on the immune cells, or a combination of both. As such, there may be potential opportunities to repurpose already approved metabolic drugs as immunomodulators.

In a nutshell, we propose that harnessing the full potential of the growing field of immunometabolism will involve studies that combine diverse expertise to address the immune consequences of metabolic disorders, and in analogy, by the use of metabolic drugs.

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