Fundamentals of immunometabolism and implications for health and disease

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1. Introduction

Immunometabolism is an emerging field focusing on the interplay between immunological and metabolic processes[1]. The first hint of the relationship between immunity and metabolism came at the end of the 19th century from the clinical practice. Physicians observed that patients suffering from meningitis exhibited a transient diabetic syndrome[2]. Groundbreaking research carried out subsequently gave insights into the underlying mechanisms, revealing that pro-inflammatory cytokines like TNF-α, that are increasingly secreted in the context of infection or obesity, can impair glucose metabolism and cause insulin resistance[3]. Conversely, over the past decade the critical role of metabolism in controlling immunity has become evident[3].

The knowledge in the field of immunometabolism has nowadays considerably expanded. It is now recognized that health depends on the immune and metabolic homeostasis, while unbalances of these two systems increase the susceptibility to numerous diseases like type 2 diabetes, cancer, cardiovascular, autoimmune and neurodegenerative diseases, among others[3,4].

Several examples of the bi-directional and multi-level interactions between immunological and metabolic processes are presented below.

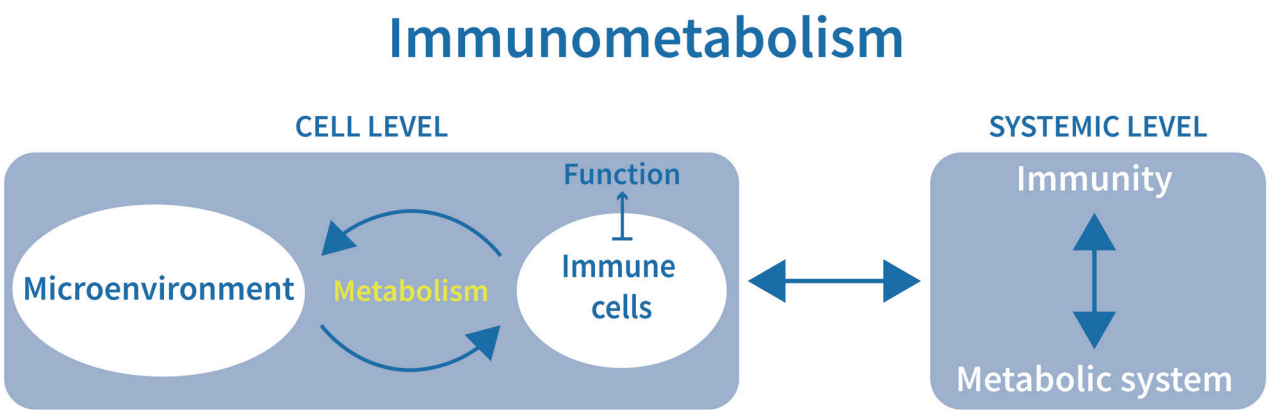

Figure 1: Crosstalk between immunity and metabolism on several levels

2. Crosstalk between metabolism & immunity

2.1 Impact of the microenvironment on immune cells and viceversa

All living cells, included immune cells, need energy and building blocks to carry out life processes like growth, proliferation and maintenance[5]. Nutrients such as carbohydrates, lipids and amino acids, among others, supply the metabolic and biosynthetic pathways that enable these functions to be performed. Therefore, it is evident that not only antigens and cytokines but also the availability of these nutrients in the microenvironment determines cell fate[6,7]. For example, it has been acknowledged that deprivation of glucose and glutamine from the microenvironment impairs the capacity of T cells to proliferate and perform their effector function[7].

Moreover, there is emerging evidence that nutrients and metabolites not only serve as "fuel" for the metabolic pathways but can actively influence immune cell metabolism via nutrient sensing pathways (e.g. AMPK, mTOR, PPARγ), thus, affecting their effector/regulatory function[6,7]. In this sense, it is known that intake of saturated fatty acids (such as palmitate and stearate) drive a more pro-inflammatory state in immune cells, whereas unsaturated fatty acids (in particular polyunsaturated fatty acids such as omega-3) may reduce inflammation[8]. Another example is lactate, which is known to exert an important immunosuppressive effect and, as result, may considerably reduce anti-tumour immunity[9]. In addition, metabolites derived from the microbiota like short-chain fatty acids (SCFAs) have also been shown to act as signalling molecules[10].

Conversely, immune cells as well as pathogens and malignant cells release a variety of compounds that shape the microenvironment[6,7].

Relevance to clinical practice: Dietary and nutritional interventions and microbiome-based therapies may be used along with immunotherapies like micro-immunotherapy to favour the metabolic and immune balance in different diseases like autoimmune diseases, cancer or metabolic disorders, among others.

2.2 Cellular metabolism as a key regulator of immune cell fate

Numerous studies have now clearly shown that immune cell function determines the cellular metabolic state and that, conversely, cellular metabolism drives immune cell function[11].

In this sense, it has been observed that different immune cell subsets present distinct metabolic features. For example, quiescent immune cells utilize energetically efficient pathways such as the tricarboxylic acid (TCA) cycle, which leads to the generation of ATP via oxidative phosphorylation (OXPHOS). However, upon activation, LPS and/or IFN-γ-induced macrophages (M1 phenotype) as well as antigen-activated T cells undergo considerable metabolic reprogramming and switch toward a state of enhanced aerobic glycolysis. This metabolic pathway, although it is less efficient (generation of 2 molecules of ATP from 1 molecule of glucose), rapidly provides not only ATP but also the building blocks for the synthesis of proteins and nucleotides, necessary for these cells to proliferate and carry out their effector functions (e.g. cytokine production)[12,13,14].

T cells mainly use glycolysis and fatty acid synthesis, while IL-4-induced macrophages (M2 phenotype) and regulatory T cells preferentially rely on oxidative phosphorylation and fatty acid oxidation[12,13,14].

Furthermore, studies highlight that reprogramming cell metabolism can have an impact on immune function. For example, in an animal model of lupus, the inhibition of glycolysis and mitochondrial metabolism with a combination of metformin and 2-deoxy-d-glucose (2DG) normalized T cell metabolism and reversed disease biomarkers[15]. In addition, cytokines are also able to change immune cell metabolism and fate. In this sense, IL-10 has been shown to mediate its anti-inflammatory properties by inhibiting aerobic glycolysis and promoting oxidative phosphorylation in macrophages[16].

Relevance to clinical practice: Metabolic reprogramming of immune cells through inhibitors or activators of metabolic pathways, respectively, as well as cytokine-based therapies may be helpful in selectively redirecting immune response and controlling pathologies like autoimmunity or cancer, among others.

2.3 Systemic & Cellular Immunometabolic Crosstalk

In key metabolic tissues and organs, including the adipose tissue, muscles, liver, pancreas and brain, the specialized cells (i.e. parenchymal cells) like adipocytes, myocytes, hepatocytes, beta cells and neurons, respectively, engage in a crosstalk with immune and stromal cells, and thus maintain tissue homeostasis[17]. However, any alteration in this fine-tuned interaction may also lead to tissue dysfunction and thus to systemic metabolic abnormalities[3,17]. Conversely, systemic metabolism, which is strongly related to host nutrition and commensal-microbiota-derived metabolites, can have an impact on immunity as well[11,14,18]. It has been demonstrated that undernutrition induces immunosuppression, which is associated with increased susceptibility to infection, but at the same time may offer protection against several types of autoimmune disorders. However, overnutrition induces a state of low-grade, chronic inflammation, increasing the risk of numerous chronic diseases, as exemplified in the following chapter[11,18].

2.3.1 Example of obesity and its associations with different clinical conditions

Cardiometabolic disorders

In the lean state, anti-inflammatory immune cells, including eosinophils, M2-type macrophages and regulatory T cells (Tregs) predominate in the white adipose tissue (WAT) and favour tissue homeostasis. However, in the case of diet-induced obesity, a switch towards a pro-inflammatory cell phenotype together with a decrease in the number of anti-inflammatory cells can be observed. Cellular dysfunction in adipocytes and the associated metabolic stress due to chronic overnutrition trigger the local production of pro-inflammatory cytokines and chemokines with recruitment and activation of blood monocytes as well as other immune cells. These immune cells accumulate in the WAT and produce, in turn, large amounts of pro-inflammatory cytokines and other factors, which exert paracrine effects, inducing decreased insulin signaling and altering glucose and lipid metabolism in neighbouring cells like adipocytes[17,19].

In addition, these pro-inflammatory factors derived from the adipose tissue can enter the circulation and induce chronic inflammation in distant organs (metainflammation), contributing via their effects on other cells to systemic insulin resistance, a decrease in insulin secretion and other metabolic alterations[19]. Therefore, metainflammation is a key driver of dysmetabolism and participates in the pathogenesis of diseases like type 2 diabetes or cardiovascular diseases.

Relevance to clinical practice: Anti-inflammatory drugs and immunomodulatory strategies like microimmunotherapy might be beneficial in the management of obesity-associated metabolic and cardiovascular diseases.

Infections

Obesity is associated with a reduced T cell responsiveness, thus, compromising the antimicrobial response[20]. Indeed, studies suggest that people with an increased BMI are at higher risk of infection and are more likely to develop serious complications[21].

Relevance to clinical practice: Adequate weight reduction together with immunomodulatory treatments can help reverse immune impairments and improve host protection against pathogens.

Cancer

Obesity-induced metabolic changes can compromise the anti-tumour immune response. In this regard, an accumulation of lipid droplets in Natural Killer cells has been observed in obese patients, leading to the dampening of metabolic pathways like glycolysis and oxidative phosphorylation, therefore, limiting their effector functions like cytotoxicity or cytokine production. As a result, these patients are at higher risk of developing cancer. By reprogramming lipid metabolism (e.g. blocking of PPARα/δ), the cytotoxicty of these cells could be restored[22].

Relevance to clinical practice: Monitoring the levels of free fatty acids in plasma and their normalization through methods that may include decreased caloric intake and increased caloric expenditure or pharmacological approaches may contribute to cancer prevention in obese patients. Furthermore, in the field of oncology, these measures could help improve the efficacy of immunomodulatory strategies like micro-immunotherapy.

Autoimmune diseases

In the context of diet-induced obesity, levels of adipokines like leptin, a systemic hormone known to influence immune response, increase. Leptin upregulates T-cell glucose metabolism and promotes activation of these cells and their differentiation into Th1 and Th17

cells. At the same time, it restrains proliferation of Treg cells, thus augmenting the risk for autoimmune diseases. In animal models fasting has been shown to decrease leptin levels and thus improve the outcome in autoimmune diseases[11,18,23].

Relevance to clinical practice: Fasting may be beneficial in patients with autoimmune diseases or even contribute to the prevention of this disease in susceptible persons.

3. Summary

The discoveries in the field of immunometabolism open new perspectives in the prevention and treatment of various clinical conditions. Moreover, it is becoming increasingly clear that a combination of:

- strategies directed at regulating immune function like immunotherapy (e.g. micro-immunotherapy)
- and interventions (e.g. diet) as well as treatments targeting the cellular and systemic metabolism

may help achieve a more efficient and precise management of diseases like:

- type 2 diabetes
- cancer
- cardiovascular disorders
- autoimmune diseases
- neurodegenerative diseases
- etc.

Micro-immunotherapy, at the cutting-edge of immunity & metabolism
Micro-immunotherapy, i.e. low-dose immunotherapy, is a treatment that uses cytokines to regulate immune function and cellular metabolism towards homeostasis, and can play an important role within a global treatment plan.

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