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Review

Adipose tissue at the nexus of systemic and cellular immunometabolism

Ayano C. Kohlgruber[a,1], Nelson M. LaMarche[a,1], Lydia Lynch[a,b,*]

[a] Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
[b] School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College, Dublin, Ireland

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ABSTRACT

At the simplest interpretation of the word, Immunometabolism describes the intersection of the fields of immunology and metabolism. With rapidly growing interest in this field, the term has expanded, and now encompasses a variety of concepts and definitions shaped by an individual's scientific area of expertise, cell-type and tissue of interest, and biological approach. One scientist may be interested in investigating the intrinsic metabolic checkpoints that drive a M1 versus M2 macrophage response, while another may be interested in how macrophages affect systemic metabolism during obesity. Although both interests have very different foci, they both reflect the current interests in immunometabolism and studies over the last decade have uncovered new metabolic nodes that dictate the course of effector fate within cells, as well as an unexpected role for the immune system in controlling systemic metabolism. Thus, immunometabolism is at the frontier for many novel therapeutic targets to control both cell intrinsic and whole body metabolism in many diseases including cancer, diabetes, obesity, and sepsis among others. In this review, we hope to break down the word immunometabolism into two main themes: whole-body metabolism and cellular bioenergetics. In each instance we will focus on the adipose tissue and its resident immune cells to illustrate recent advances in both sectors of immunometabolism.

Contents

1. Introduction

1.1. Breaking down the word 'immunometabolism'

At the simplest interpretation of the word, Immunometabolism describes the intersection of the fields of immunology and

* Corresponding author at: Division of Endocrinology, Department of Medicine, Brigham and Women's Hospital, Harvard Institutes of Medicine, Room 632, 77 Avenue Louis Pasteur, Boston, MA 02115, USA.
E-mail address: llynch@bwh.harvard.edu (L. Lynch).
[1] These authors contributed equally to this work.

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metabolism. With rapidly growing interest in this field, the term has expanded, and now encompasses a variety of concepts and definitions shaped by an individual's scientific area of expertise, cell-type and tissue of interest, and biological approach. One scientist may be interested in investigating the intrinsic metabolic checkpoints that drive a M1 versus M2 macrophage response, while another may be interested in how macrophages affect systemic metabolism during obesity. Although both interests have very different foci, they both reflect the current interests in immunometabolism and studies over the last decade have uncovered new metabolic nodes that dictate the course of effector fate within cells, as well as an unexpected role for the immune system in controlling systemic metabolism. Thus, immunometabolism is at the frontier for many novel therapeutic targets to control both cell intrinsic and whole body metabolism in many diseases including cancer, diabetes, obesity, and sepsis among others. In this review, we hope to break down the word immunometabolism into two main themes: whole-body metabolism and cellular bioenergetics. In each instance we will focus on the adipose tissue and its resident immune cells to illustrate recent advances in both sectors of immunometabolism.

The global obesity epidemic and the realization that chronic, low-grade inflammation is a characteristic feature of type 2 diabetes (T2D), cardiovascular disease, and non-alcoholic fatty liver disease have triggered a massive surge in studying whole-body immunometabolism. Much to our surprise, immune cells can profoundly affect adipose tissue homeostasis and systemic metabolic tenor. The identification of specific immune cell populations resident in adipose tissue and the novel metabolism-altering factors they secrete highlight the dynamic communication between the immune system and adipocytes. This interaction has profound effects on the local metabolic homeostasis, which subsequently exerts an impact on whole-body metabolism, driven also by changes in liver and muscle. Key questions in the field are now focused on uncovering the mechanisms that incite inflammation in obesity and obesity-related comorbidities like T2D. Indeed, pharmaceutical and academic interest has surged in the past two decades with the growing demand for therapeutic interventions for the metabolic syndrome and other obesity-induced conditions. In this section, we will highlight key immune cells resident in the adipose tissue and how they influence whole-body metabolism. Thus, in this context, immunometabolism is defined as the ability of the immune system to communicate and coordinate systemic metabolic homeostasis.

The second theme of immunometabolism focuses on the fundamental bioenergetics that supports the survival, lineage decisions, and functions of the immune system at the cellular level. Since the early 1950s, immunologists have been fascinated by the extracellular cues that orchestrate effector functions and the downstream signaling cascades that organize metabolic flux. Through the years, we have learned that intracellular metabolic pathways control the effector functions of immune cells. Moreover, coupled with recent advancements in the accessibility of biochemical and molecular tools to interrogate metabolic pathways, we can now study real-time substrate utilization and metabolic flux in specific immune populations. We can also perturb these pathways to understand the effector functions they control. Surprisingly, many of these intracellular metabolic pathways are interchangeable depending on the availability of nutrient and growth factors in the environment, while others are strictly essential for a particular cell lineage, such as in T regulatory cells (Tregs). In this context, we will highlight how cellular metabolism drives key effector roles in the adipose immune system. Although the majority of cell bioenergetics discoveries were not originally based in adipose tissue, we will use adipose tissue as an example of how tissue cues can set the course for controlling metabolic phenotype at the cellular level. Understanding the metabolic decisions controlling effector fate of leukocytes will ultimately open doors to manipulate the immune system in both metabolic disorders and other situations of altered metabolism and altered substrate availability, such as in the tumor microenvironment. Moreover, learning how to modulate metabolic pathways or metabolites within immune subsets may be key to preventing or skewing the aberrant inflammatory response of the adipose tissue during obesity.

Although not a new concept, cellular immunometabolism has flourished in parallel with systemic immunometabolism in recent decades and provides critical understanding of the field at a microscopic cellular level. At the same time, understanding the effects of the extracellular environment, such as exposure to cold or excess energy intake, in controlling the soluble factors produced by the immune system may also lead to novel therapeutics for human disease. Many of these external cues like temperature and nutrient availability likely control the immune response through their intrinsic metabolism, the output of which then can regulate systemic metabolism. Thus, immunometabolism, the dynamic interaction between immunological and metabolic systems at both the organismal and cell-intrinsic level, is at an exciting time of convergence, and adipose tissue is a prime example to illustrate the power and utility of studying immunometabolism as a whole.

1.2. Immunometabolism in whole body homeostasis

In one definition, immunometabolism is the study of how the immune system modulates metabolic processes in an organism. While the immune system and immune-associated cytokines have been shown to regulate metabolism at the level of the liver, brain, muscle, and pancreas [1], the most well studied metabolic organ under immune system control is the adipose tissue. Far from being solely an energy storage depot, adipose tissue is now accepted to be both an endocrine and a secondary immune organ, replete with a unique composition of immune cells and cytokine milieu [2]. The adipose tissue has long been known to contain leukocyte aggregates termed "milky spots", which were first described in the human omentum in 1874 [3]. However, it was not until 1993 when Hotamisligil and colleagues discovered that low-grade inflammation was a feature of obese rodent adipose tissue, and moreover, this inflammation was associated with insulin resistance, that a spotlight appeared on the adipose immune system as a regulator of metabolism [4]. Since then, many studies have reported the leukocyte landscape of adipose tissue, their functions and interactions, and their effects on local and whole-body metabolism. In this section, we will describe our current knowledge of the adipose immune system's effect on metabolism and how changes in the adipose leukocyte population during obesity can lead to insulin resistance and other metabolic disorders.

1.3. Inflammatory cytokines profoundly affect adipocyte biology

In lean animals, adipose tissue is enriched with immune cells that secrete cytokines such as IL-4, IL-5, IL-13, IL-10, and IL-33 and promote an anti-inflammatory state that is beneficial for insulin signaling and appears to be important for normal metabolic homeostasis [2]. The function of these anti-inflammatory or regulatory cytokines is likely to prevent inflammatory responses at a site that constantly undergoes tissue remodeling during fasting and feeding. Keeping inflammation at bay is key to adipose and metabolic health as inflammatory pathways contribute to impaired glucose handling by adipocytes, hepatocytes, and muscle cells and interfere with insulin production and insulin signaling [5].

The first inflammatory cytokine shown to modulate adipocyte biology *in vivo* was tumor necrosis factor alpha (TNFα). In 1993, Hotamisligil and colleagues found TNFα levels were significantly