Chapter 2

Cross Talk Between the Metabolic and Immune Systems

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Abstract

Understanding the interplay between metabolic and cellular signaling systems has emerged as a focus in the study of metabolic disorders, cancer, and immune responses. Immune system is active in the regulation of metabolism. Lymphocyte activation initiates a program of cell growth, proliferation, and differentiation that increase metabolic demand. Activated lymphocytes must alter their metabolism to support these increased synthetic activities. In this chapter, we describe how signaling via the immune system integrates with metabolic functions to control immune response and vice versa. It has been explained mainly in the context of T lymphocyte activation and, to a lesser detail, in other immune cell types.

Key words Immune system, Metabolic system, Lymphocyte, T cells, mTOR, TLR, Adipose tissue, Obesity, Inflammation

1 Introduction

Immune system is required to ward off tumors and infectious particles attacking the host. It is a very balanced homeostatic system and also guards against immune dysregulation, such as in allergy and autoimmunity. There is increase in observations to investigate how immune cells affect certain nonimmune functions, including neurodegeneration, cardiovascular function, and metabolism. Thus, immune metabolism is an emerging field of investigation, which is at the interface between the distinct disciplines of immunology and metabolism. Hepatocytes and myocytes are two cell types in which metabolic pathways have been well studied. Unlike these two, resting lymphocytes do not store glycogen in a larger amount. It makes them highly dependent on the import of extracellular glucose to meet increased metabolic needs [1–3]. The behaviors of lymphocytes and other leukocytes are controlled by metabolic activities of the cells at different levels.

Investigations on the molecular aspects of immunological-metabolic cross talk have become an important field of research. During the activation of a resting lymphocyte, large metabolic

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demands are placed on the cell as it initiates proliferation and cytokine production [4]. The cell grows to approximately double its resting size and then enters into a program of rapid proliferation while also differentiating from a quiescent cell to a highly secretory one.

The role of glucose in immune system is explored initially in this chapter. Moreover, the metabolic dependency in lymphocyte activation is explained. Metabolic alterations and disturbances affect immunity of an individual. Thus obesity-associated inflammation, type 2 diabetes (T2D), and cardiovascular disease (CVD) are being explored as metabolic alterations, which result in the impairment of immune system. We have also described the role of nutrient sensors, adipose tissue, and toll-like receptors in maintaining immune–metabolic interactions.

2 Role of Glucose in the Immune System

In addition to acting as a defense mechanism for a human being, immune system also participates in the control of the resident colonizing microflora, which is essential for immunologic and metabolic health. These regulatory processes are energy demanding, and immune cells from both innate and adaptive immune systems use numerous extracellular molecules and signals as fuels [5, 6]. The exact nature of the energetic demands differs among immune cells and the nature of the required response. For example, energy demand is different from that of proliferative/secretory (B or T lymphocytes) than that of non-proliferative/secretory (macrophages or neutrophils). Observations using lymphocytes, stimulated with B- or T-specific mitogens (such as pokeweed mitogen for B cells, concanavalin-A for T cells), have revealed that the glucose uptake and catabolism are necessary to provide energy for their proliferation, biosynthesis, and secretory activities [1, 2]. It has been found that mitogen-induced lymphocyte activation leads to an increase in glucose consumption, which mostly metabolizes to lactate within 1 h of stimulation [7]. Moreover, other pathways of glucose utilization, such as the pentose phosphate pathway (PPP), have also been shown to be functional during lymphocyte stimulation and have peaked at 48 h after stimulation.

The metabolism of resting lymphocytes is limited by the availability of trophic signals and does not depend upon the availability of nutrients, such as glucose [8]. Once T cells approximately double their resting size and start proliferating, they start differentiating from a quiescent to a highly secretory state, after getting activation. These processes lead to increase in glucose consumption and hence activation of glycolysis [9].

Regulation of energy metabolism in immune cells requires coordination by signal transduction pathways as the functions of these pathways directly have an impact on the modulation of nutrient

uptake and metabolism. Glucose transporter (GLUT) and insulin receptor (InsR) proteins are expressed in immune cells, like monocytes /macrophages, neutrophils, and B and T lymphocytes [10, 11]. It has been shown that physiological doses of insulin have led to increased expression of GLUT3 and GLUT4 in monocytes and B lymphocytes [12]. In contrast, insulin does not alter GLUT expression in resting T cells and in neutrophils. However, in vitro mitogen or LPS (the ligand for TLR4) stimulation of immune cells enhances the expression of membranes GLUT1, GLUT3, and GLUT4 [13, 14]. It has been observed that expression of InsR is essential for immune cell division, size, and survival [15].

3 Role of Immune Cells in Metabolism

There has been a fair amount of increase in the understanding of the immune system organization as well as its regulators. There is a close concordance between host nutritional status and immunity. Thus the investigation on the relationship among nutrition, health, and the immune system of an individual has now become a topic of study.

In the absence of B cells or IgA and in the presence of the microbiota, the intestinal epithelium upregulates interferon-inducible immune response pathways and represses Gata4-related metabolic functions [16]. It leads to lower absorption of lipid. Further, network analysis reveals the presence of two inversely expressed and interconnected epithelial cell gene networks—for lipid metabolism and regulating immunity. The authors have also observed similarities between the gene expression patterns in gut biopsies from individuals with common variable immunodeficiency (CVID)/HIV infection and intestinal malabsorption and from B cell-deficient mice. It possibly explains a relation between immunodeficiency and defective lipid absorption in humans.

Immune deficiency has been observed in leptin-deficient obese (ob/ob) mice. It has found to be associated with an impairment of dendritic cell (DC) function. The ob/ob mice have demonstrated reduced cellular and humoral response and an altered cytokine secretion profile following keyhole limpet hemocyanin (KLH) immunization. Variations have been observed in the cytokine profile secretion in both in vivo and in vitro experiments [17]. For example, more IL-10 and IFN-γ have been secreted by splenic cells from obese animals in an antigen-specific response. However, higher amounts of IL-10 and of IL-4 have been detected in control supernatant in a protocol of mixed lymphocyte reaction (MLR). Authors have also analyzed epidermal sheets of obese mice and found higher number of dendritic cells in obese mice compared with control one.

4 Metabolic Dependency in Lymphocyte Activation

Naive and memory T cells have metabolic activities for housekeeping functions, such as the transportation and turnover of biomaterials, maintenance of cytoskeleton, among others. Glucose oxidation through tricarboxylic acid (TCA) cycle and fatty acid β-oxidation provide most of the metabolic support for these basic cellular functions in naive and memory cells [18, 19]. Immune signaling from T cell receptor (TCR), co-stimulatory molecules, and cytokine receptors activate resting T cells upon antigen exposure. Upon activation, quiescent naive T cells undergo a growth phase followed by clonal expansion and differentiation. These changes are essential for accurate immune defense and regulation. Initial growth and rapid proliferation during the expansion phase increase bioenergetic and biosynthetic demands. It requires a metabolic rewiring during the transition between resting and activation stages. It also makes active T cells to use certain metabolic pathways in the ways that naive and memory T cells do not. In naive and memory T cells, the majority of pyruvate enters into the mitochondria, where it is converted to acetyl-CoA through oxidative decarboxylation, and later fluxes into TCA cycle to generate ATP. However, in active T cells, a major portion of pyruvate moves away from the TCA cycle to produce lactate. Thus it is clear that the production of lactate via glycolysis is significantly upregulated following T cell activation. It may be noted that this change is not restricted to low oxygen (anaerobic) in the environment and is actively regulated by signal transduction pathways when oxygen is plentiful (aerobic glycolysis) [20, 21]. Glutaminolysis, the glutamine catabolic pathway, is another major carbohydrate catabolism that is significantly elevated in T cells after their activation [22, 23].

5 Effects of Metabolic Alteration on Immune Reactivity

Metabolic disturbances, like obesity, have serious effects on immunity. Obesity and related disease and disease-like symptoms, such as insulin resistance in T2D and cardiovascular diseases, have become like an epidemic. Fatty acids and glucose enter into the blood after taking a meal. For an obese individual, the body has higher levels of fat and glucose, and it alters responsiveness of the immune system. This impairment of the immune system associated with human obesity has also been demonstrated in several animal models. Leptin is an adipocyte-derived cytokine. It is secreted proportionally to the amount of fat to finely regulate body weight [24]. Complete congenital absence of leptin leads to hyperphagia and morbid obesity in both humans and rodents [25]. A study has shown that obese animals have a delayed wound healing associated

with increased polymorphonuclear cell infiltration [26]. In addition, both T and B cell-mediated immune responses are impaired in leptin-deficient obese mice (ob/ob) and diabetic db/db mice [27].

Imbalance in the cytokine network is another feature of obesity, which results in a low-grade systemic inflammatory status. It has been observed in both obese humans and animals [28]. The inflammatory cytokines interleukin 6 (IL6), IL1, and tumor necrosis factor-α (TNF-α) have found to be abnormally elevated in obesity, which mostly originate from the activated macrophages infiltrating the white adipose tissue [29, 30]. Investigations may be carried out to explore the reason behind the obesity-associated inflammation, the extent of obesity and inflammation being related, and the pathway(s) responsible for inflammation-induced T2D, cardiovascular disease, and other related pathologies. On the practical side, as inflammation mediates many pathological consequences of obesity, it may lead to exploration of anti-inflammatory drug discovery and drugs for the patients with obesity-associated metabolic and cardiovascular disorders.

6 Role of Nutrient Sensors, Adipose Tissue, and Toll-Like Receptors in Maintaining Immune–Metabolic Cross Talk

In most of the cases, immune cells use and respond to nutrients similarly as found in other cells. There are cell-intrinsic metabolic processes that influence the performance of immune cells [31]. The interesting aspect is to have a completely different perspective on the immunological metabolic interface to find out the extent and the precise mechanisms of typical cell-intrinsic metabolic processes that influence the functional performance of immune cells.

AKT1-3, AMPK-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), and *LKB1*: The serine/threonine kinases AKT1-3, AMPK, mTOR, and LKB1 are cellular nutrient sensors that help to maintain energy homeostasis.

Finlay and Cantrell [32] have suggested that AKT1-3, AMPK, and LKB1 control a fate switch, from cytotoxic effector to memory CD8+ T cells, in addition to providing nutrient responses. According to the authors, AKT proteins regulate repertoires of adhesion molecules and chemokine receptors in CD8+ T cells and control trafficking and migration. This, in turn, determines decision for the memory versus terminally differentiated effector CD8+ T cells. Considering LKB1, it is mentioned that an lkb1−/− bone marrow transplant was unable to reconstitute the hematopoietic system in irradiated mice. This observation suggests that the survival of hematopoietic stem cells (HSCs) depends on LKB1 [33]. An lkb1−/− bone marrow transplant was unable to reconstitute the hematopoietic system in irradiated mice, again suggesting that the survival of HSCs depends on LKB1. Moreover, a study shows

that CD28 co-stimulation of human peripheral blood T cells enhances expression of glucose transporters, glucose uptake, and glycolysis. This increase depends on PI3K activity. Further, the majority of glucose processed by CD28-co-stimulated T cells is converted to lactate. It is not used for biosynthesis or oxidized for maximal energy extraction [34]. These observations have shown that under certain conditions, immune cells may use metabolic pathways to control fate and function in the ways that are different from other cells.

Adipose tissue and Toll-like receptors (TLRs) of the innate immune system, which are found on immune cells, intestinal cells, and adipocytes, are being studied as essential factors in the complex balance of immune and metabolic health.

6.1 Toll-Like Receptors

TLRs are broadly expressed in cells of the innate immune system, such as macrophages, epithelial and endothelial cells, and organ parenchyma cells. They have specific roles in local innate immune defense [35]. TLRs of the innate immune system, which are found in immune cells, intestinal cells, and adipocytes, are observed as essential for maintaining the complex balance of immune and metabolic systems [36]. Lipid is one of the components, which is recognized by TLRs. Some of the mammalian TLRs also regulate energy metabolism, mostly through acting on adipose tissue. This has opened a wide scope of research on the role of TLRs in pathologies related to metabolism, such as obesity, insulin resistance, and atherosclerosis. A study has reported that saturated fatty acids can induce the activation of TLR2 and TLR4, whereas unsaturated fatty acids have shown to inhibit TLR-mediated signaling pathways and gene expression [37].

6.2 Adipose Tissue

Adipose tissue is observed as an immunocompetent organ and adipocytes as components of the innate immune system. Adipocytes secrete classical cytokines (TNF- α, IL-6, IL-1 receptor antagonist, and TGF-β), levels of which are significantly increased in obesity, which contribute to the overall inflammatory status of obese persons [38]. In addition, leptin has also been shown to play an essential role in both innate and adaptive immune responses [39].

Adipocytes and macrophages have recently been described to originate from a common ancestral progenitor and to share several features as follows [40, 41]. Macrophages express some adipocyte-specific gene products, such as ap2, while adipocytes secrete macrophage-specific gene products, such as IL-6 or TNF-α. This common gene expression results in some analogous functional activities, such as lipid accumulation by macrophages in atherosclerotic lesions or phagocytic capacities exhibited by adipocytes towards certain pathogens, thereby revealing an apparent coordinated activity between these two cell types during the course of an innate immune response. Adipocytes, isolated from

diet-induced obese mice or genetically obese animals, exhibited increased TLR expression [42–44], together with higher cytokine production upon stimulation. TGF-β is positively correlated with obesity and up-regulated both in human and in ob/ob mice white adipose tissue [45].

7 Conclusions

Fluctuations in blood glucose occur in inflammatory diseases, such as obesity, diabetes, and insulin resistance. It is now becoming clear that the emerging field of immune metabolism has theoretical and practical implications for future research. Generating an efficient and effective immune response involves large increase in cellular proliferative, biosynthetic, and secretory activities and processes, which require high energy consumption. As mentioned, adaptive as well as innate immune cells must be able to rapidly respond to the presence of pathogens, shifting from a quiescent phenotype to a highly active state within hours after stimulation. For this purpose, cells must dramatically alter their metabolism in order to support these increased synthetic activities based on extracellular signals as fuels, among which glucose is the most essential one. Since activated lymphocytes have high metabolic demands, manipulation of the lymphocyte-specific metabolic control pathways may be useful in treating diseases characterized by immune hyperactivation, autoimmune disorders, and graft rejection.

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