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INTRODUCTION

Introduction to the special issue on dietary control of immunometabolism

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Introduction

A surplus of dietary fat and carbohydrates combined with physical inactivity has led to a high prevalence of overweight in affluent countries, and a concomitant increase in obesity-associated diseases. This obesity epidemic comes with substantial socioeconomic costs, posing great challenges for health care systems worldwide. The development of overfeeding and obesity-associated diseases occurs in a complex manner, involves various organs simultaneously and has both genetic and exogenous roots. In many cases, excess fat-rich diet combined with overweight and cellular aging processes have been found to cause disturbances in systemic metabolism and chronic subclinical inflammation in the intestines, in adipose tissues and in other organs [1]. The establishment of such metabolically triggered inflammation has been implicated in the development of type 2 diabetes, colon carcinoma and other diseases [2]. For women of reproductive age, calorie-rich diet and overweight are important risk factors for complications during pregnancy. These include gestational diabetes, which is frequently followed by overt type 2 diabetes at a later age [3].

The reviews in this issue of *Seminars in Immunopathology* focus on the interrelationship between overweight, metabolism and the immune system, with a specific emphasis on nutritional components. The interplay between these factors is complex and has many aspects. First, the characteristics of metabolism within immune cells—for example, whether an immune cell has a predominantly glycolytic or oxidative energy metabolism—is one parameter determining the functionality and plasticity of immune cells. Second, the metabolism of parenchymal cells such as adipocytes can have a significant impact on immune cells, for example, by creating a lipid-rich, proinflammatory environment. Lipids locally released at the site of inflammation can bind to cell surface receptors, triggering a signal cascade mediating chemotactic migration of T cells [4]. Last, dietary lipids such as cholesterol or its derivatives can transcriptionally regulate intracellular pathways by binding to nuclear receptors, thereby influencing physiological processes including differentiation, reproduction and energy metabolism. For example, recent cell culture studies have shown that cholesterol derivatives regulate the activity of the TH17 T-cell subpopulation [5]. Taken together, metabolic changes induced by overfeeding, or by specific diets, can influence the immune system in a complex organ-specific manner, which is the overall topic of this issue.

The adaptive immune system at compartmental interfaces

Research in recent years has established that tissue-resident immune cells are important for the maintenance of organ function. For example, subpopulations of anti-inflammatory, regulatory T cells (Tregs) were found to play an essential role in the prevention of tissue dysfunction and disease, whereas effector T cells (TH1, TH17) protect against potentially lethal infections but can also trigger autoimmune disease [6]. The balance of immune response and immune suppression is especially important in the intestine, where pathogenic or commensal microbiota are in direct interaction with immune cells. Bacterial molecules can leak through the gut barrier and, through pattern recognition receptors such as Toll-like receptors (TLRs), provoke immune responses. The immune system can regulate gut barrier function and, via antibacterial peptides, the bacterial composition of the gut. This topic is reviewed by Wittkowski and colleagues [7], who describe the immunometabolism of inflammatory bowel disease

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(IBD), a group of chronic disorders characterized by relapsing inflammation of the gastrointestinal tract. They describe specific interactions between gut bacteria and immune cells known to play a role in IBD. Here, the sensing of specific bacterial products, for example by TLR5, results in the production of the key cytokine IL23, which triggers inflammation via the production of secondary cytokines, especially IL22 and IL17. Depending on the context, IL22 and IL17 can be either proinflammatory or protective like the generally anti-inflammatory IL10 that boosts Treg activity. The authors put a special emphasis on the effects of diet composition on IBD and how this can be explained mechanistically. They provide examples of the different ways by which diet can influence the immune system in the gut. One important mechanism is the conversion of dietary fiber by specific bacteria into short-chain fatty acids such as butyrate, which directly acts in an anti-inflammatory manner on immune cells via cell surface receptors. In addition, they discuss how dietary carbohydrates or fat can modulate IBD by changing the bacterial composition of the gut.

Another site of 'immunological encounter' is the feto–maternal interface. During embryo implantation, endometrial cells forming the uterine lining are transformed into the so-called decidual cells, which establish contact with the trophoblast cells of the embryo, leading eventually to the formation of the placenta [8]. By its nature, the placenta exhibits a high metabolite exchange. In addition, it is the site where adverse immune events can occur, as there the immune system of the mother faces paternally inherited fetal antigens. In their review, Thiele and colleagues describe the special immunological environment of the decidua, and how a local immune-suppressive environment is created by specific molecular adaptations of maternal decidual cells and the fetal trophoblasts [9]. The profile of tissue-resident immune cells differs from other organs, containing a high number of Tregs, tolerogenic dendritic cells (DCs) and natural killer (NK) cells. Together with an altered antigen presentation of trophoblasts and the production of anti-inflammatory mediators, these adaptations support the maintenance of tolerance towards the fetus. The authors emphasize the relevance of metabolic pathways that are used by specific immune cells and how changes in intracellular metabolism of glucose, amino acids and fatty acids may contribute to immune cell plasticity in the placenta. For example, glycolysis is dominant in activated and rapidly proliferating leukocytes, whereas fatty acid is the prevalent source of energy in non-inflammatory and tolerogenic cells. Thiele et al. argue that changing T-cell immunometabolism through dietary regimens, including micronutrients such as vitamin D, holds therapeutic potential for the prevention of pregnancy complications related to allogeneic immune responses. Lastly, the authors discuss the critical role of maternal energy metabolism in pregnancy. A high body mass index (BMI) of the mother is associated with ample secretion of the adipocyte hormone leptin, which acts directly on most immune cells. Together with reduced secretion of the anti-inflammatory hormone adiponectin, high leptin is believed to promote a proinflammatory milieu, thereby affecting the maintenance of tolerance towards the fetus. The authors argue that these mechanisms explain, at least in part, the association of overweight with pregnancy complications and gestational diabetes.

Major metabolic organs and the role of the innate immune system

Liver and adipose tissue are organs with an extraordinary metabolic capacity important for systemic fuel metabolism, faced with high fluxes in lipids, carbohydrates and amino acids. In addition, the liver, due to its location between the portal and the systemic circulation, is highly exposed to dietary components [10]. The high exposure to usually harmless antigens derived from food or from gut bacteria is probably the reason that the liver is a major tolerogenic organ, a topic discussed in the review by Carambia and Herkel [11]. The authors describe the special characteristics of hepatic antigen-presenting cells including resident macrophages (Kupffer cells), endothelial cells and DCs, which despite high endocytotic activity create tolerance to antigens through mechanisms encompassing anti-inflammatory mediators, low antigen presentation and co-inhibitory signaling under normal (homeostatic) conditions. They also discuss the role of specific diet-related molecules that influence hepatic immune cells, including amino acids, lipids, vitamins and bile acids. Carambia and Herkel explain how these molecules can exert either pro- or anti-inflammatory cell type-specific functions in the liver, for example by binding to nuclear receptors, and how this influences disease development. Overall, a concept is provided explaining how complex metabolic signals in the liver can be translated into either tolerance or immune response.

Tissue-resident macrophages and other immune cells are important modulators of tissue inflammation and physiology. This is particularly evident in adipose tissue, an organ with considerable potential to expand in the presence of excess calorie intake and shrink in times of negative energy balance. Continuous feeding of a high-calorie diet leads to an altered immune cell profile in adipose tissue of mice [12]. For example, more proinflammatory (M1) macrophages and fewer anti-inflammatory (M2) macrophages are found in the adipose tissue of mice fed an obesity-inducing high-fat diet. This inflammatory state promotes the development of insulin resistance, a blunted organ response to insulin, and eventually the progression from mere insulin resistance to type 2 diabetes. In

their review of adipose tissue immunometabolism, Kumari and colleagues describe in detail the changes occurring when adipose tissue expands in obesity [13]. They explain the adipose tissue remodeling that takes place when adipocytes grow in size, eventually leading to unhealthy tissue characterized by tissue fibrosis, inflammation and insulin resistance. They also discuss the contribution of resident and infiltrating professional immune cells—in particular, the role of proinflammatory M1 macrophages—to the development of unhealthy adipose tissue. The authors describe the signaling pathways involved in changes in immune cell phenotypes and how these are modulated by fuel metabolism, and particularly fatty acid metabolism. Lastly, Kumari et al. discuss how diet and caloric restriction can influence the inflammatory state of adipose tissue. The authors delineate molecular mechanisms that are put forward to explain the relationship between fatty acid classes, such as rather unhealthy saturated fatty acids, and metabolic health. Another aspect discussed is the impact of diet on gut permeability, and hence the exposure of adipose tissue to lipopolysaccharides (LPS) and other inflammatory mediators, as well as the effects of caloric restriction on immunometabolism in adipose tissue.

The essential role of immunometabolism in the blood circulation

It has long been known that atherosclerosis is linked to disturbed lipid metabolism, overweight and high dietary fat intake [14]. More recently, it was recognized that the disease is accompanied by non-resolving inflammation in the arterial wall, with the accumulation of cholesterol by proinflammatory macrophages playing a key role. Groh et al. [15] discuss the role of macrophage metabolism and inflammatory phenotype in the development of atherosclerosis. They review recent literature describing how inflammation-inducing stimuli including cytokines and oxidized low-density lipoproteins, as well as hypoxia, induce a metabolism characterized by high glycolytic flux and an elevated rate of fatty acid synthesis within macrophages located in the arterial wall. In addition, the authors describe the impact of intracellular cholesterol and amino acid metabolism on the polarization of macrophages towards either a pro- or an anti-inflammatory phenotype, and the implications for atherosclerosis. Another focus of the review by Groh et al. is how changes in macrophage metabolism can result in a long-term inflammatory memory of macrophages. The authors discuss how this relates to epigenetic modifications at promoters of inflammatory regulators and how this can promote the development and progression of atherosclerosis.

Overweight and diabetes are important risk factors for the development of vascular diseases such as myocardial infarction and stroke [16]. A significant part of this disease risk can be traced back to endothelial dysfunction and to a higher propensity for blood coagulation. Grandl and Wolfrum [17] describe the studies which established that diabetes is a hypercoagulable state and define mechanisms explaining how hyperglycemia in combination with low insulin action leads to more pronounced blood clotting and platelet aggregation. They also review the literature describing how arterial vascular reactivity is compromised in prediabetic or diabetic states through oxidative stress and inflammation, leading to reduced nitric oxide (NO) synthesis by endothelial NO synthase. In addition to impaired insulin signaling, elevated availability of postprandial metabolites such as glucose and lipids reduces the activity of endothelial NO synthase. The authors discuss how fatty acids and the NO synthase substrate arginine derived from either endogenous metabolism or the diet may contribute to endothelial dysfunction, and eventually to general insulin resistance and metabolic disturbances in insulin target tissues.

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