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The Interplay between Immunity and Metabolism Dictates Health and Disease

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Abstract

Apart from its traditional role in anti-infectious and anti-neoplastic defense, the immune system has been recently implicated in regulating systemic metabolic balance. Likewise, several metabolic processes were also engaged in the maintenance of immune homeostasis. Given the importance of this immune-metabolic alignment in promoting "metabolic health" and its fundamental role in endorsing appropriate adaptations to the ever changing environmental setup in a host, we highlight the current understanding of this immune-metabolic cross-talk and illustrate the role of the gut microbiota, diet and host genetic and epigenetic factors in this immune-endocrine communication, opening up to future avenues of research and promising therapeutic approaches to diverse metabolic and inflammatory disorders.

Keywords: Immunity; Metabolism; Gut Microbiota; Diet; Genetics; Epigenetics; Heath; Disease

Abbrivations: LPS: lipopolysaccharides; AMPs: Anti-Microbial Peptides; TLRs: Toll-Like Receptors; SNPs: Single Nucleotide Polymorphisms.

Introduction

The entwined alliance between immunity and metabolism is considered very ancient and goes back to a few billion years ago when general practitioners considered infection a ground for metabolic pathologies [1]. With time, several studies have reinforced this immune-metabolic coalition. In the 1800s for instance, acute inflammatory diseases like meningitis were highly correlated with diabetes in humans [2]. During the 1900s, additional studies have associated obesity with hyperinsulemic-insulin resistant-diabetic patients, pointed out to the role of gram-negative bacterial lipopolysaccharides (LPS) in revoking the ability of insulin to induce glucose uptake in muscles, promoting insulin resistance in dogs, and showed that acute infections in humans is accompanied by a decrease in the ability of insulin to bind to its receptor on blood cells [3-5]. These findings opened up to emerging venues relating obesity to insulin resistance and diabetes and underlined the occurrence of metabolic disorders in the context of infection.

Congruent to the role of the immune system in maintaining metabolic balance, it was marked that several metabolic processes are, in turn, involved in promoting immune homeostasis. The fact that the immune system cannot function under mal-nutritional circumstances and

that the activation of many immune pathways requires intense metabolic reprogramming of immune cells to meet their sufficient energy demands strengthens the existence of such an adjacent concordance between the host nutritional status and its immune system [6]. The transcription factor FOXO for example, a key regulator of metabolism, activates anti-microbial peptides (AMPs) production independent of any immunoregulatory pathway [7]. Similarly, in a high glucose milieu in human peritoneal mesothelial cells, the relative transcript expression of some Toll-like receptors (TLRs) has been detected and associated with fibrosis and inflammatory disorders [8]. In this context as well, a few studies suggest that the function of TLRs is actually metabolism-related [9]. The activation of some TLRs and the expression of target gene products is directly modulated by some macronutrient metabolites like saturated fatty acid [10]. Branched palmitic acid esters of hydroxy stearic acids, one class of endogenous lipid, regulates gut innate and adaptive immune responses in mice [11]. Indeed, the aforementioned role of some metabolites in orchestrating this immune-metabolic alignment discloses the important role of the commensal flora in this process as well. An overgrowth in the array of the intestinal microbiota, for instance, compromises host nutrition, promoting the activation of the host intestinal immune machinery to reduce the population of the commensal bacteria. This anticipated alignment doesn't seem to be directed against the gut flora only, but could be also used by the host to fight off invading pathogens, especially that ingested nutrients often contain large numbers of bacteria, necessitating the presence of such a protective gastrointestinal-immune defensive strategy [12-14]. Interestingly, several studies have shown that the maintenance of the immune system homeostasis necessitates the existence of such an interaction between the gut microbiota and some immune receptors including TLRs [15].

The intimate communication between these two outwardly disparate systems has mystified scientists for many years. One consideration overseeing this immune-metabolic arrangement is the idea of competition over energy resources and the existing trade-off between metabolically conserving energy, on one hand, and draining energy by immune defensive mechanisms, on the other.

Taken together, all these observations and lines of evidence inspired ongoing studies to understand the immunological nature of a metabolic disease and the metabolic foundation of an immune poise. Our current understanding of the molecular and cellular factors involved in coordinating this immune/microbe-mediated metabolic equilibria and metabolic/immune-medicated microbial equilibria in normal and altered environments is still at its infancy. Here, we provide an overview of the principles of this immune-metabolic communication and portray the importance of the gut microbiome, diet, and host genetics and epigenetics in health and disease.

Gut Microbiome in Immune-Metabolic Interactions

The microbial community of the gut includes 10^{14} bacteria normally residing in the gastrointestinal tract [16]. This bacterial "factory" is in charge of a broad range of metabolic and biochemical processes required by its host. Several studies uncovered the importance of the gut microbiota in regulating nutrient absorption, weight loss and obesity through nutrient acquisition, energy harvesting, and the regulation of numerous host metabolic pathways [17]. Altered nutritional loads of either low or high caloric intake, for example, induce rapid changes in the bacterial composition of the gut microbiota and therefore cause relative variations in the stool energy in lean individuals [18]. The main metabolic functions of the gut flora include synthesis of micronutrients, catabolism of carcinogens and dietary toxins, assistance in absorbing minerals and electrolytes, and fermentation of complex-indigestible food constituents. This role of the gut microbiome in maintaining a balanced gastrointestinal function; however, is thought to be immune-related. It has been hypothesized that the inflammatory response observed in high-fat diet-induced metabolic syndrome is initiated by the LPS of gram-negative bacteria in the gut flora [19-21]. Along those lines, recent studies have explored the role of the gut microbiota in regulating TLRs-mediated insulin signaling. In one of those studies, it has been shown that mice deficient in the microbial pattern recognition receptor TLR5 display hyperphagia and obesity and exhibit various features of metabolic syndrome including hypercholesterolemia, hypertension, dysregulated interleukin-1β signaling, and insulin resistance [22]. Another study also showed that TLR2-deficient mice have an altered gut microbiota, with greater abundance of Firmicutes and less Actinobacteria of the genus Bifidobacterium, and develop glucose intolerance, insulin resistance, and obesity [23]. It has been also revealed that intestinal bacterial products serving as TLR 4 and 9 agonists cause severe hepatic steatosis, inflammation, and obesity [24]. Captivatingly, recent data have pointed out to an important role of the gut microbiome in regulating type 1 diabetes [12]. These findings are intriguing and require supplementary studies like 16S rRNA sequencing,

whole genome metagenomics and metabolomics in metabolic diseases, accompanied by bioinformatics resources and large databases similar to those derived from the Human Microbiome Project to lead the way into a proper understanding of the role of the gut microbiota in a broad spectrum of metabolic disorders including diabetes, metabolic syndrome, and obesity.

Diet in Immune-Metabolic Interactions

Nutrition impacts the activity of the immune system either directly by interacting with immune cell receptors or indirectly through modulating the metabolites of the gut microbiota. Commonly consumed food products containing Vitamins A, Vitamin D, and Indole 3-carbinol, for example, activate local hematopoietic cells and maintain the gut mucosal barrier integrity. Also, saturated and polyunsaturated fatty acids interact with the immune cells of the adipose tissues, modulating the immune system and exerting metabolic effects [25]. It has been well documented that nutrition levers the programmed development of the gut flora, and thereby affects the mucosal architect of the gut, its digestive function, immune tolerance, and various metabolic pathways, mainly those associated with conjugated bile acids and short chain fatty acids [26]. Dietary fat, Western-style diets, and even high-fat diets can disrupt co-regulated metabolic and inflammatory processes within the gut. This explains the aberrant profiles of the gut flora and the impaired immune status in patients suffering from obesity, diabetes, metabolic syndrome, non-alcoholic fatty liver disease, early dementia and Alzheimer. It is thought that the onset of those diseases associated with low-grade systemic infections partly originates from the gut and further spreads out and causes pathogenesis and accelerated aging in other organs including the liver, brain, and adipose tissues [26].

Host Genetics and Epigenetics in Immune-Metabolic Interactions

In addition to the gut microbiota and diet, the host genome is considered another intrinsic factor that contributes to the induction and maintenance of an immune-metabolic balance. Large scale genomic approaches have identified several genetic players involved in metabolic disorders, some of which are immune-related genes [26,27]. The immune cell-receptor CD44, for example, was shown to be implicated in type 2 diabetes mellitus [28]. Likewise, other studies identified a significant link between single nucleotide polymorphisms (SNPs) and predisposing metabolic readouts associating IL6 variant rs7801406 with lower fasting insulin levels, and TNFA variant rs3039662 with elevated fasting insulin levels. Moreover, SNPs in TNFA and CRP genes were highly allied with variations in the serum HDL-C levels [29]. These findings not only unveil the important contribution of genetics to networking immunity and metabolism, but also present interesting settings to identify potential genetic biomarkers for the early detection of metabolic diseases.

Besides genetics, epigenetics also play an important role in regulating the cross-talk between immunity and metabolism, as it constitutes an important mechanistic link between the environmental cues and the host gene expression. Latest studies embarking upon epigenetic alterations in peripheral blood leukocytes in obese people identified changes in the methylation of two genes involved in modulating macrophages and T cells [30]. Likewise, methylation in TLR2 and TLR4 genes was correlated with the microbiota and associated with obesity [31]. A recent epigenome-wide-association study in obese people has elucidated methylation markers in genes related to inflammatory pathways including TNFRSF4, MAP3K2, and IL5RA [32]. Interestingly, another study suggested that hyperglycemia can alter the histone methylation landscape, eliciting epigenetic activation of inflammatory genes like NF-κB-p65 [33]. On a wider scale, increased global methylation levels in the natural killer cells of type 2 diabetic patients and in the B cells of obese and type 2 diabetic patients has been also detected [34].

This global elevated methylation in the epigenetic plot of specific immune cells correlates with insulin resistance and greatly links functional modifications in immune cells to metabolic disorders. Recent studies have demonstrated that obesity can displace adipose tissue macrophages from an anti-inflammatory M2 stage to an opposing pro-inflammatory M1-like stage, where DNA methyltransferase 3a and 3b carry out de novo methylation [35]. Remarkably, saturated fatty acid, a major feature of obesity, was shown to increase DNA methyltransferase 3b, resulting in M1 polarization, a trademark of adipose tissue in obesity and inflammation [36]. Interestingly, the gut microbiota, mainly through short chain fatty acids, was also shown to cause epigenetic alterations, affecting both immunity and metabolism. Short chain fatty acids inhibit histone deacetylase and therefore regulate the expression of immune-related genes, attenuating inflammation [37,38]. The importance of those microbe-derived compounds, including short chain fatty acids, falls in their ability to readily cross the placenta and get involved in epigenetic immune reprogramming and long-term metabolic

deregulation in the descendants of susceptible mothers [39]. Additional epigenetic mechanisms, associated with certain microbiome compositions, like methylation in the promoter region of genes involved in immunity and metabolism, has been also detected in diabetic and obese individuals [40-42].

Conclusion

Our emerging potentials of understanding the role of the gut microbiota, diet, and the host genetic and epigenetic factors in maintaining an adjacent mechanistic concordance between immunity and metabolism opens up for promising therapeutic approaches against a number of metabolic and inflammatory disorders.

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