Immune System and Gut Flora Interactions Are Important Episodes in Metabolic Diseases

Shalini Jain1, Francesco Marotta2, Roberto Catanzaro3, Hariom Yadav1

1) National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA; 2) ReGenera Research Group for Aging Intervention, Milano; 3) Department of Gastroenterology, University of Catania, Catania, Italy

The immune system is the most complex system in human body. It is comprised of diverse types of immune cells such as T-cells, B-cells, macrophages, neutrophils and NK cells that play an important role to protect our body from various illnesses, i.e. infections [1]. The mucosal immune system provides the biggest area of immune reactions in the human body that facilitates the interaction of outer environment, i.e. microbes, food and other environmental stimuli with immune cells [2]. The gut-mucosal immune system plays a critical role in the control of the immune functions against various antigens [3, 4]. The human gut comprises trillions of bacteria; those are in close interaction with intestinal cells and mucosal immune areas, the Peyer’s patches (PPs) [4]. Peyer’s patches are lymph nodes present on the intestinal wall and composed of various types of immune cells. Immune cells present in the PPs also directly interact with gut flora. Gut flora not only directly interacts with immune and intestinal cells but also releases various chemokines such as lipopolysaccharides (LPS), bacteriocins, and end product metabolites (short chain fatty acids, rare amino acids) that ultimately affect the response of immune cells in various pathological conditions [6]. In addition, metabolites and signals derived from gut flora also affect endocrine cells of gut, i.e. L-cells to release various gut hormones such as glucagon like protein-1 (GLP-1), peptide YY (PYY) and cholecystokinin (CCK), that regulate function of metabolic organs: brain (called gut-brain axis), liver, adipose tissue, muscles and pancreas [7, 8].

Immune cells play an important role in the regulation of metabolic function [9]. Metabolic diseases such as obesity, diabetes and cardiovascular diseases (CVDs) are associated with low grade chronic inflammation [10]. An inflammatory state is characterized by an increased inflammatory cytokine overload (IL-6, TNF-α, MCP-1, PAI-1 etc.) in the bloodstream as well as in the local systemic environment [10]. It is now evident that metabolic pathways are functionally integrated with immune responses [11]. The association of innate immune system with metabolic diseases has been increasingly recognized in the last decade [11]. During the development of obesity and diabetes, infiltration of immune cells (macrophages, T-cells and NK cells) into the adipose tissue have been known to elicit insulin resistance and glucose intolerance [12, 13]. In addition, activation of macrophages Kupffer cells residing in the liver is strongly associated with hepatic insulin resistance and impaired endogenous glucose production [13].

Not only adipose tissue and hepatic immune dysregulation disrupt the insulin sensitivity and energy balance, but the concomitant imbalance of immune response (inflammation) in skeletal muscle, pancreas and brain (neuro-inflammation) also plays a critical role in the pathophysiology of obesity and diabetes [14]. In the brain, inflammatory cytokines not only impair insulin sensitivity, but also detrimentally interfere with leptin signaling (critical regulator of food intake) and induce leptin resistance, that ultimately leads to increased food intake and decreased energy expenditure [15]. Indeed, recent work has shown that gut flora can initiate the inflammatory responses that lead to progression of obesity and diabetes through activity of LPS [16]. Lipopolysaccharides are a component of Gram negative bacterial cell walls and are known to trigger an inflammatory response in various pathological conditions including obesity and diabetes.

There are still couple of critical issues in the field of gut flora-immune system- metabolic health axis (Fig. 1), which remain unknown: 1) how gut flora modulates the whole body immune function, and 2) which types of gut flora species play an important role in the immune response switch (beneficial versus deleterious effects). We believe that not all species residing in the gut of human body exhibit deleterious effects; even various bacteria derived from human gut show health beneficial effects i.e. probiotics [17]. Although, various
tentative studies have been carried out on the modulation of immune system by probiotics, it still remains unclarified how these probiotics can interact with immune cells and modify the metabolic function.

Together with other research groups, we are trying to explore this area and encourage the initiation of such studies investigating the gut-flora-immune interactions and their role in metabolic functionality. These studies will not only give the basic understanding of how our gut microbiome communicates with our body, but also would create great opportunities for designing novel therapeutic strategies to ameliorate metabolic and immune diseases and overall, protect gut integrity against endotoxin overload, as our group has recently shown [17].

References

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