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Symbiosis and cohabitation/Symbiose et cohabitation

The microbiota, a necessary element of immunity☆,☆☆

Gérard Eberl [a,b,*]

[a] Institut Pasteur, Microenvironment & Immunity Unit, 75724 Paris, France
[b] INSERM U1224, 75724 Paris, France

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ABSTRACT

The intestinal microbiota is essential for digestion, the production of physiological metabolites, and defense. More than 10^{13} bacteria are present in the intestine, inspiring awe as well as fear of potential infections. By definition, the immune system protects us from infection, and is given the task to recognize dangerous pathogens from useful mutualists. Nevertheless, the definition of pathogens and mutualists is often contextual, and the immune system reacts to all types of microbes. In fact, immune reactivity to microbiota is necessary for the development of the immune system. If the host-microbe cross-talk is perturbed before birth or weaning, the immune system develops "pathological imprinting" and increased susceptibility to inflammatory pathology later in life. Reactivity to microbiota is also important in adulthood to regulate immune responses and maintain homeostasis.

1. Maintaining homeostasis

For half a century, the recognition of non-self has been the central hypothesis of immunology, attempting to explain how the immune system develops, and how microbes, including pathogens, are recognized and destroyed [1]. This hypothesis has been modified to the recognition of danger, suggesting that non-dangerous microbes do not elicit an immune response [2]. Nevertheless, even apparently innocuous microbes, such as symbiotic bacteria in the intestine, induce an immune response, indicating that such responses are not primarily directed at microbes for destruction, but rather for control and maintainance of an equilibrium between microbes and host [3]. Along this view, the evolution of adaptive immunity, allowing the recognition of billions of different microbial structures, may have allowed for the stable colonization of vertebrates with complex microbiotas that include thousands of microbial species [4]. I have thus proposed that the fundamental role of the immune system is to maintain homeostasis within the individual, a consequence of which is the development of a symbiotic microbiota, another consequence being the destruction of invasive pathogens that threaten homeostasis [3].

2. Microbes and the development of the immune system

The continuous reactivity of the immune system to the microbiota has important consequences for the development of the immune system, and possibly for other systems, such as the nervous system. In the pregnant mother, bacterial metabolites are recognized by the immune system and passed to the fetus and the newborn, where they reinforce innate immunity and resistance to pathogens [5]. After birth, structural components of the bacterial cell wall are recognized by innate immune receptors expressed in intestinal epithelial cells, which induce a cascade of signals culminating in the formation of

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* Correspondence. Institut Pasteur, Microenvironment & Immunity Unit, 75724 Paris, France.
E-mail address: gerard.eberl@pasteur.fr.

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hundreds of lymphoid tissues in the intestinal lamina propria [6]. These so-called isolated lymphoid follicles play an important role in maintaining the equilibrium of the host with its microbiota through the production of IgA. Several observations indicate the existence of a "window of opportunity" between birth and weaning, during which exposure to the colonizing intestinal microbiota is required for the normal development of the immune system. If the microbiota is perturbed or absent during this period, a pathological imprinting of the immune system predisposes the host to inflammatory pathology later in life, such as allergy and inflammatory bowel disease (IBD), both in mice and humans [7,8]. Modification by microbes of the epigenetic code of immune genes is involved in immune imprinting, but intriguingly, such modifications must occur before weaning to prevent pathological imprinting [9].

The mechanisms by which microbes alter the epigenome are not yet elucidated, but involve the production of short chain fatty acids (SCFA). In the fetus, SCFA produced by the maternal microbiota imprint the fetal immune system for decreased susceptibility to lung allergy in the adult [10]. SCFAs are inhibitors of histone deacetylases (HDAC), and thereby modify the epigenetic code of genes involved in the development of regulatory T cells (Tregs) that dampen inflammation [11]. Myeloid cells also play an important role in the imprinting of the immune system early in life, through epigenetic modification of chemokines genes in dendritic cells [9] and regulation of the expression of the so-called checkpoint control receptors [12].

3. Regulation of inflammation

The hygiene hypothesis states that the reduced exposure of industrialized populations to pathogens has increased their susceptibility to inflammatory pathology, such as autoimmunity and allergy [13]. More broadly, this hypothesis proposes that decreased exposure to microbes, because of excessive hygiene and usage of antibiotics, is associated with inflammatory pathologies. In agreement with this hypothesis, antibiotic consumption during early childhood is associated with an increased risk of allergy [14], while exposure to dirt [15] or farm animals decreases this risk [16]. In particular, germfree animals develop high levels of IgE, the antibody isotype associated with allergic inflammation [17], and the loss of immune cells reacting to bacteria leads to severe allergic inflammation [18].

Three types of immune reactions develop in response to the type of microbes and pathogens encountered [19]. Type-1 immunity recognizes and reacts to intracellular perturbators, such as viruses, certain species of bacteria and tumors, whereas type-3 immunity reacts to extracellular microbes, including most bacteria, fungi, and protists. Type-2 immunity, on the other hand, reacts to damage caused by large parasites, such as helminths, and co-opts repair mechanisms to protect tissues from invasion and remove the pathogens. In an animal harboring a normal and complex microbiota, the three types of immune responses are elicited continuously, as viruses are present in internal organs, bacteria colonize mucosal surfaces and tissue damage is unavoidable as animals grow and move. Importantly, these three types of immune responses antagonize each other, and only one type of immune response can develop at a time in a specific location. Consequently, homeostasis within the immune system is dependent on a balance between the three types of responses, and thus, on the presence of microbes. The "equilibrium model of immunity" [19] predicts that a lack of microbes, as a consequence of excessive hygiene or use of antibiotics, leads to a decrease in type-1 or type-3 immunity, and therefore, to the deregulation of pro-allergic type-2 responses, or of type-3 or type-1 responses thatdrive autoimmunity.

4. Conclusion

The microbiota is required for optimal digestion of nutrients, production of physiological building blocks, and defense. It is also a source of potential pathogens that the immune system must face. Nevertheless, the ubiquitous presence of microbiota, in time and space, has been incorporated in mammalian ontogeny and physiology as a source of signals that continuously trigger immune reactions. In the absence of microbes, the development of the immune system is therefore incomplete, and immune reactions are deregulated and potentially pathogenic. I propose that microbes are just another type of cells that complements the purely eukaryotic mammalian host at birth, and that adds new functionalities to the host to reach optimal fitness. In this context, the role of the immune system is to maintain homeostasis, and therefore to make sure that no cell, microbial or eukaryotic, evades control and becomes pathogenic.

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