Impact of commensal microbiota on the host pathophysiology: focusing on immunity and inflammation

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All living things on earth are classified into three domains: archaea, bacteria, and eukarya [1]. Bacteria are the oldest and most prosperous among the three; they are estimated to occupy 1/3–1/2 of terrestrial biomass [2]. They inhabit virtually the entire planet, even in extreme environmental conditions such as the stratosphere (ultralow temperature and atmospheric pressure), volcanoes (ultrahigh temperature), and the bottom of deep trenches in the ocean (ultrahigh pressure). Our body is no exception. Many bacteria with a wide variety of species exist on the skin and mucosa. In fact, the colon is the most suitable environment for bacterial growth on earth, with their density reaching as high as 10^{11-12} /g content; overwhelmingly exceeding the densities of any other known bacterial niches around the world. In the whole gastrointestinal lumen, we retain more than 100 trillion commensal bacteria, gut microbiota, classified into 500–1000 different species [3]. Nevertheless, the diversity of gut microbiota is largely limited and biased; out of 28 phyla identified to date, gut microbiota are virtually composed of the members of only four phyla, namely *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria*. This is thought to be basically attributable to the coevolution between the host (i.e., ourselves) and commensal microbiota. The number of the gut microbiota (~100 trillion) well exceeds that of somatic cells constituting our body (~40 trillion) [4]. Thus, gut microbiota is often compared to a measurable organ consisting of prokaryotic cells that

create a unique gut ecosystem together with their host eukaryotic organism. In light of these considerations, the Nobel laureate Joshua Lederberg proposed to deem the host and its commensal microbiota as a “superorganism” [5]. To understand the physiology and pathology of human beings, therefore, it is critical to understand the gut ecosystem in the superorganism as a corollary of host-gut microbiota interaction. However, previous studies had mainly focused on either the host or bacteria, with few, if any, interdisciplinary studies to deal with both host and gut microbiota. In addition, bacterial studies have been skewed to understanding pathogens rather than commensal bacteria.

The gut microbiota is thought to possess a variety of functional properties resulting in a broad range of impacts on human physiology and pathology. For example, it has a diversity of metabolic capabilities that contribute to host nutrition and energy harvest by fermentation of indigested food components. The microbiota also contributes to intestinal epithelial homeostasis, development of the immune system, and protection against pathogens [6]. Early studies implicated imbalances of microbiota in the etiology of a variety of disease states ranging from inflammatory bowel diseases to allergy and obesity. Many of these studies were based on the in vitro culture of bacteria. However, the majority of the gut microbiota are unculturable with existing culture protocols, limiting the ability to robustly monitor microbial populations. Therefore, in these early studies, it was difficult to ascertain what role the microbiota was playing in these disease states.

Understanding of human gut microbiota has recently seen great progress, thanks largely to the emergence of next generation DNA sequencers [7–9]. In these studies, DNAs isolated from feces are directly subjected to shotgun sequencing followed by bioinformatic processing to assemble microbial genomes. This kind of ‘metagenome’ analysis enables us to identify culturable as well as unculturable bacterial genomes and to more accurately estimate the unbiased number of each

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Fig. 1 Schematic view of symbiosis and dysbiosis of gut ecosystem in pathogenesis

bacterial strain in the microbial population. More importantly, metagenome analysis reveals the number and kinds of genes possessed by gut microbiota as a whole; in other words, we have now been obtaining the gene catalogue of gut microbiota. As a result, it turned out that gut microbiota in each individual carry ~600,000 genes, more than ten times the number of genes on our own genome (~25,000) [10]. Comparisons of the gut microbiota gene catalogues between healthy controls and patients with diseases such as inflammatory bowel disease, obesity, and type 2 diabetes have revealed that the diversity of gut microbiota is lost in patients, with the number of genes in patients' gut microbiota decreasing to ~400,000 [9–11]. Moreover, it has recently been suggested that the changes in gut microbiota composition and the loss of their diversity are not the consequence but rather the cause of these diseases [12–18]. That is, in healthy individuals, gut microbiota are robust and resistant to perturbations such as from antibiotics and infection, and maintain their composition in a normal range to sustain homeostasis, symbiosis. However, in susceptible individuals, genetic predispositions may make it difficult to maintain homeostasis once their microbial composition is perturbed and the change becomes irreversible—the resultant abnormal microbiota, or dysbiosis, has a causative role in those diseases (Fig. 1).

Among a wide variety of physiological and pathological roles of gut microbiota emerging rapidly in recent years, this issue of *Seminars in Immunopathology* especially focuses on the immunological and inflammatory aspects. Furusawa et al. discuss gut microbiota-regulated T cell development/differentiation, while Moro and Koyasu review the possible interaction of microbiota with innate lymphoid cells, the emerging counterpart of T cells in the innate immune system.

Host and microbiota tightly interact with each other to maintain homeostasis. Inflammasomes are involved in this homeostatic mutualism. Levy et al. summarize the involvement of inflammasomes in host-microbiota interactions, focusing on the role of commensal as well as pathogenic bacteria in inflammasome signaling. Host-microbiota interaction is

often mediated by bacterial metabolites. Aw and Fukuda introduce a metabolomics-based integrated omics approach for understanding the gut ecosystem.

As mentioned above, the gut ecosystem impacts on the pathogenesis of various diseases. Among those, this issue deals with three pathological conditions: cancer (Ohtani), inflammatory bowel diseases (Matsuoka and Kanai), and allergy (Inoue and Shimojo).

The skin is another site of residence for commensal microbiota, with the total number of microbes reaching as many as 1 trillion. Skin microbiota also affects host physiology and pathology. Nakamizo et al. review the role of skin microbiota in skin immunity and diseases.

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