

BIOLOGY AND MEDICINE OF MICROBIOME

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Received: 01 November 2016, Revised and Accepted: 03 November 2016

ABSTRACT

Humans are super organisms as they host microorganisms to comprise 90% of cells in body and trillion foreign genes in contrast to <30 thousand of their own. That speaks of intricate role of microbes in human health, disease, and even evolution. Medical wisdom on these aspects needs to evolve fast as modern society increasingly suffers diseases with epigenetic determinants responsible to a great extent. Appropriate address to microbiome is mandated to prevent and manage diseases due to environmental, dietary, lifestyle, and medication effects. Diverse biomedical perspectives of microbiome are briefly discussed here.

Keywords: Microbiome, Microbiota, Metagenome.

MICROBIOME, THE SUPERORGANISM

Over 90% cells in human body are microbial (not human) and about a million microbial genes express within us compared to about 20500 human genes. Body of individuals is indeed an ecosystem inhabited by microbes in skin, oral cavity, intestine, and score of other tissue including uterine cavity and lungs. Monocytes and macrophages move through body carrying microbes and their metabolites. A huge load of metabolites - the small molecules generated from the enzymatic protein products of over million microbial genes interact with the limited number of protein products of our genes. Nuclear receptors are natural to have evolved liganding products from microbes associating for generations, and impacting undiscovered facets of human biology, health, and disease [1-3].

Nobel laureate Joshua Lederberg proposed the term MICROBIOME, referring the totality of microbes (commensals and pathogenic), their genomes (METAGENOME), and environmental interactions, in a defined biological community or niche. Human metagenome is a composite of Homo Sapiens genes and genes present in the genomes of the trillions of microbes that colonize over adult bodies or the microbiome.

It is obvious that unless the collective human-microbiome "SUPERORGANISM" is adequately understood, full understanding of health, and disease may not be possible. There is growing appreciation that the microbiome plays a key role and active role in the development and function of basic physiological processes, including digestion, growth, immune defense, and even brain development. Microbiome is a dynamic entity, evolving over host's lifetime, particularly in first 3 years, wherein stable microbiome is established. Changes in diet, stress, infections, drugs, etc., inflict changes in microbiome. Such environmental influences meet with lost genetic mechanisms in determining the adult core microbiome [4,5].

MICROBIOME IN HUMAN HEALTH AND DISEASE

Microbiome is found important in neurodevelopmental disorders such as autism and stress-related disorders in which environmental events in early postnatal life become crucial steering developmental process on pathological course. The critical period of vulnerability needs sound definition in the context [6].

The evidence that composition of gut microbiota can be different between healthy and obese or with Type 2 diabetic patients suggests the link between gut microbiota and pathophysiology of metabolic

disease [7]. Several mechanisms appear to link the events in colon to regulation of energy metabolism, i.e., the energy harvest from diet, the synthesis of gut peptides involved in energy homeostasis (GLP-1, PYY), and the regulation of fat storage. Diet high in usual trans-fatty acids and omega-6 acids affects gut microbiota and may propagate metabolic endotoxemia leading to typical low-grade chronic inflammation seen in diabetes and obesity [8]. Change in gut microbiota, attempted with prebiotics (microbes) and probiotics (fiber) is helpful in controlling the development of metabolic diseases associated with obesity. Specific strategies of modifying gut microbiota to impact on occurrence of metabolic diseases would be most worthwhile to evolve [9].

The connections between microbiome and the immune system are well established. Gut microbiota regulates Th17 cells and regulatory T cell. The development of other specialized T cells is also influenced, but specific microbial species are yet unidentified. Earlier, the microbes were considered to provoke autoimmunity by mimicry of host molecules. The current focus is shifted to microbial metabolites and products influencing host immune cell function. Host cell gene expression and protein formation are more affected by intracellular microbes. The nuclear Vitamin D receptor regulates transcription and expression of many immune genes. Many viruses inhibit the expression of these Vitamin D receptors and thereby affect immunity. The inherited genetic variation involving both common and rare variants probably, create a disease-favoring milieu around immune cells. Metabolites from gut microbes can influence such milieu. Combined change in milieu due to genetic and microbial factors, facilitates epigenetic changes through induction or suppression of specific mRNAs or through altered expression of chromatin regulators. Such changes, along with specific microbial insults, would contribute to induction of autoimmune disorders. Recent studies suggest microbiota influence on immune system and innate immune susceptibility independently involved in the development of inflammatory bowel disease. Replacement of commensals flora through fecal transplantation and prebiotics provide relief [10,11].

The celiac disease involves altered Th1 and innate response. Environmental factors may alter microbiota influencing disease development. Gluten-free diet in the patients helps to reverse gut flora to normal and renders benefit. Type 1 diabetes is shown to be preventable through neonatal exposures to certain microbes and their byproducts, in babies with genetic susceptibility the disease. Psoriasis involves disruption of cutaneous immune responses, and differences are seen in bacteria in psoriatic skin lesions and the

uninvolved skin. Viral dysbiosis is implicated in multiple sclerosis, causing activation of autoreactive T cells in central nervous system which recruit autoantibody producing B lymphocytes. Both host and environmental factors interplay in etiology of rheumatoid arthritis. Immune alteration inflicted by microbes is implicated in pathogenesis. In predisposed individuals, local immune response appears to promote systemic autoimmunity involving autoreactive Th17 cells and B cell activation and autoantibody production. Interactions between gut commensals and host gender and genetic background influence susceptibility to rheumatoid arthritis. Antibiotics display benefit, further supporting role of the microbiome. Microbiome researches are progressing in a big way to define the roles in autoimmune disease induction, progression, maintenance, and therapy [12-14].

CURRENT BIOMEDICAL PERSPECTIVES

Several questions demand answers for biomedical understanding of microbiome pertaining to organismal and genetic diversity of human gut microbiome. How diverse it is among individuals and variation within an individual over time. How are a microbiota and microbiome transmitted following birth, what is relative role of early environmental exposures (to microbes and diets) versus our human genotype in defining postnatal microbial community assembly, and the structures of our adult microbiota? Is there a core microbiome shared between humans, and should this core be defined in terms of organisms, genes or functional characteristics? Finally, are there genes and/or metabolic pathways in the human microbiome that can be identified as being associated to the disease? The field of metagenomics emerged from rapid advances in DNA sequencing methods, with a focus on the use of culture-independent methods to study the structures, functions, and dynamic operations of microbial communities. It extends also to the profiling of gene expression at the level of RNA (meta-transcription) and protein (meta-proteomics) as well as community metabolism (metabolomics). There is promise of advancement in understanding of host-microbe interactions in health

and disease and the potential for therapeutic manipulation of the microbiota.

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