The Microbiota, Chemical Symbiosis, and Human Disease

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Abstract

Our understanding of mammalian–microbial mutualism has expanded by combing microbial sequencing with evolving molecular and cellular methods, as well as unique model systems. Here, the recent literature linking the microbiota to diseases of three of the key mammalian mucosal epithelial compartments—nasal, lung, and gastrointestinal tract—is reviewed with a focus on new knowledge about the taxa, species, proteins, and chemistry that promote health and impact progression toward disease. The information presented is further organized by specific diseases now associated with the microbiota: *Staphylococcus aureus* infection and rhinosinusitis in the nasal-sinus mucosa, as well as cystic fibrosis, chronic obstructive pulmonary disorder, and asthma in the pulmonary tissues. For the vast and microbially dynamic gastrointestinal compartment, several disorders are considered, including obesity, atherosclerosis, Crohn's disease, ulcerative colitis, drug toxicity, and even autism. Our appreciation of the chemical symbiosis ongoing between human systems and the microbiota continues to grow and suggests new opportunities for modulating this symbiosis using designed interventions.

Introduction

Focusing on literature from the past 5 years, this review will consider three of the central “inside out” mucosal epithelial membrane-containing compartments relevant to mammalian–microbial mutualism: the nasal sinuses, the lungs, and the gastrointestinal (GI) tract. Each region is involved in constant and essential chemical communication between the local microbiota and both local and systemic tissues critical to human physiology. Furthermore, each compartment can be considered as a simple system, with overall sources of input and output, as well as local give-and-take occurring between the mammalian and microbial cells at the epithelial surface; the figures in this review attempt to represent these basic systems (Figs. 1–3). The goal is to provide a framework to understand the chemical, macromolecular, cellular, tissue, and systemic relationships between components of the three domains of life that coexist within the human body, although only bacterial and mammalian cells are considered here. Sections are also organized by disease states related to roles the microbiota play in human health. This review is not intended to be comprehensive, however, neither in the complexity of the tissue systems considered nor in its coverage of the primary literature from the past 5 years. As an example, the oral oropharynx and subgingival crevice tissues, which interact intimately with the microbiota, are not covered. Key reviews on several topics will be cited to provide access to more comprehensive information. The disease states associated with the microbiota and considered here are *Staphylococcus aureus* infections and rhinosinusitis within the nasal-sinus compartment; cystic fibrosis (CF), chronic obstructive pulmonary disorder (COPD) and other non-asthma pulmonary disorders, and allergic asthma in the lung compartment; and the following disorders related to the GI and its resident bacteria: obesity, atherosclerosis, ulcerative colitis, Crohn's disease, autism, and drug and xenobiotic toxicity.

Sequencing efforts have provided organized and highly evolving data that significantly expand our understanding of the locations and activities of

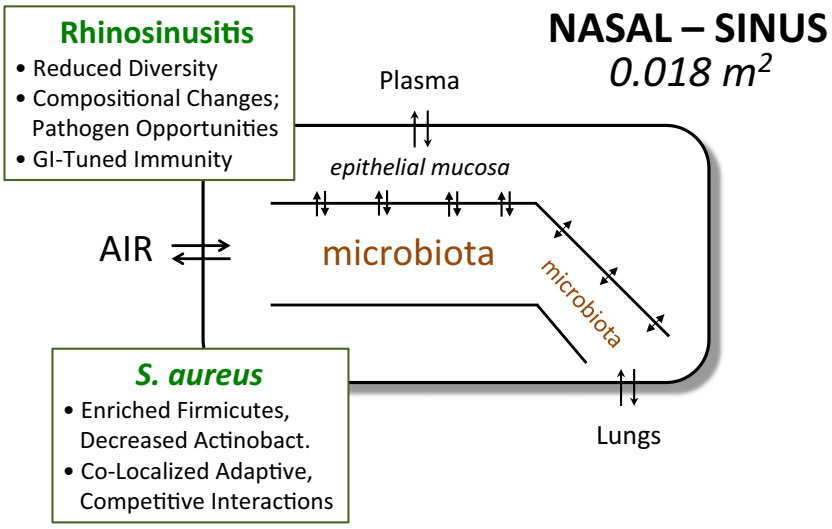

Fig. 1. The small surface area of 18 cm^2 of the nasal-sinus compartment is skin-like at the nostrils but is then lined by mucosal epithelia (mucosa) and colonized with microbiota (orange). Air, including particulate and some biological matter, is passed through on its way to the lungs, the major output, although some mucus-entrapped matter is passed to the GI tract. Small arrows across the mucosa indicate local absorption and secretion, including mucus delivery. Chemicals absorbed across this still external nasal-sinus mucosa then enter the human body, passing through the plasma and into the heart for circulation. Diseases associated with the nasal-sinus compartment represented are *S. aureus* infection and rhinosinusitis, with some features highlighted (see the text for details).

human symbiotic microbes [1]. In 2012, Human Microbiome Project (HMP) reported results from 242 healthy US adults sampled three times from 15 to 18 body sites. These efforts revealed 5177 bacteria taxa from 16S rRNA sequencing, as well as 3.5 Tbp of metagenomic sequencing data, including the assembled sequences of 800 reference bacterial strains [2]. Considerable data continue to be added to such resources, which are publicly available both in readily annotated and in pre-annotation forms. Some very general conclusions that can be drawn from the initial data analyses are that healthy people differed in bacterial composition at these body sites but that a baseline for the Western microbiome (the genetic material present in commensal microbiota) could be defined and that ethnic–racial clinical trends correlated with distinctions in microbial compositions [1,2].

On an individual basis, prior work had indicated that bacterial composition is unique to each body part and significantly changes with time in each individual during infancy and early childhood and, as born out in more detail by the HMP, compositions are distinct from individual to individual [3]. Perhaps not surprisingly, the skin's surface area of ~1.7 m^2 appears to host the most diverse microbiota, as it has a myriad of ways by which it samples the bacteria present in our environment. In terms of volume and number of cells, however, the human GI's surface of ~250 m^2 is home to trillions of bacterial cells and is by far the largest and most intimate connection between cells from both domain of life. The lungs are the next largest surface area, at ~85 m^2, and are capable of containing a volume of 6 L; the lungs are not abiotic, even in the lower airways, as outlined below. Finally, the relatively small 0.02 L volume of the nasal and paranasal cavities is populated by a distinct set of bacteria and potential pathogenic microbial species. This review will start with the smallest compartment considered here, the nasal/sinuses, then transition to pulmonary system, and finally to the large, dynamic and robustly populated GI.

Nasal-Sinus Compartment

The nasal cavities are portals to the lungs and, to some extent, to the GI. They are a pass-through with mucosal membranes that contend with an onslaught of particulate and microbial material with each breath (Fig. 1). A minor but important component of the nasal output is the GI, where mucin-entrapped particles are often sent for excretion. The nasal passages are clearly a key site of human viral and bacterial infection. The paranasal sinuses are also non-sterile and play enigmatic roles in physiology, and they are similarly subject to viral and bacterial infection. An important component of the local, tissue-specific secretions essential for nasal function, as well as the functions of all the compartments considered here, are mucin-producing cells of each epithelial layer.

Nasal microbiota and *S. aureus*

While ~30% of humans are carriers of *S. aureus* in their nasal/pharynx, it is usually not pathogenic in healthy subjects. One early human study in 2000 demonstrated that the nasal microbiota are distinct from that of the pharynx and that they are distinct between individuals [4]. They defined a set of nasal