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Mini review

A dynamic partnership: Celebrating our gut flora

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Abstract

Emerging data indicate that humans enjoy health through a productive collaboration with their colonizing flora, the majority of whom reside in the colon. This minireview provides a perspective on recent data and the exciting scientific challenges ahead.

Keywords: Intestinal flora; Gut flora; Colonic flora; Bacteroides; Intestinal immunity; *Bacteroides fragilis*; *Bacteroides thetaiotaomicron*; Mucosal immunity

1. Introduction

Among body sites normally sporting a community of microbes, the human gut, predominately the colon, harbors the greatest number and diversity of organisms, primarily bacteria. Pasteur with prescient insight postulated that our health is intertwined with our resident flora [1]. Dr. Joshua Lederberg, a Nobel Laureate (1958) at the age of 33, later coined the term 'microbiome' or the collective genome of our indigenous microbes and further proposed that a comprehensive view of human genetics and physiology is a composite of human and microbial genetics [2]. Later, the human genome project revealed 233 proteins with homologues only in bacteria, suggesting that we have acquired these genes from our resident flora [3]. This has led to a fundamental question; namely, to what extent is human life dependent on its microflora? [4] Investigations addressing this question have spawned two new scientific disciplines. The first titled 'Eco-Devo' or ecological developmental biology pursues the hypothesis that human development is both hardwired in our genes and derived from our interactions with microbes [5]. The second field, cellular microbiology, is built on the principle that studies of normal flora as well as microbial pathogens provide new insights into host cell biology, biochemistry and development [6]. The goal of this paper is to provide a perspective on recent data supporting the hypothesis that the relationship between the host and the gut flora is not simply commensal (i.e. living together without injury to either partner) but rather symbiotic or mutualistic; namely, an interdependent relationship essential to our well-being (Table 1) [2,7].

2. Basic facts about the human gut flora

Comprised of 500 to 1000 bacterial species with two to four million genes, the microbiome contains about 100-fold more genes than the human genome and the estimated 10^{13} bacterial cells in the gut exceeds by 10-fold the total ensemble of human cells [2]. At least half of these organisms cannot be cultured but no one discounts the importance of these elusive microbes. In this vast community of gut bacteria, anaerobes outnumber aerobes by estimates of 100–1000 anaerobes to one aerobe. The mechanisms accounting for composition of the gut flora and how it is assembled are incompletely understood. However, it is clear that, at birth, humans become colonized with facultative aero-

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bes including streptococci and *Escherichia coli* but, at the critical juncture of weaning, there is a dramatic shift in the flora with obligate anaerobes, particularly *Bacteroides* species, becoming preeminent (Fig. 1) [5]. Intestinal *Bacteroides* consist of at least four key species, *B. thetaiotaomicron, B. vulgatus*, *B. distasonis* and *B. fragilis*, and comprise about 30% of the total gut flora suggesting that these organisms are likely the key anaerobes in health and disease [8].

Of these species, two dominate the medical literature and investigations, *B. fragilis* and *B. thetaiotaomicron. B. fragilis* are not only constituents of the normal gut flora of most humans but are the leading human anaerobic pathogens [8,9]. *B. fragilis* show an impressive capacity to regulate their surface structures by DNA inversions permitting display of up to nine distinct polysaccharide capsular variants as well as L-fucose-containing glycoproteins reminiscent of host proteins [10–13]. Further, decoration of *B. fragilis* with fucosylated molecules confers a competitive survival advantage in vivo [12]. The high level of antigenic variability and surface display of antigens similar to host intestinal epithelial cells may permit a certain 'tolerance' for *B. fragilis* allowing them to associate intimately with the mucosal surface [14]. In contrast, *B. thetaiotaomicron* lack adhesive molecules and are located in the gut lumen where they appear to assist in polysaccharide digestion (see below) [7].

Table 1
How the gut flora promote human health

Polysaccharide utilization and nutrient release
Enhanced fat storage
Induction of mucosal glucose transporters
Induction of villous capillary formation
Induction of select proteins of innate immunity
Contribute to mucosal homeostasis and repair capacity
Stimulate secretory IgA production
Induce development of gut-associated lymphoid tissue
Promote diversification of lymphoid populations and immunoglobulin genes

3. Nutritional benefits of the gut flora

In 1983, Wostmann and colleagues observed that germ-free rodents require 30% more calories to maintain their body mass than conventional rodents (possessing their 'normal' gut flora) [15]. The potential mechanisms accounting for this observation remained obtuse until recently when seminal studies by Drs. Lora Hooper, Jeffrey Gordon and others using germ-free mice colonized with conventional gut flora or *B. thetaiotaomicron* suggested that the gut flora contribute to carbohydrate and lipid absorption [7,16–19]. Sequencing of the *B. thetaiotaomicron* genome revealed, remarkably, that a majority of this genome is devoted to polysaccharide utilization and, importantly, contains enzymatic capacities lacking in the human genome permitting, for example, the digestion of nutrients otherwise inaccessible to the host [16]. The genome of these bacterial glycophiles, termed a 'glycobiome', predicts that they display receptors for complex polysaccharides as well as secrete a vast array of carbohydrate-degrading enzymes into the bacterial periplasm or extracellular fluid [7]. Consistent with the hypothesis that the metabolic capabilities of *B. thetaiotaomicron* are critical to host nutrition, these organisms are observed to associate with food particles and mucus and to modify their glycan foraging behavior (via differential gene expression) depending on the available nutrient sources [19].

The gut flora also likely regulates fat storage [17]. Eight-week-old germ-free mice have puny epididymal fat pads compared to the adipocyte hypertrophy evident in either conventional mice or mice conventionalized with gut flora at the time of weaning (10 to 14 days of age). In fact, colonization of germ-free mice with normal gut flora produces a 60% increase in body fat and the emergence of insulin resistance within 14 days despite a 30% reduction in food intake. Leptin, an adipocyte-derived hormone whose expression correlates with adipocyte lipid content and also suppresses appetite, glucose and insulin levels, increases significantly by 14 days after colonization of germ-free mice. The potential

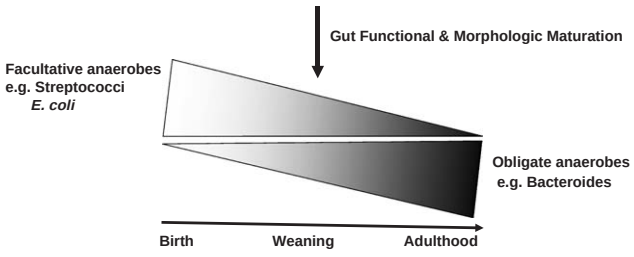

Fig. 1. Reproduced with permission from Trends in Microbiology 12:129, 2004.