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Commentary

Gastrointestinal Microbiota Dysbiosis and Crohn's Disease

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Abstract

The broad label of dysbiosis has been advanced as a catch all for a growing number of medical conditions in which reorganization of the gastrointestinal microbiota have been documented. That significant differences exist between the gastrointestinal microbiota of individuals with Crohn's disease and non-afflicted individuals put into question a possible role in disease causation. The paper presents the argument that inflammatory induced changes within the microbiological environment is responsive for the deregulation of interbacterial dominance and that the "dysbiosis "of Crohn's disease is a cause and not an effect.

Keywords: Dysbiosis; Crohn's Disease; Pathogenesis

Infectious Diseases Incorporated Perspective

New diagnostic technologies have permitted ready assessment as to qualitative and quantitative delineation of bacterial composition of the gastrointestinal microbiota. Mass funding of microbiome projects within the Human Microbiome Project and Integrative HMP Research Consortium and within the pharmaceutical industry's quest for marketable products have resulted in a growing number of measurement type publications seeking clinical relevance for the documented reorganization of the gastrointestinal microbiota.

The term dysbiosis has been affixed to a reorganization of the gastrointestinal microbiota from a prior status that has now been documented for growing number of medical conditions.

A proportionally large number of medical publications have documented disparities in the gastrointestinal microbiota between healthy individuals and individuals afflicted with Crohn's disease [1-13]. Individual investigators have used demonstration of microbiota dysbiosis in Crohn's disease as a platform to infer clinical relevance and a new potential point of therapeutic intervention; "Microbial-based and microbial-target therapy …." [1]; "The treatment-naïve microbiome in new onset Crohn's disease" [2]; "…. role of microbiome replacement therapies" [3]; "Remission in Crohn's disease is accompanied by alterations in the gut microbiota and mucin production" [6];" Analysis of gut microbiome and diet modification with Crohn's disease" [6];" Dysbiotic gut microbiome. A key element of Crohn's disease" [9]; "Infectious enteropathogenesis of Crohn's disease" [10]; "Role of pathogenesis and role of microbiome replacement therapies" [12]; "Dysbiotic gut microbiota causes transmissible Crohn's disease …." [11] etc.

A new observation carries with it two requisite questions: WHY and HOW.

The WHY of Crohn's disease dysbiosis

In 2015, a pathogenesis for Crohn's disease (Hruska Postulate) was first delineated. It was contended that Crohn's disease is

an immune-mediated disease whose mechanism of disease creation is the consequence of a newborn, in the absence of its acquired immunity, becoming infected by a bovine pathogenic mycobacterium, *Mycobacterium avium* subspecies *paratuberculosis* (MAP), embedded in adulterated milk products [14]. In aborting continued MAP replication, the newborn's inherent immune system's pro-inflammatory response could become so stressed as to be maintained fixed within immunological memory. For effector arm of the immune-mediated disease to manifest, MAP had to become widespread within the food supply. The proposed hypothesis has been used to explain every single facet of the natural history of Crohn's disease. It formulates the foundation for newest therapeutic interventions in Crohn's disease [15,16]. Once it could be demonstrated that incubation of mononuclear cells from individuals with untreated Crohn's disease with selected MAP antigens resulted in the production of pro-inflammatory cytokines, the Hruska Postulate ceased to be a postulate.

Crohn's disease is the consequence the cytotoxic pro-inflammatory cytokines/MAP interactions at sites of maximum mucosal adherence, destruction of mucosal integrity resulting in inflammation, and microbiota access to the underlying tissues. The resultant, sustained inflammation alters the microbiological environment that, in turn, causes a reregulation of the gastrointestinal microbiota hierarchy.

The HOW of Crohn's disease dysbiosis

The initial gastrointestinal microbiota is acquired at birth from the bacterial flora of the female vagina. Lacking acquired immunity, a newborn is analogous to a germ-free animal. Its initial bacterial gastrointestinal inoculum is derived from the bacterial flora of the female genital tract in which facultative anaerobic lactobacillus species normally govern. This microbial inoculum initiates the newborn's acquired immunity. The importance of facultative anaerobic lactobacilli being the inoculum controller is inferred by the apparent enhanced immunity of infants delivered vaginally versus those delivered by Cesarean section and its subsequent near absolute dominance of the bacterial flora of the female genital tract.

Through their evolutionary development, the aerobic lactobacilli amassed an impressive amount of armamentarium in the form of acid production, bacteriocins (compounds that function as regional antibiotics) and hydrogen peroxide production [17,18]. The effectiveness of these mechanisms can be readily assessed using comparative growth inhibition technology. The effectiveness of a given mechanism of suppression varies among the numerous strains of lactobacilli. When other bacteria are concomitantly isolated, they are present in numerically inferior numbers to the governing lactobacillus strain.

The bacterial simplification of the female genital tract had facilitated identification of the mechanisms of bacterial governance. Anatomically, the female genital tract has but one portal for ingress and egress. The only powerful environmental challenges are menstruation and coitus. Prior to coitus, its microbial composition is extremely stable. In young prepubescent girls, a strain of lactobacillus is dominant to the virtual exclusion of recoverable other bacteria. If other bacteria are present in detectable numbers, the most common co-isolate is a group B streptococcus. The prevailing strain of group B streptococcus can suppress all other group B streptococcal strains. As with the governing lactobacillus strain, they are kings within a secondary domain [19,20]. Their defense mechanisms are complimentary to those of the governing lactobacillus strain. If the group B streptococcal strain escapes lactobacillus governance, it acquires pathogenic potential [21,22]. These principles of governance govern with the gastrointestinal microbiota, but only on a more complex platform. At a given anatomical point within the gastrointestinal tract, the governing bacterial pyramids are the consequences of the prevailing pH, availability of molecular oxygen, presence of bile, digestive enzymes, diet intake and metabolism and gastrointestinal peristalsis which collectively define the prevailing microbiological environment.

Crohn's disease and dysbiosis

Chronic inflammation causes an alteration of the local oxidation-reduction potential which, in turn, causes a realignment of the sequences of bacterial dominance. Shiga *et al*. analyzed the fecal microbiota in patients with Crohn's disease before and after treatment with elemental diet and total parenteral nutrition [13]. Their data demonstrate a significant reversion of the gastrointestinal microbiota to its prior status following therapy with elemental diet and total parenteral nutrition. The projected WHY is that these dietary manipulations excluded most potential

MAP adulterated foods and the resultant induction of inflammation. To date the most effective current therapies for Crohn's disease involve dietary manipulation in which all milk-based products and meat from herbivores that may have been adulterated by MAP are excluded from the diet. With mucosal restoration and the absence of inflammation, the microbiological environment facilitates a realignment back to the prior microbiota hierarchy.

Summary

Gastrointestinal microbiota dysbiosis of Crohn's disease is primarily the consequence of changes in the microbiological environment that reregulates microbial dominance patterns. Inflammation secondary to MAP antigens/targeted mononuclear cell induced inflammation disrupts the ability of key microorganisms to suppress replication of other bacteria which then put in place, alternate replication sequences which then define bacterial governance.

The "dysbiosis" of Crohn's disease is an effect and not causation. Knowledge of polymicrobial regulation and of the pathogenesis of Crohn's disease should have precluded cluttering the medical literature with speculation as to clinical relevance of dysbiosis in the causation of Crohn's disease [23].

The metabolic workings of the gastrointestinal tract microbiota constitute a treasure trove of untapped knowledge that stand to lead to a better understanding of developmental immunity, its long-term carryover, and, more importantly, its influences on higher cortical function (the microbiota-brain axis).

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Conflict of Interest

None.

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