The Gut Microbiota in Inflammatory Bowel Disease

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KEYWORDS

• Ulcerative colitis • Crohn's disease • Microbiota • Fecal microbial transplantation
• Inflammatory bowel disease

KEY POINTS

- Environmental factors that shape the composition and function of the microbiota are maximally active during the earliest perinatal and postnatal phase of life.
- The neonatal and infant microbiota shapes the development and maturation of the immune system.
- Most of the genetic risk factors for inflammatory bowel disease code for proteins that sense or regulate the host response to the microbiota.
- The molecular mechanisms by which genes, microbes, and the immune system interact in the pathogenesis of inflammatory bowel disease are becoming clarified.
- Strategies for manipulating the microbiota have been remarkably effective in experimental animals but attempts to translate these to the human context have been resoundingly disappointing.

INTRODUCTION

Therapeutic strategies for inflammatory bowel disease (IBD) have increased over the past decade, but considerable unmet needs remain. Increasingly, patients seek safer, long-term options and alternatives to immunomodulatory and immunosuppressive drugs. The prospect of modulating the microbiota in both Crohn's disease and ulcerative colitis is conceptually appealing and is based on sound rationale.[1–4] However,

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clinicians wait expectantly for translation of advances in understanding the gut microbiota to clinical therapeutics and some may feel blinded by a blizzard of inconclusive publications. In this overview, we try to make clinical sense of a large body of factual data, explore the clinical implications of the relationship between the microbiota and IBD and summarise the lessons learned.

BROKEN BIOME OR BROKEN HOST?

For many years, the cardinal question surrounding the pathogenesis of IBD has been: Is this an abnormal immune response to a normal microbiota or is this an appropriate response to an abnormal microbiota? It is now clear from various animal models that both situations may arise and may overlap.[5,6] Genetically determined anomalies of the innate immune system can lead to a modification of the microbiota, which becomes colitogenic upon transfer to an otherwise normal recipient. In addition, because the microbiota shapes the maturation of the immune system in early life,[7] any disruption of the microbiota such as that caused by antibiotic exposure may lead to suboptimal immunity and/or risk of IBD in later life.[5]

THE ENVIRONMENTAL INFLUENCE ON INFLAMMATORY BOWEL DISEASE

Despite much focus on genetics within the past decade, 2 lines of evidence confirm the environment as a risk factor for IBD. First, the concordance rate in genetically identical twins (approximately 40%-50% for Crohn's disease and approximately 10% for ulcerative colitis) suggests a substantial environmental influence, particularly in ulcerative colitis. Second, the increasing frequency of both conditions has occurred over too short a period to be owing to changes in the population pool of genetic risk factors. Indeed, the known genetic risk factors are relatively common in society and, in most instances, are insufficient alone to cause disease.

Clinicians might despair at inconclusive and occasionally futile epidemiologic surveys chasing putative environmental risks, such as notional north/south and east/west gradients but amid this fog one can make cogent epidemiologic conclusions. First, the environmental influences on Crohn's and ulcerative colitis seem to be similar but with 2 noteworthy exceptions. Cigarette smoking has a polarizing influence on the 2 main forms of IBD, whereby smoking is both a risk and aggravating influence for Crohn's disease, whereas in ulcerative colitis, the cessation of smoking is a risk factor for relapse and active smoking has a modest beneficial influence. In addition, an episode of acute appendicitis, particularly in childhood or early adolescence, has a protective influence on the risk of developing ulcerative colitis but not Crohn's disease or celiac disease. Second, like many immunoallergic disorders, both forms of IBD may be considered as diseases of a modern lifestyle. As countries undergo socioeconomic development, the incidence and prevalence of ulcerative colitis increases first and then is followed by similar trends in Crohn's disease. Thus, many of the epidemiologic observations of the past actually represent the variable influence of socioeconomic development.[5,8]

MICROBIOTA AS A PROXY MARKER OF ENVIRONMENTAL INFLUENCE IN INFLAMMATORY BOWEL DISEASE

Although some environmental and lifestyle factors such as stress, drug therapy, pollution and radiation might have independent influences on disease activity, most, if not all, of the elements of a modern lifestyle in socioeconomically developed countries shape the composition and functional activity of the gut microbiota. Because the