Nutrition, Gut Microbiota and Immunity: Therapeutic Targets for IBD

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Nutrition, Gut Microbiota and Immunity: Therapeutic Targets for IBD
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Inflammatory bowel disease (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC), are chronic debilitating diseases that occur in populations around the world. The diseases can manifest at any age, and therefore represent a clinical challenge for pediatricians, internists, family practitioners, and surgeons. The underlying etiology is multifactorial, where host genetic polymorphisms account for a minority of the risk for disease development, emphasizing the importance of environmental factors such as the gut microbiota. Supportive of this notion, epidemiologic associations show a significant increase in IBD incidence over the past few decades associated primarily with residence in industrialized nations.

Current therapeutic modalities for IBD are largely targeted at suppression of the innate and adaptive immune response. Commonly used therapies include mesalamine, corticosteroids, thiopurine analogues (azathioprine or 6-mercaptopurine), methotrexate, and anti-tumor necrosis factor-α agents. There is also limited use of natalizumab, a biologic targeting the α4-integrin adhesion molecules. While effective for many patients, these therapeutic strategies are not universally effective. Furthermore, they are each associated with the risk of serious and sometimes fatal adverse events.

An alternative approach to the treatment of IBD is to change the environmental factors that contribute to the etiology or perpetuation of inflammation. Leading targets for this alternative approach to therapy are the principal contents of the gastrointestinal tract – our diet and the human gut microbiota. Indeed, there is reason to believe that the composition of our diet and the gut microbiota might have a synergistic effect on inflammation related to IBD.

This monograph includes summaries of talks presented at the 79th Nestlé Nutrition Institute Workshop held in New York on the 28th and 29th of September 2013. The speakers in the symposium addressed our current understanding of the epidemiology and biologic underpinnings that manifest as CD and UC; the gut microbiota, its function, and how it may interact with...
nutritional status in perpetuating IBD; the potential for manipulation of the gut microbiota through the use of prebiotics, probiotics, antibiotics, and fecal transplantation, and the current role of and future prospects for nutritional interventions in the management of these diseases.

Despite advances in the treatment of IBD, a substantial proportion of patients experience relapse of the disease every year. Many of these patients still require surgery. Although surgery represents a cure for UC, it is associated with lifelong alteration in bowel function and risks of other complications. For CD, surgery is generally only a temporizing measure as disease recurrence is common. Given the incomplete effectiveness of our current immunosuppressive therapies and their associated toxicities, there is a real need for alternative treatment strategies. Altering key environmental exposures that drive the inflammatory response could open new avenues to treat these debilitating lifelong diseases.

James D. Lewis
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Foreword

Inflammatory bowel disease (IBD) currently affects 1 in 200 people in the United States. The incidence of IBD has been gradually increasing globally in the past several decades. While the explanation for this increase is not totally clear, environmental factors, including changes in the diet, may be a key factor.

The 79th Nestlé Nutrition Institute Workshop held in New York City in September 2013 carries on the theme from the 77th Nestlé Nutrition Institute Workshop, where world experts gathered in Panama City to present their latest findings on how nutrient status can modulate immunity and improve health conditions in pediatric patients. This workshop chaired by Prof. Lewis, Prof. Ruemmele and Prof. Wu focused on the complex relationship between nutrition, inflammation and the microbiome as it relates to IBD; this is arguably the hottest area of IBD research currently.

Previously, the theories on pathogenesis of IBD suggested a combination of genetic susceptibility and immune and external environmental factors. In recent years, the gut microbiota has greatly gained in importance and has been accepted as the 4th element in the pathogenesis of IBD. These relationships are complex and not independent since IBD patients may have a genetic susceptibility that leads to abnormal immune responses directed against the intestinal microbiota.

Currently, over 160 genetic susceptibility genes have been identified for IBD, the most prevalent of these are Nod2, an important intracellular pathogen recognition sensor, and ATG 16L1, important in autophagy, killing and processing of phagocytized bacteria. However, the function of many of the other genes identified has not been fully characterized.

The gut microbiota consists of both protective and aggressive microbes, and the balance between these populations is important, not only in the pathogenesis of IBD, but also in the ongoing inflammatory response. A better understanding of the complex interactions, particularly the role of the gut microbiota in the inflammatory process, holds the key for potential for targeted therapy in
the future. The ability to selectively alter the composition and thus the function of the gut microbiome through diet, prebiotic and probiotic therapy may be a very attractive treatment alternative for patients with IBD. There is already good evidence in the medical literature that total enteral nutrition is highly efficacious in inducing remission in pediatric Crohn’s disease. In these patients, there is a significant shift in the gut microbiota following the successful enteral therapy; however, the causal relationship has not been established to date.

On behalf of Nestlé Nutrition Institute and Nestlé Health Science, we would like to thank the Chairmen, Prof. James Lewis, Prof. Frank M. Ruemmele and Prof. Gary Wu for their diligent work in assembling such a distinguished group of researchers, clinicians and speakers. We would also like to thank all the speakers for their hard work in putting together such outstanding presentations. The energy throughout the meeting, the interest among the participants and the quality of the questions posed to the speakers were all testaments to the quality of the meeting and the importance of this topic. We hope that important collaborations will result from the many positive interactions during this workshop.

Finally, we would like to thank Natalia Wagemans, Mélanie Costinas, Bernice Hammer and Mélanie Pittier who worked tirelessly in the background to ensure the meeting ran smoothly and made it the resounding success that it was.

We look forward to a follow-up NNI Workshop in the near future to review the advances in this exciting field of research.

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A Review of the Epidemiology of Inflammatory Bowel Disease with a Focus on Diet, Infections and Antibiotic Exposure

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Abstract

Inflammatory bowel disease (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC), are chronic debilitating diseases that occur in populations around the world. The underlying etiology is thought to be multifactorial. There is a well-defined genetic contribution to the diseases, but this does not fully explain the epidemiology. Environmental factors, including the composition of the gut microbiota, are also important. There is wide geographic variability in the incidence and prevalence of IBD. High incidence rates have been observed in the United Kingdom, Northern Europe, Canada, and the United States. Globally, there is evidence of increasing incidence of CD and UC over time. The rising incidence of IBD in Western countries has generally predated that in developing nations, supporting the hypothesis that ‘Westernization’ of our lifestyle has led to the increased incidence of IBD. Smoking, antibiotic use, and diet are potentially reversible risk factors for IBD. Recommendations to avoid smoking are appropriate for all people, for numerous reasons. Antibiotic use should be limited to appropriate indications, a recommendation that too is appropriate for all populations. Detangling the relationship between diet, the gut microbiome and IBD raises the potential to reduce the incidence of IBD through dietary modification, an approach that might be considered among those at the highest risk.

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Inflammatory bowel disease (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC), are chronic debilitating diseases that occur in populations around the world. The diseases can manifest at any age, and therefore represent a clinical challenge for pediatricians, internists, family practitioners, and sur-
The underlying etiology is thought to be multifactorial. There is a well-defined genetic contribution to the diseases, but this does not fully explain the epidemiology. Environmental factors, including the composition of the gut microbiota, are also important. This review will focus on the relationship between IBD and other environmental factors, such as diet, infections, and medications.

**Incidence and Prevalence of IBD**

Studies of the incidence and prevalence of IBD were recently summarized in a review by Cosnes et al. [1]. Within North America, the prevalence of CD is approximately 44–201 per 100,000, with increasing incidence until approximately age 30. Similarly, estimates of the prevalence of UC range from 37.5 to 238 per 100,000, with incidence increasing until approximately age 40. Although early research suggested a bimodal pattern of incidence with a second peak later in life, this has not been consistently observed.

There is wide geographic variability in the incidence and prevalence of IBD. High incidence rates have been observed in the United Kingdom, Northern Europe, Canada, and the United States. The incidence of IBD is generally lower in the Asia-Pacific region, with the exception of Australia [2]. In many regions, there is evidence of increased incidence and prevalence as one moves further from the equator [3]. Similar patterns have been seen with other immune-mediated diseases such as psoriasis and multiple sclerosis [4, 5].

Globally, there is evidence of increasing incidence of CD and UC over time [6]. Furthermore, the rising incidence of IBD in Western countries has generally predated that in developing nations. In general, the incidence of UC has risen before that of CD within any given area. For example, in 2012, the ratio of UC to CD in Asia was 2.0, while in Australia it was 0.5 [2].

The rising incidence of UC and CD across the world, but earlier in developed nations, has contributed to the hypothesis that ‘westernization’ of our lifestyle has led to the increased incidence of IBD. Before focusing on the specific evidence that supports an association between a Western lifestyle and the development of IBD, it is important to consider possible alternative explanations for the geographic patterns that have emerged. The most obvious alternative explanation is that improved access to healthcare and improved diagnostic tools led to more frequent diagnosis of IBD. It is possible that some patients with mild IBD who previously went undiagnosed throughout their entire life are now diagnosed because of greater availability of colonoscopy and cross-sectional imaging modalities. Increased awareness of IBD by clinicians could also contribute to rising incidence rates. Likewise, cultural norms may have evolved in some re-
regions, such that there is greater willingness to discuss one’s bowel symptoms. Each of these could contribute to an apparent increased incidence and prevalence even if there were truly no change in the epidemiology of these diseases.

Arguing against detection bias is the observation that incidence rates of numerous other immune-mediated diseases have also increased in a pattern similar to IBD [7–10]. Diseases such as asthma and psoriasis are diagnosed without the need for invasive or expensive tests. Given the frequent co-occurrence of immunologic diseases, it seems more likely that one or more environmental factors have contributed to the rising incidence rates of all of these diseases [11, 12].

This review will focus on several hypotheses related to the changing epidemiology of IBD, with a specific focus on environmental factors. Although the human gut microbiome can be considered an environmental factor, this will not be addressed in detail in this review, as it is the focus of another chapter in this book. Likewise, the important contribution of genetics to the epidemiology of IBD will not be discussed in detail since this will also be covered in another chapter.

**Emigration**

Some of the regional variation in incidence and prevalence of IBD is likely due to genetic factors. Increased access to care and diagnostic tests could also lead to higher incidence rates in more industrially developed nations. A recent systematic review demonstrated significantly higher incidence rates for both CD and UC among urban populations [13]. The strength of association was greater for CD than UC, although there was significant heterogeneity in each analysis without an obvious explanation. In addition to greater access to healthcare, environmental factors such as diet, pollution, climate, hygiene, and crowding may also contribute to these differences, and would be associated with urban residence.

Studies of people who move between regions of differing IBD incidence and prevalence provide an opportunity to assess the impact of environmental factors on the risk of developing IBD. Several investigators have examined the incidence of IBD within Israel because Jews residing in Western countries are known to have an increased incidence of IBD. In early studies from Israel, immigrants to Israel had higher incidence rates than did Israeli-born populations [14–16]. However, by late 1980s, the incidence and prevalence of CD was comparable among Jews in southern Israel regardless of whether the patient or the patient’s father was born in Israel, Asia, Africa, Europe or America [17]. In contrast, the prevalence was much lower among Arab Israelis, which could be due to genetic or environmental differences since during this time period the Israeli Bedouin population led a lifestyle ‘more characteristic of Third World countries’ [17].
More recent data from Sweden suggest that the incidence of IBD is generally lower in first-generation immigrants, but by the second generation is comparable to that of the Swedish population [18]. Taking advantage of a unique population-based registry, Li et al. [18] observed that the incidence of CD was significantly lower among all first-generation immigrants, and that this was most evident among immigrants from Africa (SIR 0.54, 95% CI: 0.37–0.77), Asia (SIR 0.64, 95% CI: 0.54–0.74), Baltic countries (SIR 0.45, 95% CI: 0.23–0.79) and Latin America (SIR 0.43, 95% CI: 0.28–0.63). Only among those from Latin America was there a significantly lower incidence rate of CD among second-generation immigrants. Generally, similar results were observed for UC, with second generation incidence rates for most immigrants being similar to that of the Swedish population, while second-generation immigrants from southern and Eastern Europe continued to have lower incidence rates. Notably, if both parents were immigrants from the same country, the second generation continued to have a lower incidence of CD. Whether this is due to greater retention of lifestyle customs from the parents’ native land or other reasons is unknown.

Leicester, UK, is home to a large south Asian immigrant population. In the 1990s, the incidence of UC in Leicester was higher among south Asian immigrants than among those of European ancestry [19]. The distribution of disease differed between first- and second-generation immigrants, with proctitis being most common among first-generation immigrants whereas extensive colitis was more common among the second generation. It is likely that the second generation would have assimilated to the Western culture more than their parents, supporting a hypothesis that environmental factors not only influence incidence rates but could also influence disease phenotype.

Dietary differences are often cited as a contributor to the increased incidence of IBD among immigrants from Asia or Africa to Western nations. However, not all studies support this hypothesis. For example, Carr and Mayberry [19] observed that immigrants from south Asia to Leicester, UK, who developed UC were more likely to follow a traditional vegetarian diet than immigrants who did not follow a vegetarian diet.

Barreiro-de Acosta et al. [20] took a different approach to this question by studying people from the Galicia area of Spain where people often emigrate to other countries to find work and then return to Spain at a later time. Patients newly diagnosed with IBD while living in Galicia were more likely to have emigrated to a foreign land and returned than control subjects. Furthermore, the association was qualitatively stronger among those who had emigrated to industrialized European countries (OR 1.91, p = 0.02) than to Latin America (OR 1.48, p = 0.32). The association was somewhat stronger for UC (OR 2.24, p < 0.01).
than for CD (OR 1.56, p = 0.15). These data support the hypothesis that changes in environmental exposures that result from emigration may influence the risk of developing IBD.

The changing incidence of IBD during the last half century has occurred too fast to be attributable to changes in the underlying gene pool. Far more likely is that changes to our environment have led to the ‘epidemic’ of immune-mediated diseases and IBD in particular. That immigrants from low-incidence regions to high-incidence regions typically continue to have lower incidence rates for the first generation but comparable incidence rates to natives of their new home by the second generation suggests that early exposure to environmental factors may be important.

**Obesity and Physical Activity**

People living in Western societies are typically less physically active and have easier access to food than our predecessors. This has led to an epidemic of obesity, including childhood obesity. One hypothesis is that the reduced physical activity and subsequent obesity could contribute to increasing incidence rates of IBD. Indeed, prior studies have documented that visceral adipose tissue produces inflammatory cytokines such as tumor necrosis factor-α and that obesity is associated with increased gut permeability [21]. Furthermore, several studies have suggested that obese patients with CD are more likely to undergo surgery [22, 23]. However, evidence linking physical activity and obesity to new-onset IBD is generally lacking. The strongest evidence comes from the European Investigation into Cancer and Nutrition (EPIC) study [24]. This prospective cohort study found no evidence that physical activity, total caloric intake or obesity was associated with new-onset CD or UC. The study included mostly middle-age and older adults, so it is possible that physical activity and obesity could still impact the incidence of these diseases in children.

**Diet and the Risk of IBD**

The bowel lumen is continually exposed to numerous antigens, including the food that we consume and the enormous population of organisms that compose the gut microbiome. Although obesity and higher total caloric intake do not appear to increase the risk of IBD, selected micro- and macronutrients, additives, or contaminants could influence the risk through a variety of pathways. Proposed mechanisms through which diet could influence the incidence of IBD in-