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REVIEW ARTICLE

ROLE OF ENVIRONMENTAL FACTORS IN THE DEVELOPMENT OF INFLAMMATORY BOWEL DISEASE

Debjani Mandal, Manali Biswas and *Dr. Abhishek Basu

Department of Molecular Biology and Biotechnology, Sripat Singh College, Jiaganj, Murshidabad, Under University of Kalyani, West Bengal, India

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ABSTRACT

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disorder of the colon. The disease is more prevalent in developed countries and an increase in IBD cases is observed in developing countries. In susceptible individuals, IBD occur due to an imbalance between genetic and environmental factors. Alteration in the gut microbiota can influence the development of immune repertoire of an individual, thereby playing a vital role in the development of IBD. The two main disease entities of IBD are Crohn's disease (CD) and Ulcerative colitis (UC). This review focuses on various environmental factors involved in development of IBD. Such environmental factors comprise of hygiene, air pollution, smoking, oral contraceptives (OCPs), Non-steroidal Anti-inflammatory Drugs (NSAIDs), stress and diet. Higher hygiene standards will lead to greater risk of development of IBD, due to lack of exposure to enteric pathogens. Air pollutants increase the risk of development of IBD. Smoking has a protective effect in UC and an opposite effect in CD. Prolong use of OCPs and NSAIDs has been associated with the risk of IBD. Intake of high protein diet increases the risk of IBD. On the other hand, fruits and vegetables have a protective effect in IBD. Stress and depression worsen the symptoms of IBD and increases the chance of relapse of IBD in patients. However, these environmental factors do not show a consistent result and further research is required for deciphering the role of these factors in the development of IBD.

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INTRODUCTION

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disorder of the colon. It can occur at any time from childhood to late adulthood. The disease can be classified mainly into two categories, Crohn's disease (CD) and Ulcerative Colitis (UC). Crohn's disease is characterised by the presence of patchy expression of transmural lesion, apthous ulcers, cobblestone appearance and others at various sites of gastrointestinal tract from stomach to colon. Contrary to CD, in UC continuous pattern of inflammation and ulceration is observed from rectum to cecum. Symptoms are common for both the diseases. These are abdominal pain, rectal bleeding, reduced appetite, weight loss, fever and urgency to defecate. The prevalence of IBD varies significantly throughout the world with highest rates in the developed world, whereas an increase in IBD cases is observed in the developing countries (Molodecky *et al.*). The most significant events in IBD are remission, relapse and extension of disease in time, surgery, cancer and mortality. The cause of IBD is not completely understood. In susceptible individuals it occurs due to an imbalance between genetic and environmental factors and host-bacterial interaction. The intestinal microbiome, consisting of microorganisms influences the development of the intestinal immune system (Danese *et al.*). Host-microbiome interaction can have both beneficial and deleterious effects, resulting in intestinal inflammation (Bäckhed *et al.*). Intestinal epithelial cells act as physical barriers against excessive entry of bacteria and other antigens from the intestinal lumen into the circulatory system. Mucin depletion and dysregulated tight junctions can contribute for disruption of epithelial barrier, allowing sampling of bacteria by dendritic cells and induction of dysregulated immune response. This will finally lead to inflammation and development of IBD. With the advent of latest high throughput technologies and multiple genome wide association studies (GWAS), huge datasets have been generated with large number of samples. GWAS allowed the identification of various loci common in IBD. A total of 163 loci have been identified, out of which 110 loci are common in both CD and UC, 30 and 23 loci are being specific to CD and UC, respectively (Jostins *et al.*). The pathways which are highly established in pathogenesis of IBD are helper T (T_H) 17 and interleukin (IL)-12/IL-23 pathway (Anderson *et al.*).

Corresponding author: **Dr. Abhishek Basu,**
Department of Molecular Biology and Biotechnology, Sripat Singh College, Jiaganj, Murshidabad, Under University of Kalyani, West Bengal, India.

Susceptibility genes identified in both UC and CD are *IL23R, IL12B, IL10, STAT3* and *JAK2* (Brand *et al.*). Latest evidences indicate a correlation between innate immune system and intestinal microbiota in IBD. *NOD2* has been constantly associated with autophagy in CD (Travassos *et al.*). Susceptibility loci in UC mainly include genes involved in regulation of function of intestinal epithelial barrier. *HLA-DQA1* locus has been found to be associated strongly with UC, in absence of any risk in CD (Jostins *et al.*). The increasing incidence of IBD in developing countries due to industrialization, urbanization, geographic variation and other factors has led to the assumption that environmental factors along with genetic factors are responsible for IBD. An increase in the prevalence of IBD has been observed over the past few decades in the countries with a fast changing environment and lifestyle. This increasing incidence of IBD could not be credited solely to genetics (Thia *et al.*). Study has indicated that environmental factors can manipulate intestinal permeability, by altering mucosal immune system and disturbing the intestinal microbiota, thereby increasing the risk of IBD (Loftus EV Jr. *et al.*). This review will focus on the effect of various environmental factors on the development of IBD.

Factors responsible for IBD

Hygiene Hypothesis

Industrialization, urbanization, improved sanitary conditions and urban upbringing leads to the maintenance of hygienic conditions in developing countries, which resulted in lack of exposure to microbial agents in the children. This may alter the balance between commensal and pathogenic bacteria of the intestine and can negatively affect the development of immune system. Later in life, upon exposure to new antigens, this might initiate a dysregulated immune response in susceptible individuals (Bernstein *et al.*). Therefore, bigger family size and exposure to pets would be protective due to increased chance of microbial exposure during childhood (Klement *et al.,* Bernstein *et.al.*). Alteration in intestinal microbiota may lead to the development of IBD.

Helicobacter pylori

H. pylori is a very common infectious agent of the gut. Children are more susceptible to this infectious agent. The infection is less common in the countries where IBD is more prevalent. Also *H. pylori* infection has been found to be negatively associated with IBD (Ford *et al.*). *H. pylori* infection may provide some protection against IBD by upregulating the expression of genes involved in the function of T-regulatory cells (Luther *et al.*). However, in IBD patients, *H. pylori* infection can be treated by the use of antibiotics and drugs like mesalamine (Baron *et al.*). Application of these drugs in IBD patients will reduce colonization of *H. pylori*.

Urban Environment

Hygienic upbringing of children is more common in urban areas compared to rural areas. Such differences in lifestyles and differential environmental exposures in urban and rural areas may increase the risk of development of IBD in urban societies by decreasing the exposure to enteric pathogens (Powell *et al.*). The relationship between IBD and urban lifestyle is contradictory. Various studies have indicated an increase in IBD risk with urban lifestyle, whereas others found no direct correlation between IBD and urban lifestyle (Klement *et al.*, Radon *et. al*, Bernstein *et al.*, Blanchard *et al.*, Malekzadeh *et al.*). Few studies have also proposed an inverse relationship between the two (Declercq *et al.*).

Air Pollution

Various ecological and epidemiological studies have suggested the role of air pollutants in development of IBD. There is a relation between high level of NO_2 with CD and high level of SO_2 exposure with early UC (Kaplan *et al.*). Studies with animal models have suggested that air pollutants can have a direct effect on the intestinal microbiota and can generate a pro-inflammatory response in the host by disturbing the balance between commensal and pathogenic bacteria of the intestine. Other studies have indicated the association between traffic based pollutants and development of CD (Beamish *et al.*). Also air pollution is correlated with the rate of hospitalization of IBD patients (Ananthakrishnan *et al.*). A raising incidence of IBD has been observed in US during the period of industrialization before the implementation of environmental regulations. The reason behind such association involves rise in polymorphonuclear leukocytes and cytokines like TNF-α in the plasma (Tan *et al.*).

Diet

The role of diet has been extensively studied in IBD. Intake of yogurt and rice has been shown to improve symptoms of CD patients. Symptoms get worsen with the intake of high fibre food, spicy foods, red meat, milk, soda and alcohol (Cohen *et al.*). Animal protein has been directly related with the development of IBD (Jantchou *et.al*.). Intake of fruits and vegetables reduces the chance of development of the IBD. Fruits and vegetables confer protection in IBD by enhancing the production of enzymes involved in removing reactive oxygen species (Amre *et al.*). Source of nutritional factor can acts as an important determinant of disease risk. Consumption of soluble fibres from vegetables and fruits reduce the risk of development of IBD, contrary to the effect of insoluble fibres from whole grain. Omega-3 fatty acids intake can reduce the symptoms to some extent because of its anti-inflammatory properties. However, due to insufficient data, omega -3 fatty acids could not be recommended for maintenance of remission in CD patients (Turner *et al.*). Excessive intake of linolenic acid and increasing level of tissue arachidonic acid has been associated with two fold increase in risk of UC (Tjonneland *et al*., de Silva *et al.*). Intake of several n-3 PUFA like docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are inversely associated with risk of UC (John *et.al*.). The biological mechanism behind the association between saturated and unsaturated fatty acids and IBD could be due to the role of fatty acids in inflammatory response. They modulate the Toll-like receptors on macrophages (Lee *et al.*). Similarly vitamin D can also affect the disease activity, even in newly diagnosed IBD cases. Its role in calcium metabolism and bone health has been well recognized. Recently its role in immunological disorders has been recognized (Cantorna *et al.*, Zhu *et al.*). Reduced physical activity, malnutrition and inadequate dietary intake of Vitamin D in IBD patients can lead to Vitamin D deficiency (Farraye *et al.*, Garg *et.al*.).

Smoking

A paradoxical relationship exists between smoking and IBD. Development of UC is less prevalent in active smokers

compared to non-smokers and ex-smokers. Smoking causes reduction in the rate of relapse and there is a reduced requirement of colectomy in active smokers (Cosnes *et al.*, Lakatos *et al.*). This was opposite to the observation, in the case of CD. Active smokers followed by ex-smokers are at high risk of developing CD (Calkins *et al.*). A dose-response relationship has been suggested between smoking and IBD (Franceschi *et al.*, Persson *et al.*). On the other hand, it boosts the risk of CD by two folds (Birrenbach *et al.*, Higuchi *et al.*). However, passive smoking in childhood is not found to be associated with IBD, as passive smoking provides low level of exposure and leads to insignifcant association (Jones *et al.*). Nicotine is one of the components of cigarette smoke. It acts through nicotinic acetylcholine receptor on T cells and mucosal epithelial cells of bowel, therefore, it can regulate T-cell function directly and subsequently modulating the cellular immunity (Birrenbach *et al.*, Richardson *et al.*, Miller *et al.*, Razani-Boroujerdi *et al.*). Nicotine can also alter colonic mucus production (Cope *et al.*). Studies have suggested that the effect of smoking is mediated through oxidative stress and smoking can affect the secretion of various cytokines (Bergeron *et al.*). For example, in contrast to non-smokers, fewer amounts of anti-inflammatory cytokines like interleukin IL-10 and IL-23 and IL-8 are secreted by the mononuclear cells of active smokers with CD (Bergeron *et.al.).* Such kind of differential secretion is absent in case of healthy controls and UC patients. These findings suggest that smoking has a differential effect on pro and anti-inflammatory cytokines. Its clinical effect on UC and CD patient may be due to the protection it provides against oxidative stress. Administration of nicotine reduced colitis in animal models but failed to show such result in clinical trials (Cosnes *et al.*, Nikfar *et al.*). Therefore, nicotine may not be the only factor determining the effect of smoking in IBD patients; other factors might influence its role in the development of IBD. Thus, the exact mechanism by which smoking influences the development of IBD is a matter of future research.

Oral Contraceptives Pills

Oral contraceptives Pills (OCPs) have been proposed to be associated with increased risk in CD. A 2-3 fold increase in IBD risk has been observed in 80,000 women in cohort studies. However, the result was not significant after adjusting for cigarette smokers (Loftus *et al.*). The risk of CD increases with increase in exposure to OCPs. The risk mitigates upon discontinuation of OCPs but not by reduction in the dose of OCPs. Studies on OCPs use and development of UC have showed contradictory results, probably because of the small sample size (Cornish *et al.*, Godet *et al.*). Past history of smoking in women complements the use of OCPs in development of UC. Pro-inflammatory properties and thrombotic potential of estrogen could be responsible for its effect in IBD leading to gastrointestinal infarcations (Dubeau *et al.*). Estrogen acts as an immune enhancer, specifically enhancing the humoral immunity and allowing proliferation of macrophages (Cutolo *et al.*). Therefore, the present evidences suggest a moderate association between CD and exposure to OCPs, where the risk of CD increases with increase in intake of OCPs and cessation of OCPs reverses the risk of CD. But the dose of estrogen and progesterone in OCPs has not been taken into account in these studies. Also, the family history of the patients included has not been considered in the above studies. According to the available evidences OCPs cannot be recommended in IBD patients.

Non Steroidal Anti-Inflammatory Drugs

Management of pain is very difficult in IBD. Non-Steroidal-Anti-Inflammatory Drugs (NSAIDs), acetaminophen, or opiates are often used for the management of pain. Though no previous study have suggested any kind of relationship between use of aspirin and UC, a six fold increase in risk of CD has been observed in regular aspirin users, with the effect being more prominent in non-smokers (Chan *et al.*). The comprehensive relationship could not be established between the dosage and exposure period of aspirin with incidence of CD and UC (Ananthakrishnan *et al.*). In contrast to this, high dose of NSAIDs with prolonged duration, and frequent usage of NSAIDs showed increasing risk of CD and UC. Also, administration of acetaminophen, diclofenac, and indomethacin in patients of IBD with remission showed a rise in level of fecal claprotectin and symptomatic flares (Takeuchi *et al.*). Also patients in remission stage of UC and CD showed high risk of clinical relapse upon intake of NSAIDs (17%-29%) (Takeuchi *et al.*). NSAIDs show its effect by damaging the intestinal mucosa of stomach, small bowel and large bowel (Felder *et al*.). By inhibiting cyclooxygenase, an enzyme involved in reducing prostaglandin production, it can increase permeability of intestine (Berg *et.al*). However, prostaglandin inhibition inhibits tumor necrosis factor and induces anti-inflammatory cytokines like IL10, thereby showing an immunoregulatory effect in IBD (Cipolla *et al.*). Though neither of the studies has demonstrated the protective effects of NSAIDs against the disease, they have suggested a strong correlation between intake of NSAIDs and incidence of UC and CD. Thus, recommendation of NSAIDs in IBD patients should be monitored very carefully for deterioration of the disease activity.

Stress

Stress may play a vital role in the onset and course of IBD (Mawdsley *et al.*, Hanauer *et al.*). The occurrence of major depressive disorder (MDD) is high in IBD patients compared to general population (Persoons *et al.*). There is a relation between depression and anxiety with increased risk of CD (Graff *et al.*, Walker *et al.*). Depression and anxiety can also affect disease activity and time of relapse (Mittermaier *et al.*, Walker *et al.*). Prediction can be made for the relapse in IBD patients by observing the stress and coping strategies (Bernstein *et al.*, Bitton *et al.*). IBD patients often complain about sleep disturbances. Increased flares have been observed in patients with depression and anxiety (Ananthakrishnan *et al.*, 2012). Depression and anxiety can be treated by pharmacotherapy and psychotherapy, which can have a positive effect on quality of life, coping strategies and obedience to medications in patients with IBD (Graff *et al.*, Guthrie *et al.*, DiMatteo *et al.*). Though changes in intestinal permeability, motility, gut microbiota and mucosal inflammation have been observed in animal models of acute stress, such studies on human are lacking because of methodological deficiencies (Mawdsley *et al.*). Therefore, depression and anxiety should be regularly monitored in active IBD patients (Graff *et al.*, Ananthakrishnan *et al.*, 2013).

Management of IBD

The management of IBD is a long term process and depends on the use of various drugs on the basis of severity, location, duration and number of disease relapse. The management

mainly involves use of anti-inflammatory drugs like 5-amino salicylic acid (5-ASA) and mesalazine, corticosteroids like hydrocortisone, prednisolone and others and immune modifiers like azathiopurine and methotrexate. The route of administration of drugs is either orally or through rectum or intravenously depending on the severity and location of the disease. 5-ASA and mesalazine are usually prescribed both for maintenance of remission as well as for treating flare-ups. Corticosteroids are used to give an immediate relief from the symptoms. In severe cases hydrocortisone is given intravenously. In most of the cases corticosteroids are used after the failure of patients' response to 5-ASA. Also long term use of corticosteroids give rise to various side effects like hypertension, weight gain, psychiatric disorders, hypoadrenalism etc. Thiopurines like 6-mercaptopurine and azathiopurine and other immune modifiers are mainly used for reducing the dependence of a patient on corticosteroids. They are not suitable for the treatment of flare-ups rather suitable for maintenance of remission. These immune modifiers show their action very slowly. When the treatment by drugs fails, surgery is considered as an option for the treatment of IBD.

Conclusion

Various studies have highlighted the role of environmental factors in the development of IBD. But except for smoking, none of the factors have showed consistent results. Smoking shows opposite effects in UC and CD, the two main disease entities of IBD. There is an increase in the risk of IBD with the use of OCPs and NSAIDs, however, some of these studies have limitations like small sample size, absence of family history of the patients and recall bias. Effect of air pollution, hygiene and lifestyle on the disease activity is unclear. Diet plays a significant role in the development of IBD. Source of nutrition is an important determinant of disease risk. Contradictory and inconsistent results indicate the need of further research to understand the role of these environmental factors in the development of IBD.

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