Review Article

Inflammatory Bowel Disease: An Idiopathic Disease and its Treatment

*Sugandha Chaudhari, Jigar S. Desai, Aditya Adam, Preetesh Mishra

Department of Pharmacology, Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar, Maharashtra, India.

ABSTRACT

Recent advancement in healthcare field made several disease and disorder curable by knowing their etiology and pathophysiology. But, there are many idiopathic diseases which are needed to be get more focused. Inflammatory bowel disease (IBD) is one of them. IBD, its exact cause is still unclear but there is involvement of genetic change or translocation or mutation which is provoked by unknown factor. IBD is classified into Crohn's disease and ulcerative colitis. Both are differing in their pathophysiology as well as part of gastro intestinal tract where it affects. Crohn's disease can affect any portion of the GI tract from the mouth to the anus and it mainly act through Th-1 cells. In Ulcerative colitis, inflammation begins in rectum and extends to the proximal colon and it is continuous without any 'skip areas'.Th-2 cells play major role in pathophysiology of ulcerative colitis. Treatment of IBD requires proper diagnosis with endoscopy, pathology, radiology and careful attention on symptoms. Many pathways are involved in pathogenesis of IBD. Targeting or altering these pathways can be potential gear to treat disease and prevent its remission. This review underlines pathophysiology of IBD and targets which are available for its treatment.

Keywords: Crohn's disease, inducible nitric oxide synthase, NF-κB, Th-1cells, Th-2 cells, ulcerative colitis

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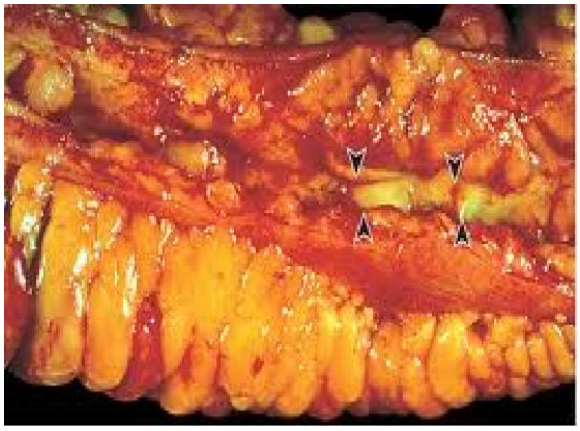
***Address for correspondence:**
Sugandha G. Chaudhari
Department of Pharmacology, Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar, Maharashtra, India.
E-mail: Chaudharisg@gmail.com

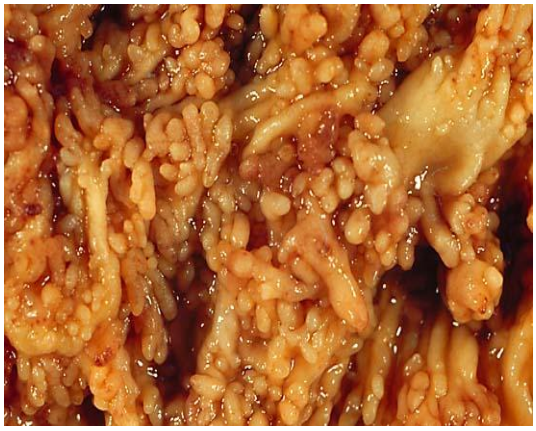
INTRODUCTION

Inflammatory bowel disease is multifactorial disease it involves an immune reaction against intestinal tract. The two major types of IBD are Ulcerative colitis and Crohn's disease. Ulcerative colitis is restricted in colon whereas Crohn's disease can involve gastrointestinal tract from mouth to anus.

Ulcerative colitis is characterized by the thinning and continuous inflammation of colon wall without intermittent healthy tissue. It shows ulcerated mucus lining of the large intestine and it never progresses beyond the inner lining. Ulcerative colitis is devoid of granuloma formation. Patient with ulcerative colitis often feel pain in lower left of the abdomen.



Crohn's disease



Ulcerative colitis

Figure 1: Polyps formation in Crohn's Disease and in Ulcerative colitis

Crohn's disease is characterized by the thickened colon wall with 'cobblestone' appearance due to intermittent healthy tissue. It shows deep ulceration and might extend to the all layer of bowel wall. Granuloma formation is the best isolating symptoms of Crohn's disease from Ulcerative colitis. Granuloma are inflamed cell localize and lumped together to form lesion. Patient with Crohn's disease feel the pain in lower right of the abdomen.

Ulcerative colitis and Crohn disease share many extra intestinal manifestations but some of these occur more commonly with either of one. Extra intestinal manifestations of IBD include iritis, episcleritis, arthritis, and skin involvement, as well as pericholangitis and sclerosing cholangitis. Systemic symptoms are common in IBD and include fever, sweats, malaise, and Arthralgias.

The rectum is always involved in ulcerative colitis, and the disease primarily involves continuous lesions of the mucosa and the sub mucosa. Both ulcerative colitis and Crohn's disease usually have waxing and waning intensity and severity. When the patient shows symptoms and significant inflammation then disease is in an active stage (the patient is having a flare of the IBD).When inflammation insignificant or is absent or less and patient doesn't show any symptoms, then it is considered to be remission.

EPIDEMIOLOGY

United States statistics

Earlier, incidence of ulcerative colitis was higher than that of Crohn's disease. But recently found that the cases of Crohn's disease are approaching that of ulcerative colitis which reflects high recognition and diagnosis rate.

An estimated 1-2 million people in the United States have ulcerative colitis or Crohn's disease, with an incidence rate of 70-150 cases per 100,000 individuals. Among persons of European descent in Olmstead County, Minnesota, the incidence of ulcerative colitis was 7.3 cases per 100,000 people per year with a prevalence of 116 cases per 100,000 people, and the incidence of Crohn's disease was 5.8 cases per 100,000 people per year, with a prevalence of 133 cases per 100,000 people [1-3].

The prevalence of IBD among Americans of African descent is estimated to be the same as the prevalence among Americans of European descent, but the prevalence is lower among Americans of Asian and Hispanic descent. The incidence of IBD among white individuals is approximately 4 times that of other races, with the highest rates reported to be in Jewish populations, followed by non-Jewish white populations. The prevalence rates of IBD among the American Jewish population are approximately 4-5 times that of the general population. In fact, however, data suggest that the incidence rates in non-Jewish, black, and Hispanic populations are increasing.

The male-to-female ratio is approximately equal for ulcerative colitis and Crohn's disease, with females having a slightly greater incidence. Both diseases are most commonly diagnosed in young adults (i.e., late adolescence to the third decade of life).

Incidence of IBD is higher in people of age 15-40 years and is low in young children and elderly person. Of IBD patients, 10 % are younger than 18 years.

International statistics

The incidence of IBD varies within different geographic areas, with the highest rates assumed to be in developed countries and lowest in developing regions; colder climate regions and urban areas have a greater rate of IBD than those of warmer climates and rural areas. Internationally, the incidence of IBD is approximately 2.2-14.3 cases per 100,000 person-years for ulcerative colitis and 3.1-14.6 cases per 100,000 person-years for Crohn disease. Overall, the combined incidence for IBD is 10 cases per 100,000 annually [1, 2].

ETIOLOGY OF INFLAMMATORY BOWEL DISEASE

The exact cause of development of IBD is unknown. Therefore, IBD is called an idiopathic disease.

An unknown factor or reagent provokes the immune reaction which progresses continuously without any regulation, which leads to the disruption of intestinal mucosa and underlying layers. This factor can be

Genetic, infectious, immunologic, and psychological.

There is involvement of genetic changes or translocations or mutations (or may be its susceptibility) to the development of Inflammatory bowel disease. However, the factor which can trigger the immune system has yet to be identified. Factors that can turn on the body's immune system include an infectious agent (as yet unidentified), an immune response to an antigen (eg, protein from cow milk), or an autoimmune process. The intestines are always exposed to things that can provoke immune reactions and leads to the pathogenesis. In other words there is a failure of the body to turn off normal immune responses [4].

Genetics

Persons with IBD have a genetic predisposition (or, perhaps, susceptibility) for the disease and many studies has been undertaken to discover the potential gene linked to IBD. *NOD2 (CARD15)* gene identified on earlier discovery chromosome 16 (IBD-1) is the first gene which is associated with IBD. Studies have also shown IBD susceptibility genes on chromosomes 5 (5q31) and 6 (6p21 and 19p). *NOD2/CARD15* is a polymorphic gene involved in the innate immune system. It is important to note that they appear to be permissive (i.e., allow IBD to occur) but not causative (i.e., its presence doesn't cause the disease) [5].

Smoking

The risk of developing ulcerative colitis is higher in nonsmokers and former smokers than in current smokers. The onset of ulcerative colitis occasionally appears to coincide with smoking cessation. This does not imply that smoking would improve the symptoms of ulcerative colitis; interestingly, some success in the use of nicotine patches has been reported. Instead, patients with Crohn's disease have a higher incidence of smoking than the general population, and those patients with Crohn's disease who continue to smoke appear to be less likely to respond to medical therapy.

PATHOPHYSIOLOGY

The pathophysiology of IBD is under active investigation. The common end pathway is inflammation of the mucosal lining of the intestinal tract, causing ulceration, edema, bleeding, and fluid and electrolyte loss.

Many inflammatory mediators involved in pathogenesis and clinical characteristic of these disorders. Cytokines released from macrophage due to the antigenic stimuli, which binds to their respective receptor and produces autocrine, paracrine and endocrine effects. Cytokines differentiates the lymphocytes into different types of T-cells. Th-1(Helper T cell-1) are associated with Crohn's disease and Th-2 are associated with Ulcerative colitis [6].

Several animal models are used to study IBD. A local irritant like acetic acid, Trinitrobenzen sulphonic acid (TNBS) is administered intra-rectally to mice, rats and rabbits to induce ulcerative colitis. Interleukin-10 (IL-10) knockout mice have some characteristics similar to those of a human with IBD. The cotton-top marmoset, a South American primate, develops colitis very similar to ulcerative colitis when the animal is subjected to stress.

Ulcerative colitis

In Ulcerative colitis, inflammation begins in rectum and extends to the proximal colon in uninterrupted fashion, which eventually progresses into entire length of large intestine. Rectum is always involved in Ulcerative colitis and it is continuous without any 'skip areas'.

Approximately, in 25% cases the disease remains confined to the rectum and in other cases ulcerative colitis spreads proximally and contiguously. Pancolitis occurs in 10% of patients. The small intestine is never involved in Ulcerative colitis.

When the distal terminal ileum is inflamed in a superficial manner, it is referred as backwash ileitis. Even with less than total colonic involvement, the disease is strikingly and uniformly continuous. As ulcerative colitis becomes chronic, the colon lacks its usual haustral markings, becomes a rigid shortened tube that leading to the lead pipe appearance observed on barium enema. The inflammation is commonly superficial (i.e. Mucosal) with infiltration of lymphocytes and granulocytes. Histologically shows loss of goblet cells and crypt cell abscesses [7].

Many factors are responsible for the stimulation of immune response. Many

microorganisms when come in contact to colonocyte it adheres mucosa and then it provoke the immune reaction through release of some chemicals or dysregulating the epithelial lining or barrier e.g. Helicobacter pylori, pathogenic strain of E.coli. Some genetic mutations in NOD gene, smoking and many other unknown factors can lead to the ulceration through Th-2 cells. Ulcerative colitis thought to be Th-2 mediated yet remain to prove.

Figure 2: Endoscopy of Ulcerative Colitis Patient

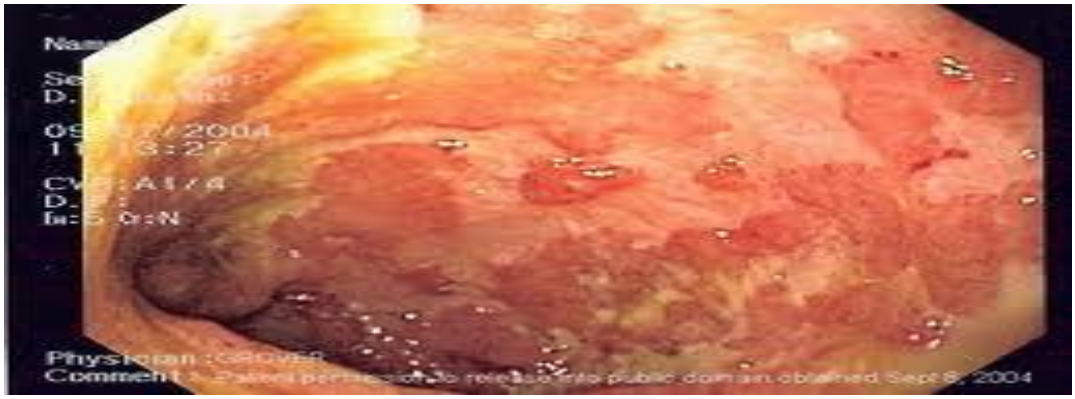
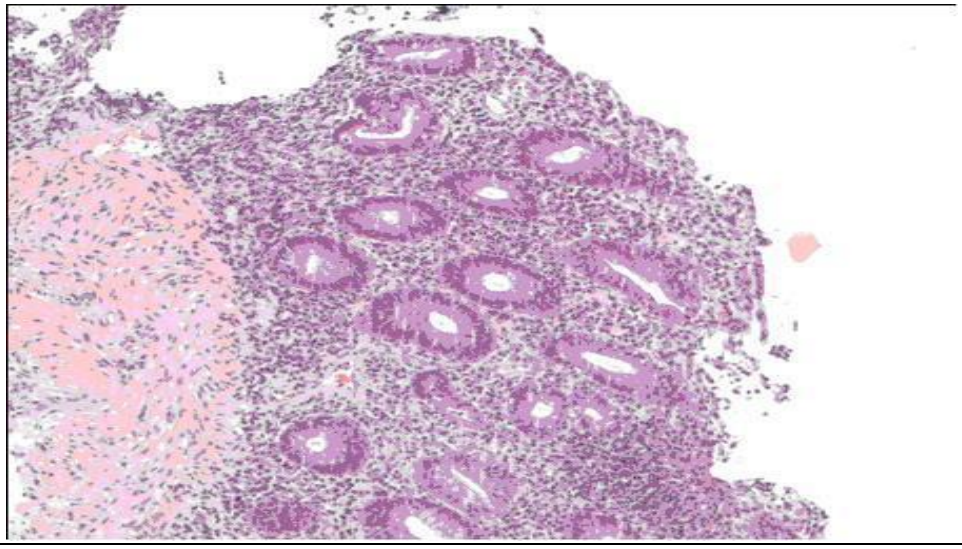


Figure 3: Histologically shows Loss of Goblet Cells and Crypt Cell Abscesses



IL-5 increases which is Th-2 cytokine but not IL-4 which is another Th-2 cytokines. IgG increases which also indicate Th-2 activation. Th-2 cells releases the IL-4, IL-5 and other cytokine stimulates the Natural killer cells through various T-cell receptors. NKT releases the IL-13 which is toxic to epithelial lining leads to the inflammation. Oxazolone induced colitis in lab animals is based on the same principle [6].

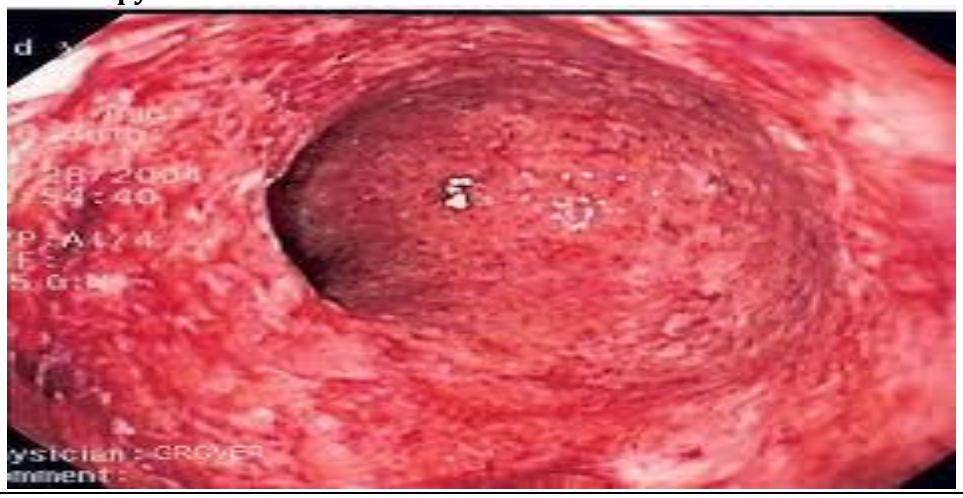
An increased amount of colonic sulfate-reducing bacteria has been observed in some patients with ulcerative colitis, resulting in higher concentrations of the toxic gas hydrogen sulfide. The role of hydrogen sulfide in pathogenesis is unclear. It has been suggested that the protective benefit of smoking that some patients report is due to hydrogen cyanide from cigarette smoke reacting with hydrogen sulfide to produce the nontoxic isothiocyanate. Another unrelated study suggested sulphur contained in red meats and alcohol may lead to an increased risk of relapse for patients in remission [8].

Crohn's disease

Crohn's disease can affect any portion of the GI tract from the mouth to the anus. It causes 3 patterns of involvement: inflammatory disease, strictures (abnormal narrowing of the passage), and fistulas (an abnormal passage that leads from an

abscess or hollow organ or part to the body surface or from one hollow organ or part to another). This disease involves intermittent non- specific granulomatous inflammatory processes. The most important differentiating feature of Crohn's disease from Ulcerative colitis is involvement of all layers of bowel (Transmural) not just mucosa or sub mucosa. Furthermore, Crohn disease is discontinuous, with skip areas interspersed between one or more involved areas [9].

Figure 4: Endoscopy of Crohn's Disease Patient



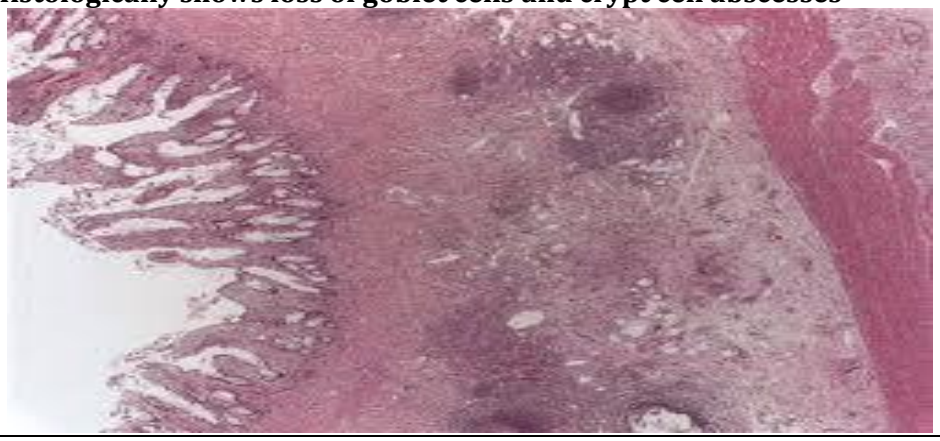
Late in the disease, the mucosa develops a cobblestone appearance, which results from deep, longitudinal ulcerations interspersed with intervening normal mucosa. The 3 major patterns of involvement in Crohn's disease are disease in the ileum and cecum (40% of patients); disease confined to the small intestine (30% of patients); and disease confined to the colon (25% of patients). Rectal sparing is a typical but not constant feature of Crohn disease. However, anorectal complications (e.g. fistulas, abscesses) are common. Much less commonly, Crohn's disease involves the more proximal parts of the GI tract, including the mouth, tongue, esophagus, stomach, and duodenum. Biopsies may also show chronic mucosal damage, as evidenced by blunting of the intestinal villi, atypical branching of the crypts, and a change in the tissue type (metaplasia). One example of such metaplasia, *Paneth cell metaplasia*, involves development of Paneth cells (typically found in the small intestine) in other parts of the gastrointestinal system [10].

Underlying pathophysiology involves Th-1 cells. Due to various factors may be genetic or environmental Th-1 cells get stimulated and triggers cell mediated immune response. Th-1 cell releases IL-12 which in turn increases Th-1 response and upregulate the macrophage leading to the cycle of uncontrolled inflammation by releasing INF-γ, TNF-α and other mediators. TNF-α binds to TNF-R1 or R2 receptors and initiate the NF-κB mediated inflammation, Activation of MAPK pathway , cell death signaling which leads to cell damage. IFN-γ can further activate macrophage and natural killer cells which synergize the inflammation [11-13].

Patient with Crohn's disease are more prone to kidney stone and gallstone because of malabsorption of fat and bile salt. Gallstone is formed due to reduced bile salt pool which leads to increasing cholesterol concentration in bile.

Patients who have Crohn's disease with ileal disease are also likely to form calcium oxalate kidney stones. With the fat malabsorption, unabsorbed long-chain fatty acids bind calcium in the lumen. Oxalate in the lumen is normally bound to calcium. Calcium oxalate is poorly soluble and poorly absorbed; however, if calcium is bound to malabsorbed fatty acids, oxalate combines with sodium to form sodium oxalate, which is soluble and is absorbed in the colon. The development of calcium oxalate stones in Crohn disease requires an intact colon to absorb oxalate. Patients with ileostomies generally do not develop calcium oxalate stones.

Figure5: Histologically shows loss of goblet cells and crypt cell abscesses



TREATMENT AVAILABLE

At the present time, there are five basic categories of medications used in the treatment of IBD. They are:

- Aminosalicylates
- Corticosteroids
- Immunomodulators
- Antibiotics
- Biologic therapies

Medical treatment for Crohn's disease and ulcerative colitis has two main goals: achieving *remission* or cure symptoms and, once that is accomplished, *maintaining* remission. To accomplish these goals, treatment is aimed at controlling the ongoing inflammation in the intestine—the cause of IBD symptoms [14-16].

There is no proper regimen available to treat and prevent remission of IBD. It depends on diagnosis of disease. It requires proper diagnosis by pathological, radiological and endoscopic examination. Treatment is not only based on medical therapy but also on careful attention to details and judicious common sense.

Despite advances in medical therapies, some people with IBD eventually will require surgery—either to control their disease or to address various complications. Surgical intervention is integral to the care of people with IBD, and surgical consultants experienced in IBD are vital to proper treatment.

TARGET FOR IBD

A. NF- B and ICAM cascade

The NF-kB pathway is prompted by proinflammatory cytokines such as TNF-α and IL-1β. As shown in figure TNF-α and IL-1β actually activate NIK via different receptors. Regardless, the signal converges with NIK which then degrades IkB. The degraded protein then releases NF-kB which translocates to the nucleus and promotes the transcription of ICAM-1. The resultant NF- kB response is the most common inducer of ICAM-1 in cells

Interferon gamma (IFN-g) also has a signaling effect on the transcriptional control of ICAM-1. As ICAM-I is adhesion molecule and require for the localization of phagocytes by blocking this pathway phagocyte localization can be stopped which helps in preventing disease to get worse [17].

B. COX and PGE_2

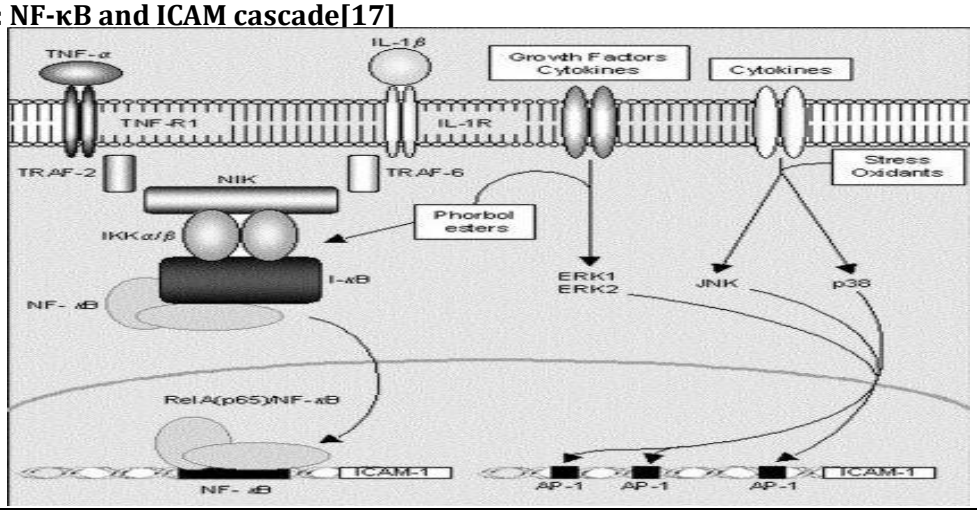
Fatty acid cyclo-oxygenase (COX) are of two types Cox-1 and Cox-2. Cox-2 is responsible for the formation of many inflammatory mediators which includes prostaglandinE_2 which contracts bronchial and gastrointestinal smooth muscle stimulates intestinal fluid secretion, potent vaso-dilator and hyperalgesic. This pathway normally acts in late phase of IBD which helps in disease progression. So, by blocking activity of Cox-2 selectively inhibit the inflammation which can aid in curing IBD. Non-steroidal anti-inflammatory drug acts by this pathway [18].

C. T-cells involvement in IBD

Whenever any antigen comes in contact then primary mechanism comes in action and macrophage and other phagocytic cell engulf antigen. Macrophage further processes the antigen and becomes antigen presenting cell which presents MHC class II cell on its surface with specific antigen protein. This cell is then binds to Th-0 cell

by MHC class II complex and T-cell receptor. This binding is aided by CD4 and CD28 receptor as shown in figure-8. Depending on the antigen Th-0 cell differentiate into Th-1 or Th-2 cells. When cell differentiate in to Th 1 cell and its over expression can lead to Crohn's disease. Unregulated immune response to Th-2 cells can leads to ulcerative colitis. IL-4 is Th-2 cell marker can helps in diagnosis of disease [19].

Figure 6: NF-κB and ICAM cascade[17]



D. <u>NO and iNOS pathway</u>

Macrophages are important for early immune reaction to invading microorganisms and the production of nitric oxide (NO) is central to this function. NO is generated by inducible nitric oxide synthase (iNOS, macNOS, Type II NOS) following exposure to certain cytokines, such as interferon-g (IFN-g). When interferon or other cytokines binds to the receptor results in dimerisation of receptor brings Janus Kinase (JAK) into close proximity and Trans phosphorylate each other in turn it phosphorylate specific Signal transducer and activators of transcription (STAT) Proteins. Activated STAT dimerise and translocates to nucleus by transporter mechanism where it binds to DNA and increase expression of the transcription factor, IRF-1, that,in turn bind to specific iNOS gene promoter region increases inducible-NO synthase gene expression and which increases NO production and release as iNOS is soluble enzyme and doesn't require elevated intra cellular Ca^{++} levels for activation which is require for eNOS and nNOS. Nitric oxide is responsible for early inactivation of microorganism before other immune response activate. As in IBD expression of iNOS is high so by blocking any component in this pathway can help in preventing the pathogenesis for example blocking JAK by JAK inhibitor can prevent further cycle but till date JAK inhibitors are still in clinical phase for anti inflammatory activity [19,20].

Figure 7: T-cell pathway and involvement of this pathway in IBD

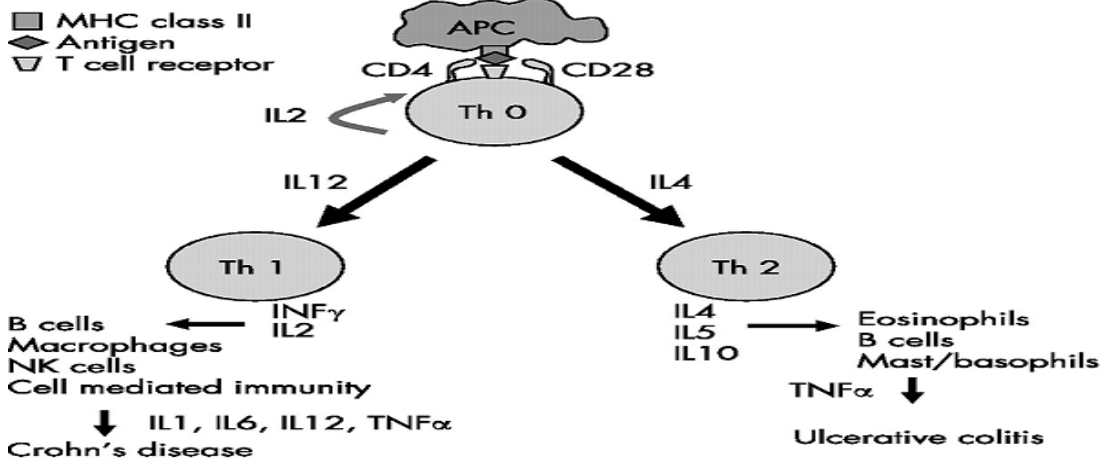
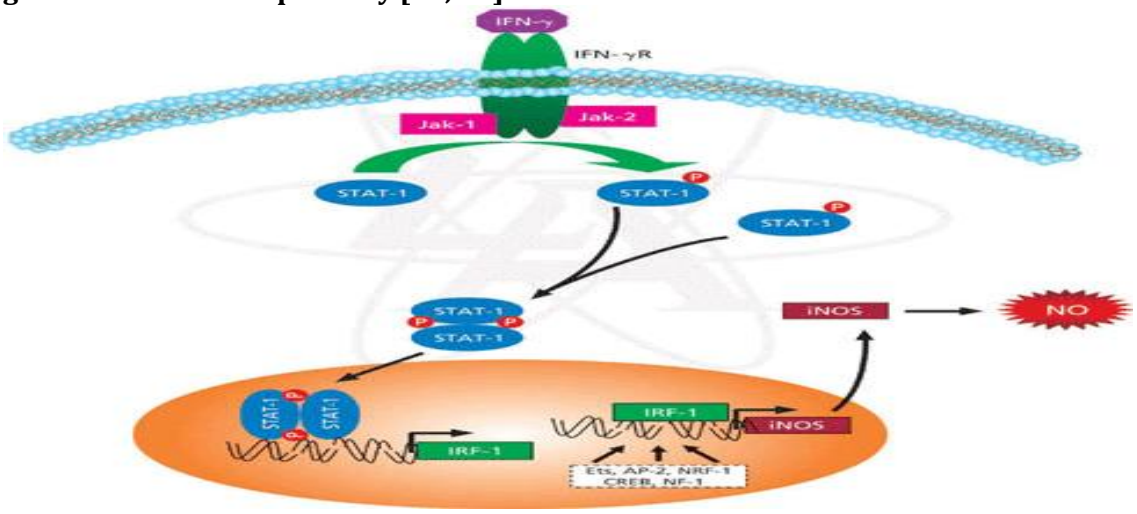


Figure 8: NO and iNOs pathway [19, 20]



IFN-γ Interferon-γ
IFN-γ R Interferon-γ receptor
STAT Signal transducers and activated transcription
Jak Janus Kinase
iNOS inducible nitric oxide synthase

CONCLUSION

Inflammatory bowel disease is an idiopathic and multifactorial disease affecting many part of the immune system. By knowing the pathophysiology many targets for the treatment of IBD comes into the scenario. Inhibitors of NF-κB and ICAM pathway, Cox and PGE_2 pathways and effecting mechanism, NO and iNOs pathway, and T-cell mainly get involved in the pathophysiology of the disease. Targeting these pathways can open a way for finding a efficient cure for IBD.

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