CHAPTER

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Advances in the Management of Inflammatory Bowel Disease

G. Ray

Introduction

In the decades since the major form of Idiopathic Inflammatory Bowel disease (IBD) were defined on the basis of clinical manifestations, investigators have been challenged to identify the fundamental patho-physiologic processes underlying the enigmatic disorders, and clinicians have struggled to provide effective therapy for the often dismaying clinical manifestations[1]. IBD is thought to result from inappropriate and ongoing activation of the mucosal immune system driven by the presence of normal luminal flora.

Immune Response and Inflammatory Pathways

The aggregate effect of Genetic, Environmental and other processes is the sustained activation of mucosal immune responses. It remains unclear whether the immune system is activated as a result of an intrinsic defect or because of continued stimulation resulting from a change in the epithelial mucosal barrier. Substantial progress has been made in characterizing immune cell populations and inflammatory mediators in patients with inflammatory bowel disease. There is reasonable consensus that the mucosa of patients with established Crohn's Disease is dominated by CD4+ lymphocytes with a type -1 helper T-cells(Th-1) phenotype, characterized by the production of Interferon γ, TNF α and IL- 12. In contrast the mucosa in patients with ulcerative colitis may be dominated by CD4+ lymphocytes with an atypical type-2 helper T cell (Th-2) phenotype, characterized by the production of IL-4, IL-5, & IL-13.[2]

Signal Transduction Pathway

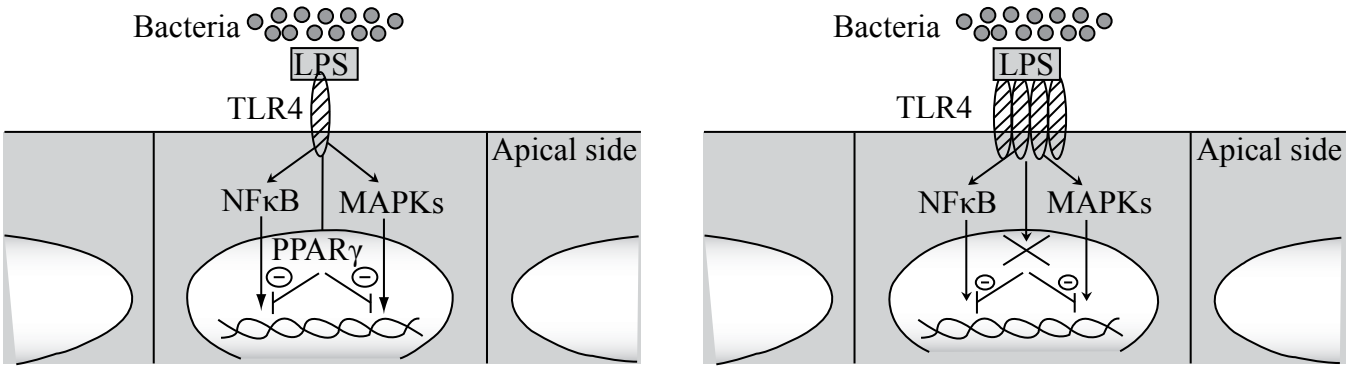
This pathway occurs through activation of two nuclear factors like NF κB and MAPK. These two factors are involved in inflammation leading to production of various cytokines, chemokines, and proliferation of inflammatory cells and expression of adhesion molecules.

Activation of these nuclear factors is regulated by another nuclear factor PPARγ, which down regulates inflammation.

PPARγ is a nuclear factor which was discovered in mammals in 1993, and was expressed in adipose tissue and involved in regulation of insulin resistance. In the recent years it has been recognized in many other tissues and next to adipose tissue, it is found most frequently in colon and ileum. There is now emerging interest in the role of this receptor in the regulation of gut homeostasis.[3]

In normal person the intestinal epithelium expresses TLR4 on the surface which attracts the LPS of the bacteria and leads to activation of TLR4, which in turn leads to induction of PPARγ

Figure 1



expression. PPARγ expression down regulates the NFκB and MAPK pathways and controls inflammatory response. In patients of inflammatory bowel disease there is up regulation of TLR4 expression and impaired expression of PPARγ on the epithelial cells which might lead to heightened inflammatory response and colitis (Fig. 1).

Treatment

Until the introduction of anti-inflammatory therapies in the middle of last century, inflammatory bowel disease was a potentially lethal disorder, that could only be treated by surgery. The discovery of therapeutic efficacy of Salazopyrine and Corticosteroids for the ulcerative colitis and subsequently Crohn's disease has importantly changed the prognosis of patients with inflammatory bowel disease, and the life expectancy of these patients is now similar to healthy subjects. Immunosuppressive drugs in particular, Azathioprine, 6-Mercaptopurine and Methotrexate are effective for remission induction and maintenance of Crohn's disease; Azathioprine is also used for remission maintenance in ulcerative colitis, with the exception of Cyclosporine which has no efficacy in Crohn's disease, and limited efficacy in severe ulcerative colitis. With the exceptions of variations in corticosteroid / Salazopyrine theme, no effective small molecules have developed for the treatment of IBD in the past 50 years. Recently "biologicals" (monoclonal antibodies, therapeutic peptides, antisense oligonucleotides) have attracted significance interest as novel anti-inflammatory or immunomodulating approaches in IBD, and at least one such approach i.e. TNFα binding monoclonal antibody has been a breakthrough in the treatment of therapy refractory Crohn's disease. However compared to small molecules "biologicals" have certain disadvantages, including restrictions to non-oral routes of administration, immunogenicity and high cost. More over newer therapies for IBD are still needed, because standard therapies fail to induce remission in about 30% of patients, and because of the relative inefficacy of current maintenance therapies.[4]

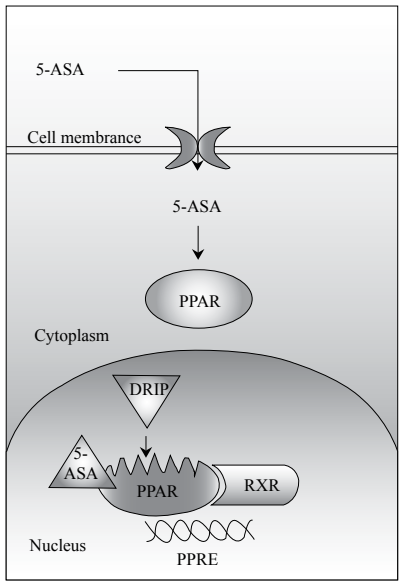
The treatment of IBD can be accomplished by 4 groups of molecules:

1. Anti inflammatory therapies
2. Immunosuppressive drugs
3. Biologicals
4. Small Therapeutic molecules

Antiinflammatory Drugs

5-Aminosalicylic acid based compounds have remained mainstay of treatment for patients with mild to moderately active ulcerative colitis and Crohn's disease since the recognition of the therapeutic efficacy of the prototypical agent Sulfasalazine. Early studies demonstrated that 5-Aminosalicylate was the functionally active moiety of this Sulfapyrizine congener. 5-ASA acts as a functional synthetic ligand for PPARγ in colonic epithelial cells[5]. After oral administration,

Figure 2



5-ASA crosses the cell membrane of the epithelial cell through a transporter and binds to PPARγ in the cytoplasm. 5-ASA then induces its nuclear translocation, promotes a PPARγ conformational change, and recruits the co-activator DRIP, leading to formation of a heterodimer between PPARγ and Retinoid X receptor (RXR), and activation of PPARγ response element (PPRE), which ultimately leads to inhibition of NFκB and MAPK (Fig. 2).

Corticosteroids have been used when 5-ASA based compounds are inadequate. They presumably act through the same functional properties relevant to other inflammatory processes, though which among these may be especially important in IBD has not been determined. The effects of corticosteroid include inhibition of the expression of pro-inflammatory cytokines, adhesion molecules, MHC Class II molecules, Leukotrienes, Elastase, Collagenase, and Nitric Oxide synthetase. Glucocorticoids bind to a cytoplasmic receptor found in all cells and then enter the nucleus to bind Glucocorticoid response elements on the chromosomal DNA, there by producing a variety of down stream physiologic effects. The anti-inflammatory effects of Glucocorticoids may follow from down regulation of NFκB and induction of Inhibitory κB. Direct cellular effects may also occur, with reduced phagocytic activity of neutrophils and in some situation apoptosis of lymphocytes[6].

Glucocorticoids are effective for short term control of symptoms of Crohn's disease but are neither effective nor safe for long term maintenance of response. Similarly glucocorticoids have no maintenance benefit in Ulcerative colitis and some patients may be dependant on steroids in which case it is necessary to depend upon immunomodulatory agents.

Immunomodulators

Azathioprine and 6MP have been extensively used immunosuppressive agents in IBD. The actual mechanism of action of these drugs remain unknown but may include suppressing the generation of a specific and long lived subgroup of T-cells which might account for the prolonged time needed to achieve a therapeutic response. Clinical studies have shown that these agents are efficacious when they are given in adequate doses in patients with IBD, allowing a gradual decrease in corticosteroids and prolonging remission. The onset of benefit takes several weeks and may require upto six months, so that these drugs are not useful in the control of acute disease activity and conversely should be used when prolonged therapies planned. The immuno- suppressants who have been tried in IBD with variable results are methotrexate, cyclosporine, tacrolimus and mycophenolate mofetil. The inherent adverse reactions, the excess cost and lack of conclusive significant benefit in long term clinical trials have prohibited their regular use in IBD.

Biological Therapy

Anti – TNF therapy - Infliximab is the prototypical anti- TNF agent, has offered an important advance in the therapy of IBD and is approved by US FDA for treatment of Crohn's disease[7] and UC.[8] This chimeric monoclonal antibody, composed of complement fixing "human" IgG_1 constant region and a murine derived antigen- binding variable region, binds soluble TNF. However its action is thought to be in part on its ability to bind precursor

cell-surface TNF, perhaps leading to monocyte apoptosis. Though Infliximab is approved for therapy in IBD, it has certain complications like reactivation of Tuberculosis, Lupus like syndrome and development of Lymphoma in some cases. Its excessive cost also limits its use in general population.

Anti-Adhesion Molecule therapy - They have been evaluated in UC. Adhesion molecules are glycoproteins expressed on the surface of endothelial cells and lymphocytes and are important in cellular trafficking in IBD. The anti adhesion molecules are Natalizumab and MNL.O2 have been found to be effective in achieving remission in UC[9].

Other Biological therapies - Daclizumab and Hasiliximab are the monoclonal antibodies against IL-2 and Visilizumab, an antibody against CD3, have shown promise in some trials. There has been a recent interest in the use of Thalidomide in the treatment of Crohn's disease, because of its presumptive action in blocking the production of TNF through the inhibition of intracellular pathways;[10] besides it has anti angiogenic properties. But potent teratogenicity of this agent requires rigorous supervision, including confirmation of adequate contraception in patients of child bearing age.

Probiotic therapy - Though antibiotics have a limited role in IBD, recent studies have shown promising results with the use of probiotics. Saccharomyces boulardii has unique action on inflammation by a specific alteration of the migratory behavior of T-cells, which accumulate in mesenteric lymph nodes. Therefore S. boulardii limits the infiltration of inflammation induced by pro-inflammatory cytokine production. This has been shown in experimental mice and to be proved in clinical trials[11].

Small Therapeutic Molecules

PPARγ— belongs to the nuclear receptor family considered as important target in the development of new drugs. It is an essential nuclear factor controlling the expression of a large number of regulatory genes in lipid metabolism and insulin sensitization, as well as in inflammation and cell proliferation.[12] In addition to adipose tissue, colon is the major tissue expressing PPARγ in the epithelial cells and to lesser degree in macrophages and lymphocytes.[13] PPARγ activation requires heterodimerisation of in the nucleus of the cells with nuclear receptor, known as Retinoid X receptor α (RXR α) (Fig. 3), leading to binding of this heterodimer to specific DNA sequence element termed Peroxisome Proliferator Response element (PPRE). These two nuclear factors play a central role in the regulation of inflammatory signaling pathways by acting on kinases and transcription factors such as nuclear factor κB (NFκB), c-Jun, c-fos and nuclear factor of activated T-cell (NFAT). This leads to inhibition of mucosal production of inflammatory cytokines (IL-1 β and TNF α), chemokines, proliferation of inflammatory cells and expression of some adhesion molecules (Fig 4). Administration of agonistic ligands of PPARγ attenuated the severity of TNBS colitis in mice; this was shown to be associated with reduction of activation of NFκB, colonic MAP p38 activity and JNK (c-Jun NH_2 terminal kinase) activation resulting in reduced production of pro-inflammatory cytokines. On this backdrop, Natural and synthetic ligands of PPARγ have been recognized which can be used in the future for treatment of IBD. These ligands attach themselves to the ligand binding pockets in PPARγ and leads to its activation. These ligands are divided into two groups:-

Natural Ligands

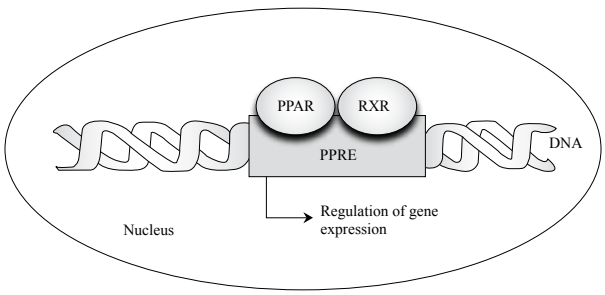
a. PUFAS – Omega 3, Omega 6, Omega 9, and Nitrolinoleinic acid (LNO2)
b. Eicosanoids – 15 deoxy- prostaglandin J_2
c. Miscellaneous – Lysophosphatidic acid 9-tetrahydro cannabinoid

Synthetic Ligands

a. **Glitazones**-(Pioglitazone and Rosiglitazone) One open level pilot trial has evaluated the efficacy of the PPARγ ligand Rosiglitazone (4

mg orally twice daily) in 15 patients with active UC, refractory to conventional treatment with either corticosteroids or immunomodulators and 5-ASA. After 12 weeks treatment of Rosiglitazone, a substantial decrease in disease activity index score was reported with clinical and endoscopic remission in 27% and 20% respectively. This study in IBD patients leads to new clinical trials in IBD with these chemical compounds, and may lead to the development of safer PPARγ agonist with topical effects and targeting selectively the colon.[14] Glitazar is a novel family of dual acting PPARα/γ agonist developed as an oral treatment in diabetes and dyslipidemia. 5-ASA is also a ligand of PPARγ and its mechanism of action has been described earlier. Though old in the treatment of IBD, the discovery that ASA is a new topical ligand for PPARγ in the colonic epithelial cells paves the way for development of new molecules specifically targeting intestinal PPARγ.

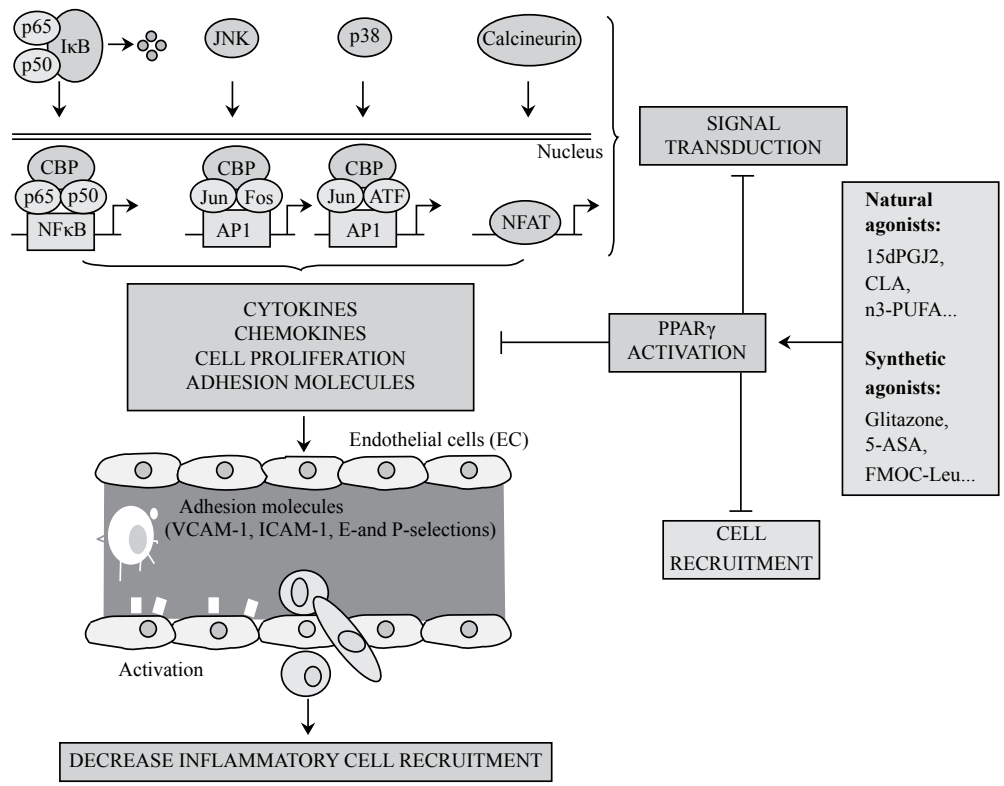
Figure 3



TNFα Converting Enzyme Inhibitor (TACE)

The post translational processing of TNFa includes cleavage of membrane bound TNF precursor molecule by a metalloprotease known as TACE. This enzyme also cleaves several other membrane bound proteins including CD-16, CD-27 and two TNF receptors. TACE is an interesting target for therapy of IBD, because structure function relations are well known and have allowed the development of (Hydroxamate based) small molecular inhibitors. In a phase II clinical trial on low dose endotoxemia in volunteers, TACE inhibition dramatically reduced the amount of LPS induced circulatory

Figure 4



TNFα. The TACE inhibitors that are currently available for use in clinical trials are not very specific and also inhibited other ADAM (a disintegrin and metaloprotease) family members. Because of the above speculations TACE remain an interesting target for development of anti-inflammatory small molecules. However further development requires generation of molecules with much greater TACE specificity than these that have been studied to date. It should be noted that the effects of specific TACE inhibitors are not restricted to membrane bound TNFα, because several other membrane expressed molecules are cleaved by TACE[4].

Signal Transduction Inhibitor

Several interacting cascades of signaling molecules regulate cellular death and survival. The importance of the transduction pathways for cytokine production and inflammation came through two independent lines of research that led to the identification of MAP kinases as regulators of the transcription and translation of TNFα. It is now known that at least three tightly linked signal transduction pathways regulate the production of pro-inflammatory cytokines i.e. the NFκB, MAPK, and JNK pathways. Not only are these pathways, regulators of cytokine production, all three pathways also act as down stream of several receptors of pro-inflammatory cytokines. There is now evidence that activation of all these pathways occur in inflammatory bowel disease and with the exception of JNK, more or less specific inhibitors of these signal transduction pathways are available and are under various phases of clinical trial. These inhibitors are future targets for treatment of IBD.

Conclusion

It is clear from the above discussion that there is still much work to be done to improve our understanding of pathogenesis and treatment of IBD. Older therapies certainly can be used more effectively; and new and emerging therapies offer intriguing possibilities. We are still quite a distance from the ultimate answer, but we are getting closer day by day.

Summary

IBD occurs due to activation of immune system in genetically predisposed persons, triggered by certain environmental factors. There is activation of CD4 lymphocytes and various signal transduction pathways leading to excessive production of pro-inflammatory cytokines, chemokines, and growth factors. These mediators enhance the inflammatory process itself and tissue destruction and eventually in the clinical manifestation of the disease. The conventional therapies like 5- ASA and corticosteroids have failed to induce and maintain remission in more than 30% of cases. The newer therapy like anti-TNFα (infliximab) has been recommended for treatment of IBD, but its excessive cost has limited its use. The future therapy has targeted PPARγ, a nuclear receptor, which is highly expressed in colonic epithelium in addition to adipocytes. Inadequate expression of PPARγ leads to activation of inflammatory cascade leading to IBD. The natural and synthetic ligands of PPARγ are recognized which lead to increased expression of PPARγ and suppression of bowel inflammations. These are the target molecules for future therapy of IBD. Besides certain small molecules for inhibition of signal transduction pathways of inflammation are under research and in the future, these molecules may prove to have promising result for management of IBD.

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