REVIEW ARTICLE

# Inflammatory bowel disease: exploring gut pathophysiology for novel therapeutic targets

**VIPUL YADAV, FELIPE VARUM, ROBERTO BRAVO, ESTHER FURRER, DANIELA BOJIC, and ABDUL W. BASIT**

**LONDON, UK AND RHEINFELDEN, SWITZERLAND**

**Ulcerative colitis and Crohn's disease are the 2 major phenotypes of inflammatory bowel disease (IBD), which are influenced by a complex interplay of immunological and genetic elements, though the precise etiology still remains unknown. With IBD developing into a globally prevailing disease, there is a need to explore new targets and a thorough understanding of the pathophysiological differences between the healthy and diseased gut could unearth new therapeutic opportunities. In this review, we provide an overview of the major aspects of IBD pathogenesis and thereafter present a comprehensive analysis of the gut pathophysiology leading to a discussion on some of the most promising targets and biologic therapies currently being explored. These include various gut proteins (CXCL-10, GATA-3, NKG2D, CD98, microRNAs), immune cells recruited to the gut (mast cells, eosinophils, toll-like receptors 2, 4), dysregulated proinflammatory cytokines (interleukin-6, -13, -18, -21), and commensal microbiota (probiotics and fecal microbiota transplantation). We also evaluate some of the emerging nonconventional therapies being explored in IBD treatment focusing on the latest developments in stem cell research, oral targeting of the gut-associated lymphoid tissue, novel anti-inflammatory signaling pathway targeting, adenosine deaminase inhibition, and the beneficial effects of antioxidant and nutraceutical therapies. In addition, we highlight the growth of biologics and their targets in IBD by providing information on the preclinical and clinical development of over 60 biopharmaceuticals representing the state of the art in ulcerative colitis and Crohn's disease drug development. (Translational Research 2016;176:38–68)**

**Abbreviations:** UC = Ulcerative Colitis; CD = Crohn's Disease; IL = Interleukin; GALT = Gut-Associated Lymphoid Tissue; ADA = Adenosine Deaminase; APC = Antigen Presenting Cells; NF-$_K$B = Nuclear Factor Kappa B; IFN = Interferon; DSS = Dextran Sodium Sulfate; STAT = Signal Activator of Transcription; SMAD-7 = Mothers Against Decapentaplegic Homolog 7; ECP = Eosinophil Cationic Protein; EPX = Eosinophil Protein X; EPO = Eosinophil Peroxidase; CARD = Caspase Recruitment Domain Family Member; TLRs = Toll-Like Receptors; TNF-$\alpha$ = Tumor Necrosis Factor Alpha; TGF-$\beta$1 = Transforming Growth Factor Beta 1; iv = Intravenous; sc = Subcutaneous; il = Intralesional; ic = Intracolonic; CAM = Cell Adhesion Molecule; ICAM = Intercellular Adhesion

From the UCL School of Pharmacy, University College London, London, UK; Tillotts Pharma AG, Rheinfelden, Switzerland.

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Reprint requests: Prof. Abdul W. Basit, UCL School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX, UK; e-mail: a.basit@ucl.ac.uk.

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Molecule; MAdCAM = Mucosal Vascular Addressin Cell Adhesion Molecule; LPS = Lipopolysaccharides; FcRn = Neonatal Fc Receptor; NKG2D = Natural Killer Activating Receptor 2D; HSP = Heat Shock Proteins; IP-10 = Interferon-$\gamma$-Inducible-Protein-10; MCP = Monocyte Chemoattractant Protein; MIP = Macrophage Inflammatory Protein; MMP = Matrix Metalloproteinases; GLP = Glucagon-like Peptide; FMT = Fecal Microbiota Transplantation; HSC = Hematopoietic Stem Cell; MSC = Mesenchymal Stem Cell; PDLIM2 = PDZ and LIM Domain 2; PTEN = Phosphatase and Tensin Homolog

## INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic relapsing idiopathic inflammatory disorder of the gastrointestinal tract leading to long-term impairment of gastrointestinal structure and function.[1] Ulcerative colitis (UC) and Crohn's disease (CD), the 2 main forms of IBD, share several pathological and clinical symptoms but also have markedly distinct features. In CD, the inflammation and damage to the mucosa can occur throughout the gastrointestinal tract but occurs more commonly in the terminal ileum and colon. It is transmural in nature and can affect all layers of the intestinal tissue. UC on the other hand is confined to the colon, most commonly affecting the rectum and distal colon (often extending from distal to proximal areas as disease progresses) and is characterized by inflammation restricted to the mucosal layer without affecting the deeper layers of the intestinal tissue.[2]

Approximately 1.4 million patients in the United States suffer from IBD, of whom around half have UC. Approximately 2.2 million people in Europe suffer from UC and CD.[3] Several factors have been proposed as possible causes of IBD, but no single agent or mechanism can fully explain all aspects of the disease etiology. Some of the proposed factors include environmental, genetic and/or psychological factors, as well as microbial infections and impaired mucosal immune system, which all appear to interact in a way to trigger a dysregulated mucosal immune response leading to chronic inflammation and potential irreversible damage to the gastrointestinal mucosal tissue.

The more conventional therapies for IBD treatment involve aminosalicylates and corticosteroids, generally indicated in mild-moderate condition, and immunosuppressive agents that are indicated in moderate-severe IBD cases. Mesalazine and corticosteroids are the first in line treatment in IBD, especially UC, but stable, long-term clinical and mucosal healing have not been observed with these agents which have also been associated with adverse effects. The immunosuppressive agents such as azathioprine or 6-mercaptopurine have been implemented to maintain steroid-free treatment but are not effective in inducing remission and require careful monitoring for adverse effects that include anemia, neutropenia, liver toxicity, and pancreatitis.[4] Owing to the limitations of efficacy and potential toxicity associated with these drugs, a new generation of biopharmaceuticals such as monoclonal antibodies infliximab, adalimumab, golimumab, certolizumab pegol, natalizumab, and vedolizumab has now been introduced in IBD management as more selective therapeutic agents, particularly in moderate to severe cases where the conventional therapies have failed. However, there is a potentially increased risk of malignancies, such as non-Hodgkin's lymphoma and nonmelanoma skin cancers and loss of response over time, seen in up to about 50% of patients on antitumor necrosis factor alpha (TNF-$\alpha$) antibodies.[5] These limitations highlight the therapeutic gaps in IBD treatment and provide a clear impetus to explore new targets and inflammatory pathways that can potentially direct the development and translation of more efficacious and safer therapeutic agents.

The aim of this review is to give an overview of the pathophysiological changes that occur throughout the gastrointestinal tract in IBD patients and their potential to be exploited as novel targets for the treatment of IBD.

## PATHOGENESIS OF IBD

**Immune response.** Both UC and CD have been associated with a defective innate and adaptive immune response, related to responses generated against the commensal microbiota. Activation of macrophages and dendritic cells in the lamina propria stimulates a proinflammatory response by secretion of cytokines such as interferon-gamma (IFN-$\gamma$), IL-1$\beta$, IL-6, IL-8, and IL-18. IL-12 and IL-23 are produced by inflammatory myeloid cells and influence the development of Th1 and IL-17 producing Th17 responses respectively, predominantly being observed in CD pathogenesis.[6]

UC pathogenesis has been more associated with an atypical Th2 response characterized by the production of transforming growth factor beta 1 (TGF-$\beta$) and IL-5.[7] Enhanced IL-13 production by an invariant natural killer T cell population in the lamina propria has been shown to be a prominent feature of the inflamed gut, driving inflammation in UC.[8,9] Studies in dextran sodium sulfate (DSS)–induced colitis models and pediatric UC patients have also demonstrated the