Immunology of Inflammatory Bowel Disease and Molecular Targets for Biologics

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KEYWORDS

• Immunology • IBD • Biologics • Innate immunity • Adaptive immunity

KEY POINTS

- Most of the recent advances in inflammatory bowel disease (IBD) have resulted from studies of mucosal immunity in the normal and inflamed intestine.
- Both murine models of IBD and human studies have shown dysfunction of the epithelial barrier, innate immune cells, and adaptive T cells in the pathogenesis of IBD.
- The insight gained from the study of the aberrant immune system in IBD has led to the identification of molecular targets in the immune system for the design of drugs, some of which are already being used in clinical practice with many others in various phases of development.
- Despite the increased knowledge gained from animal and human studies, many aspects of mucosal immunity remain unclear in patients with IBD.
- Recently, significant progress has been made in high-throughput technologies like genomic sequencing and mass cytometry that provide multiparametric data which can be used to not just define the various immune cells states but also assess how these interact with each other in a variety of conditions.

INTRODUCTION

Inflammatory bowel disease (IBD), specifically Crohn disease (CD) and ulcerative colitis (UC), are autoimmune diseases whose incidence and prevalence are increasing worldwide.[1] Over the last few decades, substantial progress has been made in

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understanding the pathophysiology of IBD, which has been translated into newer, more effective therapies (biologics) that have reduced flares, brought more patients into remission, and improved the quality of life of patients with IBD.[2–4] IBD is considered to be an immune-mediated disease that involves a complex pattern/interplay of host genetics and environmental influences.[5] Our knowledge of the immune system and its homeostatic imbalance is derived from mouse models of colitis and human studies involving clinical and laboratory experiments.

The immune system evolved in multicellular organisms/metazoans as a defense mechanism against pathogens like bacteria, protozoa, parasites, and fungi.[6] The human immune system can be broadly categorized into innate and adaptive based on the differences in timing of the response and specificity. The immune system comes in contact with a foreign challenge, which could be food, commensal flora, microbial pathogens, and xenobiotics at different sites like the skin, mucous membrane of lungs, gastrointestinal tract, and so forth. The human gastrointestinal tract, with a total surface area roughly equal to that of a tennis court (400 m^2), serves as the largest area of interface with the external environment. The gut mucosal immune system, which interacts with this large antigenic load, thus, has the most varied immune cells in the body. In a disease-free host, there is a fine balance between a protective and deleterious response of the immune system, which becomes perturbed in patients with IBD. To understand these perturbations in IBD that produce a disease state, it is necessary to first understand how the intestinal immune system works. In this review, the authors divide their article into subsections of innate and adaptive immunity and link it with the currently identified abnormalities in these pathways in IBD. In addition, the authors have summarized in **Table 1** the current and emerging therapies for IBD that target specific molecules in the immune system.

INNATE INTESTINAL IMMUNITY

Epithelial Barrier

The gastrointestinal tract has a continuous layer of single epithelial cells that are derived from a common progenitor LGR5+ intestinal stem cell.[7] The epithelial cells comprise enterocytes (intestinal absorptive cells), goblet cells, neuroendocrine cells, Paneth cells, and microfold (M) cells.[7] The epithelial cells are sealed with intercellular tight junctions that serve a barrier function and regulate the trafficking of macromolecules between the luminal environment and the host.[8] The tight junctions are composed of a meshwork of proteins like occludin, claudin family members, and the junctional adhesion molecule,[8] with zonulin as one of the physiologic modulators (of tight junctions) that controls intestinal permeability.[9] The luminal surface is covered by a thick layer of mucus, which is produced by goblet cells. Mucus is rich in secreted immunoglobulin A (IgA) antibodies,[10] proteins with antibacterial activity (ie, α- and β-defensins),[11] and proteolytic and glycolytic enzymes[12] that form the first line of defense against invasion by foreign pathogens. In spite of this barrier, gut bacteria and luminal antigens do enter the subepithelial lamina propria (an extracellular matrix compartment that contains a variety of immune and nonimmune cells), with some entering through unwanted breaks but most through the specialized, follicle-associated epithelium (FAE) that overlies the organized lymphoid tissue of the gut (gut-associated lymphoid tissue [GALT]). GALT consists of organized lymphoid compartments (Peyer patches, mesenteric lymph nodes, isolated lymphoid follicles, cryptopatches) and dispersed lymphoid cells in lamina propria and intraepithelial spaces.[13] The FAE overlies the large lymphoid aggregates called Peyer patches and, compared with other parts of intestinal epithelium, is devoid of goblet cells and has a lower