Targeting Specific Immunologic Pathways in Crohn's Disease

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KEYWORDS

• Crohn's disease • Inflammatory bowel diseases • Immunology • Target therapy

KEY POINTS

- New therapeutic agents are intended to control disease activity by inhibiting different extracellular, intracellular, and even intranuclear targets involved in the abnormal inflammatory pathways.
- Leukocyte migration in inflammatory bowel disease can be prevented by blocking of leukocyte integrins and cellular adhesion molecules expressed in the intestinal vascular endothelium.
- Interleukin (IL)-12 and IL-23 are dimeric cytokines that share the p40 subunit. Anti-p40 agents are effective in controlling the Th1/Th17 predominant response of Crohn's disease (CD).
- The Janus kinase–signal transducer and activator of transcription factors pathways are responsible for intracellular and intranuclear signaling for inflammatory cytokines and have been exploited as potential targets for immune regulation in CD.
- Novel perspectives for the management of CD besides the administration of antiinflammatory cytokines and cell-based therapies may include the modulation of epigenetic targets.

INTRODUCTION

Inflammatory bowel diseases, Crohn's disease (CD), and ulcerative colitis (UC) are characterized by chronic and relapsing inflammation of different segments of the gastrointestinal tract. The exact cause remains unknown, but the working hypothesis is that inflammatory bowel disease (IBD) results from a combination of genetic and

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environmental factors, immune deregulation, barrier dysfunction, and changes in the intestinal microbiome.[1–3] The efficacy of current therapies that target cytokines, most notably tumor necrosis factor alpha (TNF-α), has validated the essential role of cytokine pathways in the development of UC and CD inflammation.[4–6] Nevertheless, not all patients treated with TNF-α inhibitors achieve remission and many may even lose response over-time, showing that development of new therapies is warranted.[5,7,8] Understanding of the different immunologic pathways that are involved in intestinal damage is crucial for the development of new therapies that can maximize patient response (**Fig. 1**). New therapeutic agents, currently in development, are intended to control disease activity by approaching different extracellular, intracellular, and even intranuclear targets involved in the abnormal inflammatory response (**Table 1**).

EXTRACELLULAR TARGETS: LEUKOCYTE MIGRATION

After being activated in induction sites, such as mucosal lymphoid follicles and Peyer patches, leukocytes traffic to effector sites, such as the lamina propria, where inflammation takes place. This process is mediated by binding of integrin molecules located on leukocyte surfaces to cellular adhesion molecules (CAMs) expressed on the

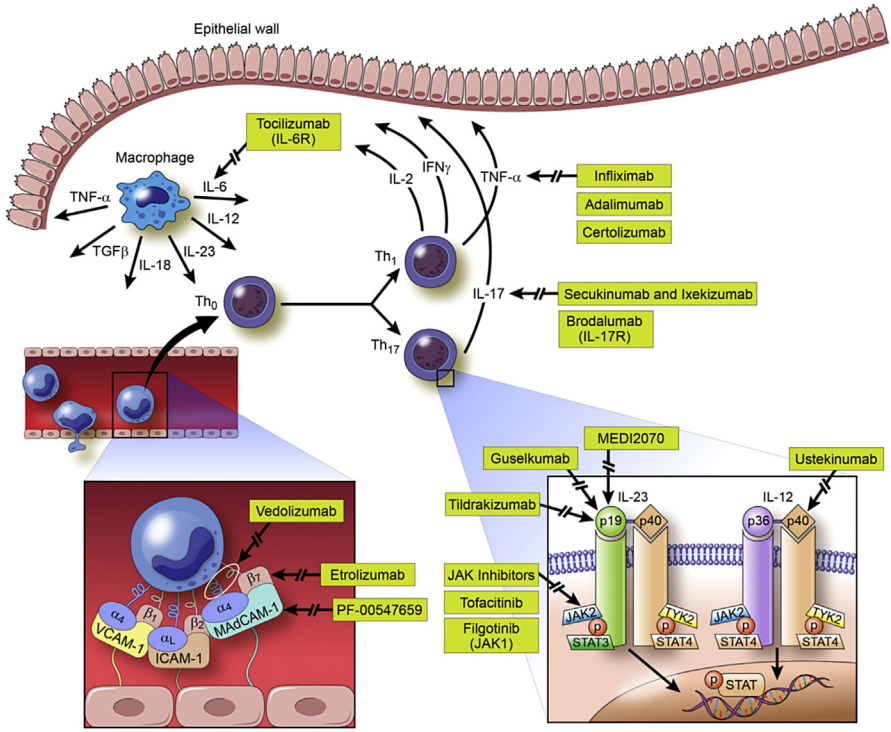

Fig. 1. Immunologic pathways involved in CD inflammation with its respective therapeutic agents. ICAM, intracellular adhesion molecule; IFN-γ, interferon gamma; IL, interleukin; IL-17R, IL-17 receptor; IL-6R, IL-6 receptor; JAK, Janus kinase; MAdCAM, mucosal addressin cellular adhesion molecule; STAT, signal transducer and activator of transcription factor; TGF-β, transforming growth factor beta; Th, T-helper cell; TYK, tyrosine kinase; VCAM, vascular cell adhesion molecule.