

Adaptive immunity in IBD: state of the art

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Purpose of review

Adaptive immune mechanisms are inherently involved in the pathogenesis of inflammatory bowel disease. This review summarizes the main discoveries made in 2007 within this field.

Recent findings

CD4⁺ T cells secreting interleukin-17 (T helper type 17) cells have emerged as a key effector population driving colitis in animal models previously associated with exaggerated T helper type 1 responses. With regard to T regulatory cells, a novel suppressive cytokine (interleukin-35) and induction of apoptosis as a means to exert suppression have been identified. The importance of specific chemokine receptors and integrins in effector and T regulatory cell function in colitis has been recognized.

Summary

An improved understanding of adaptive immune mechanisms, on which manifold genetic and environmental traits might converge, and which ultimately mediate intestinal inflammation in inflammatory bowel disease, holds promise for novel effective therapeutic intervention.

Keywords

adaptive immunity, Crohn's disease, inflammatory bowel disease, T helper type 17, T regulatory cells, ulcerative colitis

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Introduction

In the intestine the body faces the largest exposure to the microbial world, both in terms of diversity as well as abundance. To interact with it the intestinal immune system must carry out an incredibly complex task that is still only minimally understood. This requires the identification of microbial 'pathogens', which require a fast and efficient response to allow for the survival of the whole organism, among the huge abundance of commensal bacteria (intestinal microbiota), which are essential for the development and function of the whole body.

The capacity to differentiate between 'good' and 'bad' bugs is all the more astonishing as both seemingly share the same molecules, that is ligands of pattern recognition receptors like toll-like receptors (TLRs) and NOD-like receptors (NLRs), which are part of the body's 'innate' defense mechanisms. While relying on recognition of certain molecular patterns and not specific for certain targets, innate immune mechanisms contribute the first line of defense by causing an inflammatory reaction. At the same time, pathogens are taken up and presented by antigen presenting cells to the adaptive immune system cells to allow the generation of an immune response specific for distinctive molecular targets.

Current concepts of inflammatory bowel disease (IBD) have as a central hypothesis that the intestinal microbiota balance goes awry, leading to inappropriate innate and adaptive immune response towards the normal commensal microbiota in the intestine. Crohn's disease and ulcerative colitis have for a long time been associated with disparate exaggerated T-cell responses, namely T helper type 1 (Th1) [featuring increased interferon (IFN)- γ and tumor necrosis factor (TNF)- α production], and Th2 [featuring increased interleukin (IL)-13 production], respectively. The recent discovery of T cells secreting IL-17 (Th17 cells) has added another effector T-cell subset to IBD. By contrast, several types of T-regulatory cells (Tregs) maintain effector T-cell populations in check and prevent T-cell-mediated destruction of intestinal tissue. This review will discuss the main discoveries in the field of adaptive immunity in IBD reported during the past year.

T-regulatory cells

Tregs are a critical subpopulation of T cells essential for maintaining self tolerance and preventing autoimmunity, and excessive inflammation associated with infections. Several types of T cells with regulatory function have been identified. Naturally occurring CD4⁺CD25⁺ Tregs

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are thymically derived and express the forkhead transcription factor Foxp3. Natural Tregs develop in the thymus and their T-cell receptor (TCR) repertoire is mainly self-reactive. Under certain defined conditions of antigen presentation and cytokine environment, Tregs can also be generated in the periphery, and contain a TCR repertoire that includes reactivity to nonself. Other types of T cells with regulatory function are IL-10-secreting Tr1 cells produced *in vitro* by antigenic stimulation of naïve T cells in the presence of IL-10, and transforming growth factor (TGF)- β -secreting LAP⁺ Th3 cells. Furthermore, several distinct types of CD8⁺ T cells with regulatory function have also been described.

A report by Maynard *et al.* [1] investigated IL-10 and FoxP3 expression using an elegant dual reporter system to shed light on the lineage interrelationship of Tregs. Secondary lymphoid tissues, lung and liver had enrichment of FoxP3⁺IL-10⁻ Tregs, whereas the large and small intestine had enrichment of FoxP3⁺IL-10⁺ and FoxP3⁻IL-10⁺ Tregs, respectively [1]. Both FoxP3⁺ and FoxP3⁻ CD4⁺ thymic precursors gave rise to peripheral IL-10⁺ Tregs, with only FoxP3⁻ precursor cells giving rise to all Treg subsets. Notably, each Treg subset developed in IL-10-deficient mice, but this was blocked by treatment with antibodies to TGF- β .

Collison *et al.* [2^{••}] studied the molecules that mediate the suppressive function of FoxP3⁺ Tregs, and discovered that Epstein-Barr virus-induced gene 3 (EBI3), a homologue of IL-12p40 (IL-12 β), and IL-12 α (IL-12 p35) were highly expressed by mouse FoxP3 Tregs, but not by resting or activated effector CD4⁺ T cells. Similarly, an Ebi3-IL-12 α heterodimer, which was termed IL-35, was constitutively secreted by Tregs, but not effector T cells. Treg cell restriction of this cytokine seems to occur because *Ebi3* is a downstream target of FoxP3. *Ebi3*^{-/-} and *Il12a*^{-/-} Treg cells had substantially reduced regulatory activity *in vitro* and failed to control homeostatic proliferation and to cure experimental murine IBD *in vivo*. Furthermore, ectopic expression of IL-35 conferred regulatory activity on naïve T cells, whereas recombinant IL-35 suppressed T cell proliferation. Overall, these data identified IL-35 as a novel inhibitory cytokine that may be specifically produced by Tregs and might be required for maximal suppressive activity, in addition to IL-10 [2^{••}].

Pandiyan *et al.* [3^{••}] suggested another mechanism of suppressive action of Tregs in that they induce apoptosis of effector CD4⁺ T cells, which was dependent on proapoptotic protein Bim. Tregs adoptively transferred into severe combined immunodeficient (SCID) mice, which had earlier received CD45RB^{high} T cells, localized to the mesenteric lymph nodes and induced apoptosis of colitogenic T cells, while leaving their early proliferation intact.

TGF- β is a key regulator of adaptive immunity [4], secreted as an inactive precursor and activated by distinct integrins [5]. Travis *et al.* [6^{••}] reported that absence of $\alpha_v\beta_8$ integrin, specifically in dendritic cells, led to IBD and age-related autoimmunity in mice. Dendritic cells lacking $\alpha_v\beta_8$ failed to induce Tregs *in vitro*, and these mice had reduced proportions of Tregs in colonic tissue. In a parallel study, Lacy-Hulbert *et al.* [7[•]] reported that deletion of α_v in the immune system caused severe colitis, autoimmunity and cancer. These results suggested that $\alpha_v\beta_8$ -mediated TGF- β activation by dendritic cells is essential for preventing immune dysfunction that results in IBD and autoimmunity, effects that are at least partly due to the ability of $\alpha_v\beta_8$ on dendritic cells to induce or maintain tissue Tregs [6^{••},7[•]]. Interestingly, in another study [8[•]], mice with a T-cell-specific deletion of the *Tgfb1* gene developed lethal immunopathology in multiple organs, including the colon, with enhanced T-cell proliferation, activation, and CD4⁺ T-cell differentiation into Th1 and Th2 cells. TGF- β 1 produced by FoxP3⁺ Tregs was required to inhibit Th1 cell differentiation and inflammatory bowel disease in a transfer model. Furthermore, T-cell-derived TGF- β 1 promoted Th17 cell differentiation and was indispensable for the induction of another immunopathology, experimental autoimmune encephalomyelitis.

Two recent studies have investigated the role of chemokine receptors in the function of Tregs in the CD45RB^{high} T-cell transfer model of colitis. Yuan *et al.* [9] reported that Tregs deficient in CCR4 expression, which binds to CXCL25 as its ligand, failed to accumulate in the mesenteric lymph nodes at early timepoints after transfer, resulting in a failure to suppress the generation of pathogenic T cells and the development of colitis despite having equivalent *in-vitro* suppressive activity. Another study [10] implicated CCR7, which utilizes CXCL10 as its ligand, in Treg homing and function. Overall, these two reports establish an unexpected critical role of CCR4 and CCR7 in the homing of Tregs and the consequent failure to exert suppressive activity in case of their inappropriate location.

A population of CD103⁺ dendritic cells that primarily resides within the lamina propria, Peyer's patches, and mesenteric lymph nodes are responsible for imprinting a gut-homing capacity through inducing expression of CCR9 and $\alpha_4\beta_7$ on T cells by a mechanism that depends upon all-trans retinoic acid [11–13]. Coombes *et al.* [14^{••}] and Benson *et al.* [15^{••}] reported a role for the development of Tregs by CD103⁺ dendritic cells through a pathway that depended in TGF- β and retinoic acid. Moreover, retinoic acid induced FoxP3⁺ adaptive Tregs (A-Tregs) to acquire a gut-homing phenotype ($\alpha_4\beta_7^+$ CCR9⁺) and the capacity to home to the lamina propria of the small intestine [15^{••}]. Under stimulation with

TGF- β and IL-2, which favors the differentiation of A-Tregs *in vitro*, the inclusion of retinoic acid induced nearly all activated CD4⁺ T cells to express FoxP3 and greatly increased the accumulation of these cells in the gut, hence indicating that retinoic acid production *in vivo* may drive both the development and imprinting of Tregs in the face of overt inflammation [15**].

Two papers by the Snapper group recently reported on the involvement of the cytoskeletal regulator Wiskott-Aldrich syndrome protein (WASP) in Treg function. Colitis in WASP knockout mice was associated with decreased Treg numbers in the thymus and peripheral lymphoid organs [16**]. WASP^{-/-} Tregs exhibited a defective suppressive function *in vitro*, and could not ameliorate colitis in the CD45RB^{high} transfer model. Furthermore, WASP^{-/-} Tregs displayed impaired homing to both mucosal and peripheral sites upon transfer in wild-type recipients. Exogenous IL-2, combined with TCR-mediated activation, substantially rescued the suppression defects of WASP^{-/-} Tregs. These data revealed a role for WASP in Treg function and implicated Treg cell dysfunction in the autoimmunity and colitis associated with WASP deficiency in mice and humans with the Wiskott Aldrich syndrome [16**]. Notably, all WASP-deficient mice developed colitis by 6 months of age [17]. Lymphocytes were required for disease induction, and CD4⁺ T cells from WASP-deficient mice were sufficient to induce disease in lymphocyte-deficient hosts. Lamina propria T cells of WASP^{-/-} mice exhibited increased IFN- γ , IL-4, and IL-13 levels, but decreased IL-6 and no difference in IL-17 compared with wild-type controls. Colitis did not develop in WASP^{-/-} IL-4^{-/-} mice as well as WASP^{-/-} treated with anti-IL-4 [17]. Given evidence of colitis that strongly resembles ulcerative colitis in humans with Wiskott-Aldrich syndrome, these studies show how investigation of rare human monogenic diseases that are associated with colitis can shed important light on polygenic diseases such as IBD. It will be very instructive to interrogate WASP structure and function as well as its associated pathways in patients with ulcerative colitis, which also exhibits a strong Th2 bias [18–21]. A similar point can be made by study of FoxP3 given its involvement in the monogenic human disease, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) [22], and its strongly implicated role in human IBD despite the absence of observed genetic associations with polygenic IBD [23].

A potential interesting way of pharmacologic Treg intervention was reported by Tao *et al.* [24*], who identified an unexpected role of histone/protein deacetylases (HDACs) in Treg function. HDACs regulate chromatin remodeling and gene expression as well as the functions of numerous transcription factors and nonhistone proteins. Administration of an HDAC inhibitor (HDACi) *in vivo* increased *Foxp3* gene expression, as well as the production and

suppressive function of Tregs, with HDAC9 proving to be particularly important. Optimal Treg function required acetylation of several lysines in the forkhead domain of FoxP3, accounting for optimal binding of FoxP3 to the *I/I2* promoter and suppression of endogenous IL-2 production. HDACi therapy *in vivo* enhanced Treg-mediated suppression of homeostatic proliferation and decreased murine IBD through Treg-dependent effects in the dextran sodium sulfate (DSS) model of colitis [24*].

Th17 cells

Many aspects of IBD that had earlier been ascribed to the IL-12–IFN- γ axis and mediated by Th1 cells have more recently been attributed to the action of another IL-12 family member sharing the p40 chain together with a novel IL-35-related chain, p19. This cytokine, IL-23, drives the development of Th17 cells in a pathway that is also regulated by IL-1, IL-6 and TGF- β [25]. IL-17-producing Th17 cells produce large quantities of proinflammatory cytokines, and are important in antibacterial responses and autoimmune diseases including IBD. A major contribution to our understanding of the IL-23–IL-17 axis came from work by Hue *et al.* [26] and Kullberg *et al.* [27]. Using the *Helicobacter hepaticus* model of innate immune typhlocolitis, Hue *et al.* [26] reported increased expression of IL-23p19 and IL-12p40 mRNA, but not IL-12p35, in inflamed intestine. Unexpectedly, this was associated with increased IL-17 expression in Rag^{-/-} mice infected with *H. hepaticus*. Neutralization of IL-23p19 by antibody resulted in highly attenuated intestinal pathology, which was associated with decreased proinflammatory cytokine production in the intestine. Using the CD45RB^{high} transfer model of colitis, the authors showed that IL-23 is essential for intestinal inflammation, but not systemic inflammatory responses. Kullberg *et al.* [27] used another model of *H. hepaticus*-induced colitis in mice with an unimpaired T-cell repertoire that were rendered deficient for IL-10 signaling. They reported that intestinal inflammation develops similarly in wild-type and IL-12 p35^{-/-}, but not IL-12 p40^{-/-} mice. Accordingly, anti-p40 treatment prevented intestinal pathology in this model. Using an IL-10-sufficient adoptive transfer system into RAG^{-/-} mice, the authors reported that IL-12 is not required for the development of T-cell-dependent colitis in *H. hepaticus* infected mice. Interestingly, using IL-23p19^{-/-} RAG^{-/-} recipients, which lack the ability to produce IL-23, CD4⁺ T-cell reconstituted *H. hepaticus*-infected mice displayed attenuated intestinal inflammation compared with RAG^{-/-} recipients, demonstrating a crucial role for IL-23 produced by a nonlymphoid population, likely dendritic cells, in disease pathogenesis. However, compared with the absence of disease in *H. hepaticus* -infected p40^{-/-} RAG^{-/-} recipients, some residual intestinal inflammation was observed in T-cell-reconstituted *H. hepaticus* infected p19^{-/-} Rag^{-/-} mice. These data suggest that, although not absolutely required

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for intestinal inflammation, IL-12 contributes to the mild intestinal inflammation observed in the absence of IL-23 and thus both cytokines contribute to inflammation within the intestines.

The role of IL-23 and Th17 cells in intestinal inflammation was further elucidated in the C3H/HeJ transfer model of colitis, which rests on transfer of the colitogenic, bacteria-reactive Bir14 T-cell line [28]. Bir14 T cells differentiated *in vitro* toward a Th1 or a Th17 phenotype were adoptively transferred, with Th17 cells requiring substantially fewer transferred cells than Th1 cells to induce colitis [29]. Neutralization of IL-23p19 prevented and treated active colitis, along with downregulation of a broad array of inflammatory cytokines and chemokines within the colon [29].

A potentially important link between NOD2, a prevalent risk factor for Crohn's disease, and Th17 cells has come from van Beelen *et al.* [30[•]]. They reported that bacteria, but not viruses, primed human dendritic cells to promote IL-17 production in memory T helper cells through the NOD2-ligand muramyl dipeptide (MDP), a derivative of bacterial peptidoglycan. MDP enhanced obligate bacterial TLR agonist induction of IL-23 and IL-1, which promoted IL-17 expression in T cells. Such a role of NOD2 in this IL-23–IL-1–IL-17 axis could be confirmed in NOD2-deficient dendritic cells derived from selected Crohn's disease patients. These data suggest that antibacterial Th17-mediated immunity might be normally orchestrated by dendritic cells upon sensing bacterial NOD2-ligand MDP.

An interesting discovery that may contribute to our understanding about how the intestinal immune system maintains some sort of tolerance towards the commensal flora while eliciting robust immunity toward harmful pathogens came from Denning *et al.* [31^{••}]. They described a population of CD11b⁺F4/80⁺CD11c⁻ macrophages in the lamina propria that expressed several anti-inflammatory molecules, including IL-10, but little or no proinflammatory cytokines, even after stimulation with TLR ligands. By a mechanism dependent on IL-10, retinoic acid, and exogenous TGF- β , these macrophages induced the differentiation of FoxP3⁺ Tregs. In contrast, lamina propria CD11b⁺ dendritic cells elicited IL-17 production, which was in turn suppressed by lamina propria macrophages, indicating that a dynamic interaction between macrophages and dendritic cells may influence the balance between immune activation and tolerance. These studies further show that retinoic acid-induced tolerance pathways are derived from retinoic acid effects upon both innate and adaptive immune elements.

With regard to the effector role of IL-17, Qian *et al.* [32] have recently reported that the adaptor Act1 is required for

IL-17-dependent signaling. The authors reported that after stimulation with IL-17, recruitment of Act1 to the IL-17R required the IL-17R conserved cytoplasmic 'SEFIR' domain, followed by recruitment of the kinase TAK1 and E3 ubiquitin ligase TRAF6, which mediated downstream activation of nuclear factor- κ B. Act1 is highly expressed in intestinal epithelial cells. Notably, mice with a conditional deletion of Act1 specifically in the intestinal epithelial cell compartment were largely protected from developing intestinal inflammation in the DSS colitis model. They further showed that Act1-deleted mice exhibited decreased levels of neutrophil-recruiting chemokines. Overall, these results indicate that Act1 expression in colonic epithelium is critical for IL-17-dependent induction of chemokines required for the recruitment of neutrophils during DSS colitis, and highlights a specific effector mechanism of IL-17 in the intestinal mucosa that is likely derived from the impact of a proinflammatory cytokine upon the intestinal epithelium.

In a paper published by Sheibanie *et al.* [33], prostaglandin E₂ (PGE₂) was identified as a factor that tips the balance between IL-23 and IL-12/IL-27 production in dendritic cells towards IL-23, thus favoring Th17 over Th1 differentiation. PGE₂ effects are mediated through the EP2/EP4 receptors on dendritic cells. Notably, a novel 5p13.1 Crohn's disease locus is contained within a 1.25 Mb gene desert, with the closest gene being *PTER4*, encoding the EP4 receptor [34]. Furthermore, certain *PTER4* risk alleles have been shown to be associated with increased PTGER4 expression [34]. Integrating the above data into a model for PGE₂ function in mucosal inflammation, however, is complex since EP4-deficient mice develop more severe colitis in the DSS model compared with wild-type mice [35].

While in mice commitment to the Th17 lineage is dependent on TGF- β and IL-6, Wilson *et al.* [36^{••}] reported that IL-23 and IL-1 β induced the development of human Th17 cells expressing IL-17A, IL-17F, IL-22, IL-26, IFN- γ , CCL20, and the transcription factor ROR- γ t. *In situ*, Th17 cells could be identified by expression of IL-23R and CD45RO. Notably, psoriatic skin lesions contained IL-23-producing dendritic cells and were enriched in cytokines produced by human Th17 cells that promote the production of antimicrobial peptides in human keratinocytes.

Classical and nonclassical major histocompatibility complex molecules

Major histocompatibility complex (MHC) class I chain-related gene A (MICA) is a stress-induced MHC-related molecule expressed on intestinal epithelial cells and recognized by NKG2D-activating receptor on CD8⁺ T cells, $\gamma\delta$ T cells, and natural killer (NK) cells [37]. Allez

et al. [38] reported increased MICA expression in intestinal epithelial cells in Crohn's disease, along with an increase in a subset of CD4⁺ T cells expressing NKG2D in the lamina propria. These CD4⁺NKG2D⁺ T cells exhibited a Th1 phenotype and expressed perforin, and clones were generated that were functionally active through MICA–NKG2D interactions. Furthermore, the subset of T cells from patients with Crohn's disease who expressed NKG2D expressed high levels of IL-15R γ and IL-15, which further increased NKG2D expression in these T-cell clones. The pathway identified by these investigators is highly similar to that ~~which has been~~ described in human celiac disease, suggesting overlapping effector mechanisms of disease injury to the epithelium in these two diseases [39,40]. These data also suggest the presence of a unique subset of CD4⁺ T cells with inflammatory and cytotoxic properties in Crohn's disease. Notably, the murine CD45RB^{high} transfer model of colitis is characterized by an increase in CD4⁺ NKG2D⁺ T cells, and constitutive expression of NKG2D ligands, such as H60, Mult-1, Rae-1 (mouse homologues of MICA), by lamina propria CD11c⁺ dendritic cells [41^{*}]. Treatment with a nondepleting and neutralizing anti-NKG2D antibody in this mouse model led to significant amelioration of colitis, abrogated leukocyte infiltration, and reduced production of IFN- γ by lamina propria CD4⁺ T cells [41^{*}]. These data demonstrate that NKG2D might be critically involved in CD4⁺ T-cell-mediated disease progression.

Largely along similar lines was another study by Dotan *et al.* [42], which reported that intestinal epithelial cells from IBD patients preferentially stimulated CD4⁺ T cells via interaction of HLA-DR to proliferate and secrete IFN- γ . In contrast, normal intestinal epithelial cells stimulated the proliferation and cytokine secretion by CD4⁺ T cells to a significantly lesser degree than IBD cells [42]. These data suggest that intestinal epithelial cells can contribute to the ongoing CD4⁺ T-cell activation observed in IBD.

A study by Perera *et al.* [43] analyzed the expression of nonclassical MHC class I molecules by intestinal epithelial cells in IBD compared with controls. The surface epithelium of the colon and, to a lesser extent, the small bowel expressed the nonclassical MHC I molecules CD1d, MICA/B and HLA-E on their cell surface. In contrast, crypt cells expressed little or no nonclassical MHC class I molecules on the cell surface but did express mRNA for these molecules. Notably, intestinal epithelial cells derived from patients with ulcerative colitis failed to express any nonclassical MHC class I molecules, while patients with Crohn's disease expressed HLA-E and MICA/B comparable to that seen in normal colons, but failed to express CD1d. These observations reveal significant differences between the epithelium of ulcerative

colitis and Crohn's disease and implicate an important role for nonclassical MHC class I molecules and their differential expression in IBD.

Invariant and noninvariant NK T cells have been implicated in mouse models of ulcerative colitis [19] and human models [20], respectively. A recent study by Grose *et al.* [44] reported a severe deficiency of invariant NK T cells in the periphery of Crohn's disease and ulcerative colitis patients alike, with IL-4 production impaired in both forms of IBD [44]. Unexpectedly, V β 24 mRNA expression (the invariant TCR- β chain expressed by invariant NK T cells) was also severely decreased in Crohn's disease and ulcerative colitis [44]. Notably, however, V β 24⁺ T cells were decreased in Crohn's disease, but not reduced in ulcerative colitis [44]. Obviously, this study did not assess the distribution of noninvariant NK T cells that had earlier been linked to human ulcerative colitis by Fuss *et al.* [20].

Miscellaneous

Studying T cells derived from mucosal biopsies from children experiencing their first attack of Crohn's disease with those from longstanding patients, Kugathasan *et al.* [45] reported that – in a similar fashion to acute infectious colitis – IL-12 induced T cells from early Crohn's disease to acquire a strongly polarized Th1 response characterized by high IFN- γ production and IL-12R β expression. Th1 polarization was not induced in T cells from late Crohn's disease. Along the same lines, IL-12p40 and IL-12R β 2 mRNA expression were significantly higher in early compared with late Crohn's disease. Overall, these data suggest that susceptibility to IL-12-mediated modulation might depend on the stage of Crohn's disease, with a stronger Th1 bias in early compared with late disease.

Increased expression of the CD4⁺ T cell chemoattractant CCL20 has been reported in colonic epithelial cells from IBD patients [46,47]. Katchar *et al.* [48] reported that during trinitrobenzene sulphonic acid (TNBS) colitis in mice, colonic CCL20 expression was substantially increased, along with an increase in the number of CCR6⁺ lamina propria CD4⁺ and CD8⁺ T cells. Anti-CCL20 neutralizing antibody significantly ameliorated TNBS colitis, along with a decreased influx of CCR6⁺ T cells into the lamina propria. Interestingly, stimulation of intestinal epithelial cells with IL-21, a T-cell-derived cytokine that is produced in excess in IBD, resulted in increased CCL20 expression [49].

Another study [50] identified the chemokine fractalkine (FKN; CXCL1) derived from mucosal endothelial cells as involved in the recruitment of CXCR1⁺ T cells into the mucosa in IBD. Expression of FKN was markedly enhanced by TNF- α along with IFN- γ , or direct leukocyte

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contact with the endothelium, with the effect being markedly stronger in human microvascular endothelial cells (HIMECs) derived from IBD patients in comparison to those obtained from controls. Antibody blocking experiments showed that FKN was a major contributor to T-cell adhesion to HIMECs.

Conclusion

Substantial knowledge has been gained during the last year that further elucidated the function of the adaptive immune system in health and disease. Th17 cells have turned out to be major contributors to intestinal inflammation and, in fact, some of the older literature on Th1 pathology in IBD has to be revisited, though it currently seems that both populations might play a role in IBD. Furthermore, substantial novel knowledge on Treg cells has been generated that better explain the regulatory function and perhaps lead the path to future therapeutic interventions involving Tregs. Another important discovery is the identification of several novel genetic risk factors for IBD using high-density single nucleotide polymorphism-based whole genome arrays, and the appreciation that essentially all genetic risk factors (perhaps with the exception of the IL23R polymorphisms) associate with pathways of innate immune or epithelial cell function. This means that those various and divergent genetic risk factors might lead to a dysfunction of the innate immune system, leading to inappropriate activation of the adaptive immune pathways, this forming the common pathway of mucosal destruction in IBD and an attractive target for immunointervention.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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