Inflammation in the Intestinal Tract: Pathogenesis and Treatment

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Key Words

Inflammatory bowel disease · Innate immunity · Adaptive immunity · Inflammation · Intestines

Abstract

Over the past decade a major hypothesis has emerged for the etiopathogenesis of inflammatory bowel disease (IBD). This hypothesis proposes that IBD represents a dysregulated mucosal immune response to antigens derived from the commensal microbiota in a genetically susceptible host that initially derives from innate immune abnormalities leading to an excessive proinflammatory cytokine derived from CD4+ T cells (T-helper 1, T-helper 2, and T-helper 17 cytokines) over and above the response that is normally associated with tolerance and immunoregulation derived from T-regulatory cells. Given that the genetic predisposition has increasingly been recognized to affect the regulation of innate and adaptive immunity, intestinal epithelial cell physiologic barrier function and the potential inappropriate access of antigens to the mucosal immune system through this dysfunctional barrier function, a key point in understanding IBD pathophysiology is to understand the immunoregulatory pathways associated with the intestinal immune system as they apply to IBD. Therefore, immunogenetic pathways associated with innate and adaptive immunity, the cytokines secreted by innate and adaptive immune cells, the ep-

ithelial factors and leukocyte factors that are associated with inflammation and structures on the endothelium that regulate the recruitment of leukocytes define potential pathways that may be amenable to therapeutic manipulation in IBD.

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Introduction

Recent studies on the immunologic, microbiologic and genetic basis of both forms of inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC) have provided an important blueprint for understanding the pathogenesis of these disorders and directing the development of new types of therapies. In this model (fig. 1), which is now well supported by a large body of evidence, IBD represents the dysregulated mucosal immune response to the normal commensal microbial antigens in a genetically susceptible host. It is clear that the genetic basis for this disease is centered on genetic factors that regulate the components of the innate and adaptive immune responses as well as the regulation of intestinal epithelial cell barrier function and interestingly the composition of the normal commensal microbiota itself within the intestines. This state of genetic susceptibility for the development of IBD is further modified by a variety of environmental factors which together affect the probability that either form

Fig. 1. Model for pathogenesis of IBD (see text for details).

Fig. 2. Generation of T-helper cell subtypes based upon cytokine secretion. An APC such as a dendritic cell (DC) provides factors derived from the innate immune response to naive T cells (TH0) together with antigenic peptides in the context of MHC class II molecules to the TCR which is associated with the CD3 protein complex as well as secondary so-called costimulatory signals (e.g. B7-1 and B7-2 on the APC and CD28 on the T cells) that ultimately lead to polarized T-cell responses. These T-cell responses are regulated by transcription factors (e.g. T-bet in the case of TH1 cells) and either promote inflammation (TH1, TH2, TH17) or inhibit inflammation (Treg) making each of these cytokines or cell surface molecules a potential therapeutic target (see text for details).

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of IBD will develop. The environmental factors that have been supported by epidemiologic studies to be important in modifying the risk for developing IBD include tobacco, appendectomy, antibiotics, oral contraceptive pills and likely non-steroidal anti-inflammatory agents. These environmental factors can be assumed to be important to the development of IBD through their ability to regulate the

immune response of the host, the physiologic functions of the intestinal epithelial cell barrier and likely the composition and function of the commensal microbiota.

IBD is determined by the genetically defined, innate immune responsiveness of intestinal tissues to components of the commensal microbiota. Once initiated, the disease distills into a final common pathway that is char-

acterized by an exaggerated adaptive immune response as expressed by the properties of aggressive T cells and B cells through their production of IgG antibodies that drive a state of chronic inflammation. The T cells that cause the inflammation associated with IBD are T cells that have been polarized to secrete distinct patterns of cytokines under the influence from factors derived from innate immune cells (fig. 2). Such polarized T cells are highly differentiated cell types that are defined as either T-helper 1 (TH1), TH2 or TH17. TH1 cells primarily secrete cytokines such as interferon- γ and tumor necrosis factor (TNF). TH2 cells are primarily those T cells that secrete interleukin (IL)-4, IL-5 and IL-13, and TH17 cells are those that primarily secrete IL-6, IL-22, and IL-17. The polarization of T cells to these types of cytokine-secreting cells which are in general highly inflammatory are regulated by particular transcription factors that include T-bet in the case of TH1 cells, GATA-3 in the case of TH2 cells and ROR- γ T in the case of TH17 cells. In the end, these inflammatory factors that derive from the initiating innate immune response and the consequential adaptive immune response result in tissue injury and the clinical symptoms that are characteristic of these disorders. It should be noted in concluding this introduction to these disorders that IBD is a highly regulated process which accounts for the relapsing and remitting nature of these disorders. Regulation in these disorders is provided primarily by unique subsets of lymphocytes that are so-called T-regulatory cells that secrete immunosuppressive cytokines such as IL-10, IL-35 and tumor growth factor- β (TGF- β). A significant number of T-regulatory cells can be found in the inflamed intestine. Their ability to overcome the inflammatory response is hypothesized to be a major reason for remission and thus is a major goal of therapies which aim to enable the regulatory functions of these naturally immunosuppressive cells.

Innate versus Adaptive Immunity

The immune response can be defined into two basic components: innate and adaptive, respectively (fig. 3). Innate immunity represents a rapidly generated hard-wired process that enables particular types of cells within the immune system such as macrophages, dendritic cells and B cells to respond quickly to molecular patterns contained within particular types of bacterial antigens. The cells that are considered to be the major subtypes of cells that express these types of pattern recognition receptors (PRRs) are so-called antigen presenting cells (APC). Epi-

Fig. 3. Concept of innate and adaptive immune interactions between an APC and T cell (see text for details).

thelial cells of the intestine can also function as APC and express such PRRs. Another characteristic of an APC is, in addition to its expression of PRRs, its ability to internalize, process, and thus present antigens on the cell surface in the context of components of the major histocompatibility complex (MHC) encoded by genes on human chromosome 6. These MHC genes encode so-called human leukocyte antigens (HLA) that are either MHC class I (HLA-A, -B and -C) or MHC class II (HLA-DR, -DP and -DQ).

Examples of so-called PRRs are those receptors which can recognize and bind repetitive structural elements of bacteria, viruses and/or fungi. A classic example of this type of recognition is that associated with the lipopolysaccharide of Gram-negative bacteria which is bound by Toll-like receptor 4 (TLR-4). Another excellent example of pattern recognition is that associated with the so-called NOD like receptor (NLR) family such as NOD2 (or CARD15). NOD2 is an intracellular PRR that recognizes muramyl dipeptide derived from peptidoglycan contained within both Gram-positive and Gram-negative organisms. The interaction of an NLR or TLR by an APC occurs during the earliest phases of an immune response. The innate immune response to bacterial, viral or fungal antigens guides the subsequent responses of the T lymphocyte towards different types of differentiated fates that allow for a focused immune response appropriate to the antigenic encounter. Such a focusing of the T lymphocytes and especially particular CD4-positive lympho-

Fig. 4. Cascade of events associated with the development of an immune response. Each of these sequential steps is genetically regulated and subject to therapeutic manipulation. As such, the steps associated with inflammation represent a therapeutic target.

cytes or T-helper cells is associated with the so-called adaptive immune response that occurs over days to weeks and is thus delayed. Adaptive immunity is also characterized by memory for the antigen(s) that initiated the immune response. The major initial driving force for the development of an adaptive immune response is the presentation of a nominal (that is a small component antigen) antigen derived from a larger polypeptide or macromolecular structure via the HLA molecules to the T-cell receptor (TCR) that is expressed on the T-helper cell. T-cell recognition of these nominal peptides therefore in the context of HLA is the characteristic fingerprint of an initiating adaptive immune response (fig. 3). As a result of these processes, the adaptive T-cell response becomes focused into one of several different types of polarized classes of cytokine production as aforementioned: namely TH1, TH2 or TH17 or in the case of regulatory cells, T-reg.

In considering IBD, it is therefore important to understand the general development of immune response to an antigen (fig. 4). An immune response is initiated by the interactions between the innate immune system and an antigen. An inflammatory antigen characteristically has both innate and adaptive qualities. An excellent example of this is the flagellins of bacteria which are major anti-

genic drivers of CD. Flagellin has innate qualities through its repetitive structures that are able to bind TLR-5. Flagellin also is a polypeptide that upon internalization, processing and presentation by a professional APC such as a dendritic cell is able to generate nominal 14–22 amino acid peptides that are presented by MHC class II molecules (HLA-DR, -DP or -DQ) to CD4-positive T-helper cells. Thus the earliest phases of an immune response are dependent upon the recognition and interpretation of the antigenic composition of the milieu by a T cell and an APC as revealed by innate and adaptive immune responses. Subsequent to this interaction between the T cell, and APC in the context of an antigen, a series of events occur on both the T cell and APC that lead to the secretion of cytokines characteristic of each of these specific components as well as the upregulation of membrane receptors on the cell surface of the T cell and APC as a consequence of this activation. During this phase of an immune response the cytokines that are derived from these interactions can be either inflammatory (e.g. interferon- γ , IL-4, IL-13, TNF) or regulatory (IL-10, IL-35, TGF- β). These cytokines and membrane receptors also guide the responses of other cell types within the intestinal tissues or other tissues wherein an inflammatory response is initiated. This occurs through the effects of the

cytokines and other soluble mediators on the endothelium that results in the activation of the endothelium and the recruitment of additional cells into the tissues through adhesion events between the circulating leukocytes within the peripheral blood and molecules on the cell surface of the endothelium. This process which is called *homing* is an important event in amplifying the immune response. As a consequence of inflammation of the endothelial lining, inflammatory mediators are produced that result in tissue destruction and consequently the inflammation that are associated with IBD. Each of these successive steps of the immune response is likely to be genetically regulated. Specifically, polymorphisms within genes associated with innate immunity (*NOD2*), adaptive immunity (*HLA*), inflammatory cytokine production and responses to inflammatory cytokines (*IL-23R*) production of regulatory cytokines (*IL-10*), the homing of leukocytes through endothelium to the lamina propria (*CCR6*) and the development of tissue destruction secondary to responses to inflammatory mediators such as prostaglandins (*EP4R*) are all potentially genetically regulated pathways.

In summary therefore, IBD represents the interactions between genetic susceptibility and modifying environmental factors that culminate in mucosal immune dysregulation and consequently inflammation. At the foundation of this disease therefore is the genetic composition of the host and the susceptibility to IBD that is derived from this genetic composition. Thus, genes associated with innate immunity such as *NOD2* and *ATG16L1* that is specifically associated with autophagy, endoplasmic reticulum (ER) stress such as through polymorphisms in the gene that encodes the X-box binding protein 1 (XBP1) or responsiveness to inflammatory cytokines (e.g. *IL-23R*) regulate both the composition of the commensal microbiota as well as the immune response to the commensal microbiota.

Role of the Microbiota in IBD

The human gastrointestinal tract is the largest site of bacterial commensals in the human body. The concentrations of bacteria range from $<10^2$ colony-forming units per milliliter within the stomach to $>10^{12}$ colony-forming units of bacteria in the colon. In its totality, the numbers of bacteria in the human intestine achieve levels of 10^{13} to 10^{14} as compared to the number of cells within the human body which is only in the number of 10^{12} to 10^{13} . Thus there are more than ten times greater numbers of bacte-

rial cells than human host cells in a normal individual. The normal microbiota achieve or comprise approximately 50% of fecal cellular material and are composed of more than 400 different species and a larger number of quasi species. Most of these bacteria are non-culturable. The normal bacteria are important for a wide variety of homeostatic processes. The normal bacteria provide approximately 40% of the normal energy metabolism associated with the host such that germ-free mice have less weight than normally colonized mice. The bacteria in the intestine fall largely within two major phyla namely Firmicutes that largely represent the Gram-positive bacteria and Bacteroidetes which mainly comprise the Gram-negative bacteria. In addition, the normal intestine contains many other life forms including viruses, protists, fungi, and archaea as other life forms. Most of these are, as noted, contained within the normal colon. Consistent with this, IBD is mainly localized to the areas of the intestines in which most of the bacteria are congregated, namely, the distal small intestine or ileum, and the colon. This is consistent with the bacterial hypothesis that the commensal microbiota is the major environmental driver of IBD. In addition, recent genetic evidence that has revealed polymorphisms within genes associated with innate immune responses to bacteria such as *NOD2* in CD and autophagy-associated genes in CD (e.g. *ATG16L1* and *IRGM*) are also consistent with the bacterial hypothesis. Specifically, the bacterial hypothesis states that IBD represents the inappropriate response of the mucosal-associated immune system to the commensal microbiota in a genetically susceptible host such that removal of the commensal microbiota will prevent the development of IBD as supported by model systems for mice. Removal of the commensal bacteria from mouse models which are genetically susceptible for the development of intestinal inflammation that models IBD such as by establishing these mouse models under germ-free conditions or treatment of such mouse models with antibiotics will prevent the development of intestinal inflammation. Such animal models in which this has been achieved include mice which have genetic deletion of the *IL-2* gene which results in the loss of T-regulatory cells from the thymus or the *IL-10* gene or genes associated with other regulatory pathways. Similarly, treatment of humans, especially patients with CD, can result in diminution of intestinal inflammation in selected subjects. Thus in a genetically susceptible host the mucosal-associated immune system is responding to the commensal microbiota as if it were in fact a pathogen.

Fig. 5. Critical immunologic role of the IEC in IBD. There is a bi-directional cross-talk between the commensal microbiota and the IEC that regulates the function of the IEC and the composition of the commensal microbiota through the secretion of antimicrobial peptides. The IEC attracts innate and adaptive immune cells into the lamina propria and provides innate immune signals to

dendritic cells that in turn regulate the activity of T cells which feeds back to the epithelium. ER stress within the epithelium can modify both of these important functions as described in the text. There is thus a tridirectional cross-talk between the microbes, intestinal epithelium and immune cells that are contained within the lamina propria.

The Intestinal Epithelial Cell in IBD

The fact that the commensal microbiota is a critical driver of the intestinal inflammation associated with IBD focuses attention on the special role of the intestinal epithelial cell in IBD. The intestinal epithelial cell (IEC) is uniquely located as a barrier between two totally distinct worlds (fig. 5). The IEC separates the outside world which contains the commensal microbiota from the inside world contained within the lamina propria that includes a complete set of immunologically responsive cells. The lamina propria in particular contains cells associated with innate immunity such as dendritic cells, macrophages and polymorphonuclear leukocytes as well as those that are associated with the adaptive immune system such as T lymphocytes, B lymphocytes and a unique set of lymphocytes that may be associated with UC; the so-called natural killer T cells (NKT cells). The epithelial cell is thus strategically located allowing for it to both regulate the composition of the commensal microbiota as well as respond to the commensal microbiota through the secretion of a variety of antibacterial peptides and other substances. In a similar manner, the IEC responds to bacterial factors such as through innate immune receptor signaling associated with PRRs resulting in the secretion of cytokines through

the basal surface of the IEC that affects both the composition and the function of the subjacent immune cells. The epithelial cell for example in response to bacterial and other microbially associated sources leads to secretion of important regulatory molecules such as thymic stromal lymphopoietin that regulates the differentiation of T cells between TH1 and TH2 polarity by favoring the latter. The regulation of microbial composition and sensitivity to microbial products by the innate immune system of the intestines is therefore critical to the development of IBD in both forms of IBD.

IECs have therefore received a significant amount of attention in understanding IBD. IECs are derived from a common stem cell within the crypt that leads to the differentiation into four distinct lineages through the activity of specific transcription factors. These four lineages of cells include those which migrate to the apical cell surface of the villus tip (the mucus-secreting goblet cells, the hormone-secreting enteroendocrine cells and the cytokine-secreting absorptive epithelial cells) and a specialized lineage of cells that migrates deep into the crypt which is responsible for the secretion of antibacterial peptides (Paneth cell). The Paneth cell is a major site of production of antimicrobial peptides through secretion of molecules such as lysozyme and the α -defensins (so-called crypt-

dins). Paneth cells provide antibacterial protection and are primarily contained within the small intestine but not in the normal colon except during inflammation including the inflammation associated with bacterial infections and IBD. The Paneth cell has received a significant amount of attention because several different genetic risk factors have been observed to be associated with Paneth cell abnormalities in IBD – both CD and UC. Humans and mice with loss of either *NOD2* or *ATG16L1* function exhibit abnormalities in Paneth cell structure and function. These studies support the possibility that intracellular bacterial sensing through *NOD2* and the regulation of autophagy, an important housekeeping function of all cell types, is involved in the maintenance of Paneth cell function. Similarly, Paneth cells are significantly influenced by the functionality of genes associated with ER stress. ER stress is commonly observed in cells that are highly secretory such as Paneth cells. The ability of a highly secretory cell to manage ER stress through a pathway called the unfolded protein response (UPR) is of major importance to the development and function of such highly secretory cells. Deletion of at least one gene associated with the ER stress response, XBP1, has recently been linked to the functionality of Paneth cells as well as their presence in mouse models. Moreover, polymorphisms in XBP1 have been recently shown to be associated with genetic risk in humans with both CD and UC.

The UPR is a signaling pathway from the ER to the nucleus that protects cells from the stress caused by unfolded or misfolded proteins. As noted above, ER stress is quite common in highly secretory cells and may be particularly prominent in the intestine given that this is a highly stressful environment that has recently been appreciated to induce an UPR, especially in the small intestine as well as the colon. During an UPR in the context of cellular stress as would occur during the secretory requirements associated with inflammation, the cell activates a series of signaling pathways from the ER that regulate the transcription of factors that are able to compensate for the cellular stress within the ER. Studies in knockout mice have clearly shown that XBP1 is one such factor such that in the absence of XBP1 significant cellular stress to the epithelium is observed of such intensity that may lead in and of itself to primary intestinal inflammation [1].

Under normal homeostatic conditions, the IEC, given its important secretory function, maintains a UPR transcriptional program that provides for cellular vitality. In the context of hypomorphic XBP1 function as would occur in a genetically susceptible host, the IEC becomes

highly subject to the stressful environment associated with the intestines. This stress in its worse case leads to the death of Paneth cells contained within the small intestine. It is possible that the Paneth cell metaplasia within the colon that characterizes IBD may also occur. As a result, there is decreased secretion of antimicrobial peptides into the lumen which may regulate the composition of the commensal microbiota. At the same time, IECs in the context of hypomorphic XBP1 function become exquisitely sensitive to PRR signaling such as that associated with TLRs leading to an exaggerated production of proinflammatory mediators such as chemokines that attract leukocytes into the gut as well as TNF. Thus, innate immune responses associated with abnormal ER stress within the epithelium as regulated by XBP1 can be an important means for the development of IBD. In fact, these recent studies suggest that intestinal inflammation associated with IBD may originate primarily from increased sensitivity of the intestinal epithelium to the environmental factors that are contained within the normal milieu per se as well as the milieu that is observed within the context of inflammation.

Taken together, a new model has emerged in which primary (genetic) and secondary (environmental factors) can drive ER stress in the intestinal epithelium and consequently either initiate and/or promote the development of inflammation. Primary genetic factors that appear to be important for the development of ER stress that may be linked to the development of intestinal inflammation include hypomorphic polymorphisms of the *XBP1* gene as well as genes such as *ATG16L1* and *IRGM* that are associated with autophagy. The reason for this is that ER stress is a major regulator of autophagy. Autophagy is a pathway of so-called ‘self-eating’ wherein degradative organelles contained within the cell ingest other organelles as a housekeeping function to maintain cell vitality. Autophagy is an important pathway in the maintenance of cell structure but is also important during conditions of starvation and the removal of ingested pathogens. It is therefore not surprising that hypomorphic autophagy function might be involved in the pathogenesis of IBD given the importance of microbial homeostasis in the underlying pathophysiology. It can be imagined therefore that the concomitant inability of the host to both manage ER stress and autophagy could together serve as a particularly deleterious consequence for the host. In addition, it is also clear that a variety of secondary environmental factors can induce ER stress and theoretically promote intestinal inflammation. These secondary environmental factors include both those from bacteria which

Table 1. IBD – therapeutic implications

Target	Mechanism	Therapeutic
Antigen	Eliminate pathogenic bacterial strain	Antibiotic/probiotic (VSL #3®)
T-cell/APC interactions	Block innate immune signaling or manipulate co-stimulation	Anti-CD3 (Visilizumab®), CTLA4-Ig (Abatacept®), Azathioprine/6MP
Cytokines and membrane receptors	↓ Proinflammatory or ↑ anti-inflammatory cytokines	Anti-TNF (Remicaide®, Humira®, Certolizomab®), anti-IL-12p40, anti-TL1A, anti-IL-17, anti-IL-6R, anti-IL-13, IFN-β
Cellular recruitment	Block T-cell homing or endothelial cell addressins	Anti-α4β7 (Tysabri®, LDP-02®), anti-MadCAM1
Inflammatory mediators	Block inflammatory signaling	Protease inhibitors (TACEi), mesalamines
Barrier function and repair	↑ Epithelial barrier and restitution	Epidermal growth factor (?)

have been shown to inhibit XBP1 function for example such as factors from pathogenic bacteria, dietary factors such as high fat or glucose deprivation, inflammation and in particular hypoxia and cytokines such as TNF and potentially drugs or stress per se such as that due to neurogenic factors can all activate ER stress pathways. In a genetically susceptible host, such environmental factors may promote the development of intestinal inflammation and involve the IEC. Such models are currently under investigation and may be of particular relevance to IBD.

Innate and Adaptive Immune Interactions in the Development of IBD

These aforementioned comments lead to a pathophysiologic model in which a genetically susceptible host that is exposed to a particular set of environmental events that cause an alteration in the composition of microbial community associated with the intestines or the responsiveness or the level of responsiveness of the mucosal immune system can abnormally activate the innate and/or adaptive immune systems which will initiate intestinal inflammation. In this model, it can be imagined that an inability to appropriately manage ER stress or an inability to properly deal with intracellular bacterial challenges in the context of abnormal autophagy or PRR function may lead to an inappropriate innate immune response that would initiate the origins of IBD. In this model, pathogenic microorganisms may be particularly impor-

tant because of their ability to cause dramatic alterations in the composition of the commensal microbiota as well as modify the immune response. Similarly, it can be imagined that antibiotics can in the genetically susceptible host create alterations to the microbiota that are also potentially deleterious. Another example is smoking which may be particularly deleterious in CD due to the ability for example of carbon monoxide to activate TH1 pathways as discussed further below. It can be further predicted that the genetically susceptible host will also have a genetically endowed abnormalities in the regulation of the adaptive immune system such that the adaptive immune system is overly responsive to factors derived from innate immune responses. An excellent example of this hypothesis is the description of polymorphisms in the IL-23 receptor that would predict the inappropriate responsiveness of T lymphocytes to IL-23 from innate cells such as dendritic cells. Thus it can be imagined that there is a pathogenic progression of IBD that begins with a series of environmental events in a genetically susceptible host that leads to an exaggerated innate immune response and/or overly reactive adaptive immune response that is unable to be downregulated.

Cytokines Associated with Adaptive Immunity

One of the greatest types of therapy that has been shown to be particularly important in the modern treatment of IBD is the use of biologic agents that target cytokines (table 1). It is therefore appropriate to conclude this

discussion with consideration of the cytokines that are associated with transitioning from innate immunity to adaptive immunity. The exaggerated innate immune response that is believed to be associated with the development of IBD is characterized by the exaggerated secretion of cytokines derived from innate immune cells that are both proinflammatory and consequently important drivers of adaptive T-cell function. The former includes cytokines such as TNF and IL-6 both of which are important therapeutic targets in the treatment of IBD. Specifically antibodies directed at TNF or at the IL-6 receptor signaling pathways have revealed themselves to be important new approaches in the treatment of this disease [2–6]. Similarly, cytokines from innate immune cells such as IL-12 and IL-23 which are highly related to one another and which drive the development of inflammatory T cells and the inhibition of regulatory T cells have also been shown to be important therapeutic targets of CD. IL-12 and IL-23 are heterodimeric proteins. The IL-12p40 chain is shared in common between both the IL-12 and the IL-23 proteins and has shown itself to be an important potential new therapeutic target for these patients [7]. Finally, T cells under the influence of these factors from innate immune cells are forced to differentiate to either TH1 cells that secrete exaggerated amounts of interferon- γ or TH17 cells that secrete IL-17, especially in CD. Studies to evaluate the clinical responses of IBD patients to therapies that neutralize interferon- γ or IL-17 are underway and require additional evaluation [8]. In UC, there appears to be an inappropriate TH2-like cytokine response that may be associated with NKT cells and is characterized by excess IL-13 production through a less well characterized process, making IL-13 an interesting therapeutic target. Similarly, some subsets of dendritic cells and macrophages are able to induce T cells into a regulatory phenotype that inhibits inflammation through the secretion of TGF- β , IL-10 and IL-35. Thus it is the balance between regulatory T cells and proinflammatory T-helper cells that leads to the final determination of whether chronic inflammation or homeostasis will in fact occur.

Conclusion

From these comments, a common immunogenic pathway can be envisioned for the development of IBD. In this pathway, the genetically determined relationship between IECs and the commensal microbiota in the lumen and the immune cells within the lamina propria are a critical initial step in the pathogenesis of this disease. In

this model, IECs are constantly secreting antimicrobial factors into the milieu of the lumen to regulate the composition of microbiota and are in turn continuously responding to components of the bacteria. In a genetically susceptible host such as one that possesses polymorphisms in the *XBPI* gene that regulates ER stress responses, the ability to manage the commensal microbiota and to respond appropriately to the intestinal microbiota is deranged. Similarly, in a genetically susceptible host it can be envisioned that the relationship between the IEC and the innate cells within the lamina propria is also abnormal. In this context, innate immune cells within the lamina propria are inappropriately responding to bacterial components such as individuals who have polymorphisms such as the *NOD2* gene. This abnormal innate immune signaling from dendritic cells would be predicted to result in the secretion of inflammatory cytokines (such as TNF and IL-6) as well as other important cytokines that modify the adaptive immune response leading in the genetically susceptible host to an exaggerated degree of adaptive immune T cells secreting highly proinflammatory cytokines as well as an inappropriately low number of T-regulatory cells or resistance of the effector T cells to the regulatory effects of the T-regulatory cells. In this model, cytokines such as IL-12 and IL-23 derived from aggressive innate immune cells within the lamina propria would be predicted to push T cells to secrete high quantities of TH1- and TH17-associated cytokines that have been recently appreciated to be associated with the development of CD. It can be predicted that blockade of IL-12p40 which is common to both IL-12 and IL-23 will lead to amelioration of this disease. Similarly, exaggerated innate immune signaling in an UC patient may lead to exaggerated production of inflammatory mediators that drive the development of aggressive TH2 cells although this pathway is not as well characterized to date. Thus, the insights provided by understanding the immunopathogenesis of IBD is increasingly providing opportunities for new therapeutic approaches in the treatment of patients with this very important immune mediated group of diseases.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the content of this article.

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