The Role of Immune Cells in Ulcerative Colitis

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Contributor: Katarzyna Komosinska-Vassev

Ulcerative colitis (UC) is a chronic inflammatory disease with an underlying excessive immune response directed against resident microbiota and/or dietary antigens. The condition is diagnosed mostly between the ages of 20 to 40, however it can occur at every age. Characteristic of UC are alternating periods of clinical relapse and remission.

Keywords: ulcerative colitis ; immune cells ; lymphocytes

1. Introduction

Inflammation of the colon mucosa plays an essential role in pathogenesis of UC, which leads to ulcer formation. Changes observed within the intestinal mucosa are localized in the rectum and spread proximally to the other parts of the colon. The most common clinical symptoms are gastrointestinal disorders such as abdominal pain, diarrhea with mucus and/or blood, nausea and vomiting; nevertheless, general symptoms including fever, weight loss and anemia are also observed with the parenteral symptoms—peripheral arthritis, cholangitis, pyoderma gangrenosum, erythema nodosum and arthropathies [1][2]. Although the disorder is quite common, its exact pathogenesis is not fully understood; however, it is known that UC is connected with the excessive immune response to the environmental factors or resident microbiota among genetically susceptible subjects, and the immunity status plays a crucial role in the increased intestinal permeability and impaired barrier function. There are reasonable doubts if the impaired barrier function precedes the onset of the disease, or the inflammation development in the lamina propria of the intestinal mucosa induces the intestinal epithelial disfunction [3].

Patients with UC present a decreased number of the goblet cells responsible, among others, for the excretion of biologically active substances that contribute to innate immunity, such as trefoil peptides and peptides binding Fc region of antibodies, as well as for secretion of the mucin, which forms large net-like polymers that lubricate the lumen and form a barrier between sterile intestinal epithelial and gut microbiota [4]. An impaired intestinal barrier and a decreased amount of the mucus leads to increased exposure to food antigens and antigens associated with gut microbiota, which activates the mechanisms of the innate immunity.

2. Immune Cells in the Pathogenesis of Ulcerative Colitis

2.1. Cells of Innate Immunity

Immune cells play a significant role in the pathogenesis of ulcerative colitis, including cells of innate and adaptive immune response. The cells belonging to the innate immunity are neutrophils, which constitute the main component of the inflammatory infiltrate in an intestinal tissue in UC and are one of the first cells participating in the active phase of the disease. Neutrophils recognize phagocytes and take part in incapacitation of the microorganisms through releasing the neutrophil extracellular traps (NETs) or degranulation of its own grains. NETs are cross-linked structures protruding from the membrane of activated neutrophils, composed of condensed chromatin and DNA. Moreover, they contain some components of the neutrophils' grains, such as neutrophil elastase, myeloperoxidase (MPO), and cathepsin G. NETs generation is a neutrophils' response to the presence of pathogens since the biochemical composition of NETs determines the trapping and upcoming elimination of pathogens. MPO released from the cell catalyzes the HClO synthesis reaction. Further reactions with this acid affect the formation of reactive oxygen species involved in the inactivation of microorganisms, and thus contribute to tissue damage and ulcer formation [5][6][7][8]. The studies conducted so far show that, in patients with UC, the concentration of MPO was several times higher than the expression of the enzyme in the stool of healthy subjects, which suggests an increased activity of neutrophils in these patients. Factors that increase NET release include tumor necrosis factor-α (TNF-α) and bacterial lipopolysaccharides, although this phenomenon is characteristic for neutrophils' activation, not only limited to UC. NETs may also arise when stimulated by other pro-inflammatory cytokines, including IL-8 released by endothelial cells, and by NO or neutrophil autoantibodies characteristic to small blood vessel inflammation and also present in UC. Triggering properties towards releasing of NETs also fulfill

protein arginine deiminase 4 (PAD4), which is responsible for histone citrullination—a key process taking place during NETosis. Dinallo et al. [7] proved that epithelial cells and cells of intestinal mucosa exhibited higher PAD4 concentrations in intestinal tissue specimens collected from UC patients, compared to healthy individuals and patients with Crohn's disease. Moreover, comparing the expression of PAD4 in a tissue lesion and in healthy tissue collected from the same patients with UC, it has been noted that in the first case, an expression of PAD4 was significantly higher [5][7][8].

Recently, in pathogenesis of UC, the role of innate lymphoid cells (ILC), which belongs to the family of mononuclear effective cells with common lymphoid progenitor, has been highlighted. The cells take part in the immune response directed towards extra- and intracellular microorganisms, in protection of an intestinal barrier, as well as in tissue repair and remodeling. Taking into account the expression of transcriptional factors and the types of cytokines secreted by the ILC, three types of these cells were distinguished: ILC1, ILC2, ILC3 [9][10][11].

In the Forkel's et al. [10] analysis, an increased number of ILC1 cells correlated with an early stage of Crohn's disease. Additionally, Forkel et al. noted a significant increase in the number of ILC1 cells in the inflamed intestinal mucosa. ILC1 appears as a result of enhanced expression of T-cell-specific T-box transcription factor (T-bet), the expression of which is induced by IL-12. ILC1 is mainly responsible for eradication of the viruses and bacteria. In addition, after pathogens are immobilized by DCs that release IL-12 and IL-18, ILC1 is stimulated to synthesize interferon-γ (IFN-γ). Increased secretion of IFN-γ may contribute to the pathological processes seen in UC; however, the role of ILC1 is more emphasized in the pathogenesis of other type of IBD, such as Crohn's disease, than in UC [9][10][11].

In the chronic stage of UC, the number of ILC1, as well as ILC2 cells, was increased in the intestinal mucosa. Moreover, in biopsies of the inflamed intestinal mucosa collected from the patients with early UC, an increased number of ILC2 cells has also been reported. ILC2 cells appear as a result of enhanced expression of transcription factors such as GATA binding protein 3 (GATA3) and retinoic-related orphan receptor α (RORα). In response to IL-33 (secreted especially during parasite infection, epithelial cells damage or exposition to allergens), ILC2 releases IL-5, responsible for neutrophil recruitment to inflamed areas, and IL-13 that disrupts the intestinal epithelial barrier function. However, ILC2 is also able to secrete IL-4, -6, -8, -9, granulocyte-macrophage colony-stimulating factor (GM-CSF) and amphiregulin, involved in epithelial repair [10][12].

The third, and at the same time the most diversified, group of innate lymphoid cells are the ILC3 cells, which appears as a result of the action of retinoic-related orphan receptor γt (RORγt). Due to the presence of a natural receptor of cytotoxicity, ILC3 cells can be divided into NKp44+ and NKp44− cells. ILC3 cells are well known for secreting IL-22 and/or IL-17 in response to IL-23 and IL-1β [9][10][12]. Patients with IBD present a reduced number of NKp44+ cells, which negatively correlates with disease activity assessed in endoscopic examination. NKp44+ cells are dominant ILC cells in the healthy mucosa of the ileum, caecum and colon. They are characterized by high expression of IL-22 with a protective role towards intestinal epithelial cells, and low expression of IL-17, which may fulfill both protective and pro-inflammatory functions against the intestinal barrier, depending on the cytokine environment. The reduced number of NKp44+ cells may contribute to a reduction in the expression of the protective IL-22 and thus to the dysfunction of the intestinal barrier. Interestingly, no significant differences were found in the ILC population in the peripheral blood and healthy intestinal mucosa from the IBD patients compared to the ILC population in the peripheral blood and intestinal mucosa from healthy people, which indicates the native nature of these changes [9][10][12].

2.2. Antigen-Presenting Cells (APC)

Antigen-presenting cells, including dendritic cells and macrophages, are cells connecting two types of the immune response. In spite of a different origin, these two types of cells express receptors recognizing molecular patterns such as toll-like receptors (TLR) and nucleotide-binding oligomerization domain-coding protein (NOD). Unlike macrophages, DCs migrate to peripheral lymph nodes when activated, while macrophages locally activate an adaptive immune response. In a healthy organism, intestinal DCs remain immune tolerant because they secrete protective IL-10, while in IBD, DCs shift their activity and the number of pro-inflammatory DCs increases. Hart et al. [13] showed an increased expression of TLR-2 and TLR-4 on the surface of dendritic cells in the biopsy material from patients with UC, while in patients without changes in endoscopic examination, elevated TLR-2 or TLR-4 was found in only a few cases. Activation of these receptors leads to the activation of the nuclear factor kappa-B (NF-κB) and other transcription factors directly influencing the processes related to the development of inflammation [9][11][13].

Macrophages also show significant functional differences depending on the tissue environment. In the absence of inflammatory processes, macrophages perform phagocytic functions, secreting pro-inflammatory cytokines only to a limited extent, and DCs are mainly involved in antigen presentation. During inflammation, the cytokines responsible for macrophages' activation are secreted and, depending on the method of activation, macrophages can be divided into

classically activated (M1) or alternatively activated (M2). M1 present pro-inflammatory functions and significant antibacterial activity. They are activated by exposure to interferon-γ (IFN-γ), GM-CSF or LPS and, when stimulated, secrete significant amounts of cytokines (TNF-α, IL-1β, IL-12, IL-18, IL-23), chemokines (CXCl9, CXCL10), reactive oxygen and nitrogen species. M1 take part in the immune response via Th1 and Th17 cells. In contrast, M2 macrophages induced by IL-4, IL-10, and IL-13 exhibit anti-inflammatory functions and take part in tissue healing and fibrosis. M2 are characterized by the significant expression of mannose receptor (CD206) and scavenger-type receptors (CD163 and CD204), and regulate the activation of Th2 cells through the secretion of IL-10 and TGF-β. In addition, via releasing the anti-inflammatory chemokines (CCL-17, CCL-22, CCL-24), M2 promote basophils and eosinophils recruitment. Intestinal macrophages present features characteristic for M1, as well as M2 cells. On the one hand, similar to M1 cells, they present high expression of antigens belonging to the II class of the major histocompability complex (MHC), along with the expression of TNF-α. On the other hand, like M2 cells, they represent significant phagocytic activity and constitutive expression of IL-10. During IBD, the balance between M1 and M2 is shifted towards the pro-inflammatory type. Intestinal macrophages then secrete pro-inflammatory cytokines, such as IL-6, IL-23 and TNF-α, presenting at the same time increased cytotoxicity and phagocytic activity [1][9].

2.3. Lymphocytes, as an Element of the Adaptive Immune Response in the UC's Pathogenesis

Antigen-presenting cells activate the mechanisms of immune response by antigen presentation to T and B cells. This type of immune response is more time-consuming, although it is more precise than the innate immune response. Depending on the expression of the CD4 and CD8 cell surface molecules, lymphocytes can be divided into T CD8+, mainly cytotoxic cells, and T CD4+ T cells. The first type of cells contributes to the pathological changes observed in UC in the intestine through the production of pro-inflammatory cytokines (i.e., IFN-γ, TNF-α) that increase the inflammation and the secretion of pro-inflammatory cytokines and chemokines that damage epithelial cells. These actions of T CD8+ cells cause the formation of ulcers in the intestine that occurs in ulcerative colitis. The latter type, T CD4+ cells, can be subdivided into helper T cells (Th) and regulatory T cells (Treg). Moreover, Th1, Th2, Th9, Th17 and Th22 were distinguished among Th lymphocytes, based on the cytokine profile. Differentiation from naive cells to the aforementioned helper T cell types depends on the cytokine environment and the activation of individual transcription factors [9][14][15]. Inflammation within the intestine tissue is associated with an enhanced activation and maturation of T cells. Lymphocytes isolated from the peripheral blood of UC patients showed increased expression of markers of activation—HLA-DR, β1-integrin and decreased expression of CD62L, characteristic for naïve T cells, compared to lymphocytes isolated from healthy individuals. These results indicate an increased activation of CD4+ and CD8+ cells in patients with UC. Moreover, the phenotype of active cells was correlated with an increased level of systemic and intestinal inflammatory markers in newly diagnosed patients. In the same study group, the percentage of inactive T CD4+ cells expressing CD62L negatively correlated with eosinophil cationic protein and calprotectin in feces considered to be intestinal inflammatory markers. Inflammation promotes lymphocyte activation due to increased APC activity in IBD. Thus, the cytotoxicity of T CD8+ cells can lead to tissue damage, which exacerbates the inflammatory process [15].

2.4. Th2 Lymphocytes

Previous research projects have shown that during UC, the expression of Th2 subpopulation of lymphocytes is increased in the inflammatory infiltration of the intestine tissue. Th2 cells are responsible for maintaining the homeostasis of the intestinal mucosa and are also involved in immune response against parasites, pro-inflammatory pathways and tissue repair. Excessive activation of Th2 cells may lead to the development of chronic inflammatory state and progressive tissue fibrosis. Th2 cells mediate the humoral type of immune response, secreting, i.e., IL-4 and IL-10, while by increasing the secretion of IL-5, IL-13, IL-21, and IL-25, they inhibit the activity of Th1 cells involved in cellular immune response [9][16]. Secreted by Th2 cells, IL-13 fulfill a crucial role in the pathogenesis of UC. Through the signal transducer and activator of transcription 6 (STAT-6) and signaling pathways of PI3K kinase, IL-13 influences the integrity of the intestinal barrier, since it increases the expression of claudin-2, creating pores selective for water and small cations. The expression of claudin-2 in the intestinal epithelium is high upon birth, then drops, and the next rise of claudin-2 expression in the intestine epithelium can be observed in inflammatory states including IBD. In addition, IL-13 negatively affects the integrity of the intestinal barrier by inducing apoptosis of intestinal epithelial cells and inhibiting epithelial regeneration. Moreover, TNF-α enhances these effects [15][17][18].

Th2 lymphocytes arise from the activation of the GATA-3 transcription factor upon stimulation by IL-4 secreted by dendritic cells. Interestingly, Seidelin et al. [19] presented that intestinal IL-33 is able to increase the expression of GATA-3, which indicates that the increased number of Th2 cells might be caused by an increased level of IL-33. Seidelin et al. noted that the expression of IL-33 was higher in intestinal biopsies collected from patients with active UC compared to inactive UC and healthy subjects. IL-33 plays a dichotomous role in the human body. On the one hand, IL-33 has a protective function

as it reduces the expression of genes induced by NF-κB pathway; however, on the other hand, acting as an “alarmin”, IL-33 is constitutively secreted into the extracellular space and impairs immune homeostasis, leading to the development of inflammation. Its role depends, on the degree of damage, the presence of pro-inflammatory cytokines, and the stage and localization of the inflammatory process. IL-33 presents an ability to bind DNA; as a result, it can act as a transcription factor. Additionally, IL-33 is also a conventional cytokine, which binds the ST2 receptor on the cell surface [16][19][20][21][22][23]. Bessa et al. [24] examined the influence of compartmentalization of IL-33 on the inflammation development. The researchers used a mouse model with the IL-33 mutation, which lost nucleus location, and noted that mice with the mutation presented a higher expression of IL-33 and developed a multisystem inflammatory response including, e.g., intestine inflammation. At the same time, no inflammation was noted in the mice without a receptor for IL-33 [24]. Physiologically, IL-33 secretion from the cell occurs as a result of cell damage or apoptosis. IL-33 binds the ST2 receptor present on the surface of Th2, ILC2, Treg, and T CD8+ cells. Activation of IL-33/ST2 axis stimulates the secretion of Th2 cytokines, which enhance the activation of Th2 and ILC2. Via TGF-β, IL-33 stimulates the polarization of naïve lymphocytes into Treg cells and also coordinates the functions of Treg and ILC2 during tissue repair. In UC, the concentration of IL-33 and the soluble ST2 receptor in serum is increased compared to healthy individuals and patients with Crohn’s disease, and additionally correlates with disease activity, which indicates the contribution of the IL-33/ST2 axis in the initiation and/or maintenance of the inflammation [22][23].

2.5. Th9 Lymphocytes

Other T cells, including Th9, Th17, Th22 and Treg, also play an important role in the pathogenesis of UC. Shohan et al. [25] presented that, in the intestinal biopsies collected from UC patients, a number of Th9 cells was increased compared to the healthy control, which may indicate a crucial role of these cells in UC pathogenesis [25]. Th9 cells appear as a result of polarization of naïve T cells in the presence of IL-4 and TGF-β, thereby acquiring the ability to secrete IL-9. Expression of IL-9 is regulated by various cytokines and transcription factors, such as STAT-6 and GATA-3 (characteristic for Th2 cells), as well as regulatory interferon factor 4 (IRF4) and purine-rich box-1 (PU.1) associated with Th9 cells. In particular, the expression of IL-9 depends on the last of the mentioned factors, since Th9 cells are the main source of IL-9 [26]. IL-9 is involved in the elimination of parasites by activating mast cells and eosinophils. In addition, this interleukin improves mucus synthesis and neutrophil infiltration in an allergic reaction [27]. Moreover, IL-9 also influences the expression of proteins forming the tight junction between the cells, increasing the permeability of the epithelium [25].

In the intestinal mucosa of patients with UC, the expression of mRNA encoding IL-9 was increased compared to the intestinal mucosa of healthy individuals; additionally, mRNA expression correlated with disease activity expressed in the Mayo scale. In order to determine the origin of IL-9, the researchers were looking for cells with PU. 1 expression and discovered that, in UC, the quantity of T CD4+ cells with PU. 1 expression was increased compared to the control group. These results may indicate that Th9 cells play a significant role in the UC’s pathogenesis. In the following research, conducted on the mouse model with chronic colitis induced by adoptive T cell transfer, mice with IL-9 deficiency developed less intensified inflammation compared to wild-type mice. Moreover, animals with IL-9 deficiency presented a decreased expression of claudin-2—the protein regulating tight junctions—compared to the wild-type mice, and the rectal administration of recombinant IL-9 increased the expression of claudin-2 in both models of mouse. Thus, IL-9 increases the expression of claudin-2, which, as a selectively permeable pore-forming protein, is one of the factors responsible for the impairment of the intestinal barrier integrity, and promotes the activation of the immune system and increases the progression of colitis. Other factors contributing to intestinal barrier impairment and development of inflammation are the relocation and impaired expression of other proteins, creating tight junctions between epithelial cells (for example, occludin), as well as intensified apoptosis of epithelial cells [26][18][28].

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