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An Overview of the Involvement of Tumor Necrosis Factor Alpha in the Pathogenesis of Ulcerative Colitis

Sahar F. Shaban, Eman A. Abdel-Fattah, Manar M. Ali, Arigue A. Dessouky

Department of Medical Histology and Cell Biology, Faculty of Medicine, Zagazig University, Egypt.

Abstract

Ulcerative colitis is a chronic inflammatory disease affecting the colon, and its incidence is rising worldwide. The pathogenesis is multifactorial, involving genetic predisposition, epithelial barrier defects, dysregulated immune responses, and environmental factors. Patients with ulcerative colitis have mucosal inflammation starting in the rectum that can extend continuously to proximal segments of the colon. Ulcerative colitis usually presents with bloody diarrhoea and is diagnosed by colonoscopy and histological findings. Standard of care for ulcerative colitis involves long-term pharmacotherapy or colectomy. Approximately 20% to 30% of patients eventually require a colectomy because patients either do not respond or cannot tolerate the currently available pharmacotherapies. Advances in our knowledge of the pathophysiology of ulcerative colitis have highlighted the importance of cytokines such as tumor necrosis factor alpha (TNF-α) in the inflammatory process. TNF-α is a pro inflammatory mediator that plays an integral role in the pathogenesis of inflammatory bowel disease. In addition, mounting evidence indicates a genetic association between TNF-α and ulcerative colitis. Furthermore, increased TNF-α levels have been demonstrated in studies of patients with ulcerative colitis. TNF-α is likely an important component in the pathophysiology of ulcerative colitis, and thus agents targeting TNF-α in ulcerative colitis have been studied. Recent randomized controlled trials have confirmed that biologic anti-TNFα therapy is effective in ulcerative colitis.

Keywords: Tumor Necrosis Factor alpha, Pathogenesis, Ulcerative Colitis.

Full length article **Corresponding Author*, e-mail: *drmanar.m.ali@gmail.com*

1. Introduction

Inflammatory bowel disease (IBD) is a persistent progressive disabling condition, encompassing both Crohn's disease (CD) and ulcerative colitis (UC). Young people are the mostly affected, with considerable consequences on social capacity and lifestyle. The incidence of UC is estimated to vary from 0.5 to 24.5 per 100,000 inhabitants worldwide [1]. The etiology of IBD is multifactorial, including genetic predispositions, dysfunctional immunity, intestinal barrier dysfunction, and environmental risk factors. In addition, it has been widely reported that the intestinal micro biota plays a vital mediating role in the detrimental complications associated with different stages of IBD [2]. Ulcerative colitis (UC) is a chronic relapsing disease in which gastrointestinal tract inflammation is implicated, affecting mainly colonic mucosa. Increased rate of bloody stools, pain and fever are devastating symptoms of UC. Symptoms typically begin at a young age and remain throughout life. One third of patients may need surgical removal of the whole colon. Moreover, the risk of development of colorectal carcinoma in UC patients is higher than the healthy population [3]. Chronic inflammation of the intestinal mucosa is the typical feature of ulcerative colitis and results from activation of the immune system. Dysregulation of the immune system results in the production of pro inflammatory mediators, such as TNF-α, IL-1, IL-6, cyclooxygenase (COX)-2, prostaglandins and leukotrienes [4].

2. Histological Aspect

The colon is a hollow tube, having the same histological structure of the digestive tube. It composed of four main layers: the mucosa, submucosa, muscularis externa, and loose areolar tissue (also called adventitia) which is covered by mesothelium on ascending, transverse, and sigmoid colon only (also called the visceral peritoneum or serosa) [5]. The mucosa lines the large intestine inner surface and has a smooth appearance with numerous pits which represent the straight tubular intestinal glands (crypts of Lieberkühn) that extend through the mucosa full thickness. The lining epithelium of the gland is consists of absorptive columnar cells, numerous goblet cells, occasional enteroendocrine cells, and stem cells [6]. At the microscopic level, the absorptive columnar cells appear tall columnar having oval basally located nuclei and apical striated border. Ultra structurally, the oval nuclei contain one or two nucleoli and thin heterochromatin. The cytoplasm contains large numbers of mitochondria oval or spherical in shape. In

addition to, it contains a well-developed Golgi apparatus, rough endoplasmic reticulum (RER), free ribosomes [7].

The goblet cells are a glandular simple columnar epithelial cells whose role is to produce gel forming mucins, which are the main component of mucus that is secreted continuously to lubricate the bowel, smoothing the passage of the increasingly solid contents [8]. Ultra structurally, goblet cell shows a large accumulation of mucinogen granules in the apical cytoplasm. The basal part is filled by a heterochromatic nucleus, extensive rough endoplasmic reticulum, free ribosomes, and mitochondria. This characteristic shape; the narrow basal stem with the apical accumulation of granules, is responsible for the name of the cell "goblet". An extensive array of flattened Golgi cisternae forms a wide cup around the newly formed mucinogen granules beside the basal part of the cell [9]. In addition to the two previous types of cells, two different types of enteroendocrine cells are exist. Most of them rest on the basal lamina and do not always extend to the lumen; and are known as "closed" enteroendocrine cells. Secretions from the closed cells are controlled by luminal content indirectly through neural and paracrine mechanisms. On the other hand, some have a thin cytoplasmic extension bearing microvilli that are exposed to the lumen; and are denoted as "open" enteroendocrine cells.

Open cells have chemoreceptors like those of taste buds presented on the apical membrane which activate G protein signaling cascade. That result in releasing of peptides which regulate different gastrointestinal functions. Enteroendocrine cells of the human colon release several hormones (5-hydroxytryptamine, glucagon-like peptide 1, peptide YY, somatostatin) [10]. Colonic epithelial stem cells are situated in the lower half of the intestinal gland. Their differentiating progeny migrate upwards in the lower to middle region of the crypt, before becoming finally differentiated, and are ultimately shed into the lumen. The lamina propria is a loose connective tissue layer that fills the space between the glands and contains many blood vessels into which water is absorbed. The lamina propria contains very scanty lymphatics. Also, it contains collagen, as well as plasma cells and lymphocytes [11]. The muscularis mucosa consists of a continuous sheet of inner circular and outer longitudinal smooth muscle layers which lay between the mucosa and the submucosa [6].

3. Inflammatory bowel disease

Many diseases could affect the large intestine, such as irritable bowel syndrome, slow-transit constipation, colonic malignancy, post-operative ileus, colonic pseudo-obstruction, and inflammatory bowel disease (IBD). Inflammatory bowel disease principally include Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease is an IBD that causes inflammation anyplace along the lining of the digestive tract, while ulcerative colitis causes long-term inflammation in some part of the digestive tract (mainly the colon). In CD, inflammation affects all intestine layers, whereas the effects of UC are mainly limited to the mucosa. The exact etiology of IBD is unknown. There are numerous factors that have been suggested to have an effect on the development of this group of diseases [12]. It is commonly accepted that the key mechanism behind the pathogenesis of CD and UC is an uncontrolled immune response to commensal micro biota in a genetically vulnerable host. The anti-saccharomyces cerevisiae antibody (ASCA) is the most delicate and definite serological marker for CD, so the possible role of colonic fungi has been long suspected. That explain direct suggestion of composition and function of fungal and viral communities are changed in IBD and could aberrantly interact with potential bacterial pathogens [13].

Regarding genetic contribution, a mutation in the Nucleotide binding Oligomerization Domain-2 (NOD2) gene is associated with an increase vulnerability to IBD through production of pro inflammatory cytokines. Familial clustering of IBD and higher prevalence rates in monozygotic twins than dizygotic twins, particularly of CD, refer to importance of genes in IBD. Furthermore, epidemiological, molecular, and many genome-wide association studies together suggest IBD is a polygenic disease. There are more than 50 confirmed IBD associated genes [14]. While genetic predisposition plays a key role in immune mediated diseases, major stimulus appears to be due to environmental factors. Research suggested that autoimmune diseases are most widespread in highly industrial nations but rare in less developed countries [15]. Increased incidence of IBD in industrial world may be related to changes in gastrointestinal micro biota that affect immune system and stimulate risk of IBD. Moreover, studies have revealed increased consumption of milk protein, animal protein, and polyunsaturated fatty acids can increase possibility for IBD [16]. Apical tight junction proteins are serious in the maintenance of epithelial barrier function. Changes in tight junction proteins in IBD is key of understanding disease pathogenesis.

Moreover, many members of the mucosal immune system are incorporated in the pathogenesis of IBD including the cells of the innate (dendritic cells, neutrophils, and macrophages/monocytes) and adaptive (T and B-lymphocytes) immune system, and their secreted mediators (cytokines and chemokines) [17]. Cytokines are small signal molecules, produced by immune cells, simplifying communication between cells. Cytokines increase or down control different cell types in an autocrine or paracrine way. According to function cytokines can be divided into pro-inflammatory, such as tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), and anti-inflammatory, like interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) [18]. Sahoo et al. [19] found that their overproduction as well as the imbalance between the excess pro inflammatory cytokines and the relative deficient immune regulatory cytokines may cause excessive gut inflammation which disrupt intrinsic repair system, leading to refractory ulcers in gut (Figure 1). Among these cytokines, effectiveness of TNF-α has been mostly confirmed and forms basis of a biological treatment model for IBD that has become a standard therapy. Among angiogenesis markers in IBD, vascular endothelial growth factor (VEGF) is most essential. Human studies have found that VEGF levels increase and fall depending on disease activity [21].

Ulcerative colitis is a chronic IBD of the large intestine, always originates in rectum. In some patients, disease remains restricted to rectum (ulcerative proctitis), whereas in others it may spread to include a variable or entire length of large intestine (pancolitis or extensive colitis). It normally stops suddenly at the ileocecal valve. But in some cases, a limited distal ileitis, called backwash ileitis, is observed. These ileal lesions are in continuation with colonic lesions and are characterized microscopically by regular shortening of villi with diffuse inflammatory lesions [22].

Ulcerative colitis is a strong local immune reaction characterized by periods of exacerbation and remission and superficial mucosal ulceration. It has clinical signs such as weight loss, abdominal pain, diarrhea, and rectal bleeding Some cases, ulcerative colitis takes a fulminant course characterized by severe diarrhea and cramps, leukocytosis, fever, and abdominal distention. Fulminant disease occurs more frequently in children than in adults. About 15% of patients present with an attack severe enough to necessitate hospitalization [24]. Extra intestinal manifestations (EIMs) of UC may cause greater morbidity than underlying intestinal disease and may even be first presenting symptoms of IBD.

Most common EIMs are inflammatory arthropathies and primary sclerosing cholangitis. Other extraintestinal manifestations include skin (erythema nodosum, pyoderma gangrenosum), eyes (episcleritis, uveitis), and bones (osteoporosis) [25]. Pulmonary presentation that might be involved in UC including inflammatory tracheal stenosis, interstitial pneumonia, peribronchiolitis, Wegener granulomatosis, alveolitis, bronchitis, serositis, and bronchiectasis. Renal involvement in patients with UC are including renal stones, ureteral obstruction and tubular injury [26]. The therapeutic goals in UC have progressively developed from just relief of symptoms to more demanding outcomes, including generation of sustained steroid-free clinical remission, mucosal curing and ideally histologic remission. Conventional treatment of IBD used to treat UC are 5-aminosalicylic acid (5-ASA), corticosteroids, and immunosuppressive agents such as azathiopurine. Majority of these drugs often led to multiple contrary events and show limited benefits in long-term disease regulation and have side effects which can decrease patient compliance [27]. Anti-tumor necrosis factor (anti-TNF) agents such as infliximab currently approved for steroid-dependent or resistant outpatients with moderately to severely active UC and for in patients with acute severe steroid-resistant colitis [28].

4. Tumor necrosis factor alpha (TNF-α)

The inflammatory process in the intestinal mucosa is characterized by a rise in pro inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, concomitant with significant neutrophil and macrophage infiltration [29]. Cytokines play a central role in mediating inflammation, and they may, therefore, be a logical goal for IBD therapy using specific cytokine inhibitors. For example tumor necrosis alpha (TNF-α) is a vital pro inflammatory cytokine in the chronic inflammatory conditions [30]. Structurally, TNF-α is a homotrimer protein comprising of 157 amino acids, mainly produced by numerous cell types, including immune cells (B cells and T cells, dendritic cells, natural killer cells, and mast cells), non-immune cells (enthothelial cells, fibroblasts, and neurons) [31]. TNF-α is initially synthesized in a precursor form and is mandatory to be processed by TNF α converting enzyme to be cleaved from its cell-surface-bound precursor (transmembrane TNF-α [tmTNF-α]) and released as the soluble TNF-α (sTNF-α). Both sTNF and tmTNF are biologically active.

The processed sTNF-α simplifies various biological activities through type 1 receptors (TNFR1) and type 2 receptors (TNFR2). It acts on both TNFR1 and TNFR2, but its biological activities are expected to be facilitated mainly through TNFR2. TNFR1 is widely expressed on many types of cell while TNFR2 is mostly expressed on immune cells and endothelial cells and facilitates limited biological responses [32]. During IBD, elevated concentration of TNF-α is correlated with activity of the disease. It is present in both in serum and in intestinal lamina propria of both CD and UC patients as well as intestinal submucosa in inflamed region. TNF-α is synthesized principally by activated macrophages and T lymphocytes. Moreover, a positive correlation observed between CD and UC activity and serum concentration of soluble forms of TNFR1 and TNFR2 [33]. Several studies showed that TNF-α contributes to disruption of intestinal epithelial barrier allows for intestinal penetration of luminal antigens and promotesintestinal inflammation. TNF produce not only in rearrangement of junctional proteins but also in the shedding of whole cells from intestinal epithelium [31].

Furthermore, TNF-α promotes production of the other pro inflammatory cytokines such as IL-1β and IL-6. IL-6 is involved in activation of neutrophils which produce tissue necrosis and dysfunction in mucosa. Also, IL-1β stimulates more leukocytes migration to site of inflammation. Moreover, TNF-α exaggerates the inflammatory cascades by activation of immune and non-immune cells, increase endothelial expression of adhesion molecules [34]. Wan et al. [35] And Yang et al. [36] added that TNF-α play a role in promotion of the production of large amounts of reactive oxygen species (ROS) disrupt the integrity of intestinal mucosal barrier and attacking the cellular components triggering their peroxidation. Additionally, TNF-α signaling up regulated expression of inducible nitric oxide synthase (iNOS). iNOS is one of the major enzymes overexpress during inflammation and synthesize large levels of nitric oxide (NO). The latter interact with free radicals forming more toxic compounds triggering tissue damage [37]. Vega et al. [38] Reported that TGF-β is a principal cytokine in fibrosis and its secretion is promoted by TNF-α signals.

Kumar et al. [39] added that overproduction of NO has a key role in initiation of fibrosis in animal models and human. TNF-α increase iNOS expression and activity so that increase NO production. In addition to, Manilall et al. [40] stated that TNF-α reduce matrix metalloproteinase-2 (MMP-2) activity which plays a role in collagen degradation So, TNF-α has a major role in inducing fibrosis. Nuclear factor-kB (NF-κB), exists mainly as a heterodimer presented in an inactive state in the cytoplasm and activated via a variety of external signals such as TNF-α signal. It could mediate the transcription of pro inflammatory genes, including iNOS, COX-2, and others. TNF-αand oxygen free radicals are well known inducers of cell death by activating the caspase family of proteases [41]. Furthermore, TNF-α increase the migration of inflammatory cells from the systemic circulation through the bowel wall into the lamina propria of the intestinal mucosa. Such cell trafficking is mainly regulated by a vascular cell adhesion molecule 1) VCAM-1(and intercellular adhesion molecule 1) ICAM-1(which overexpressed by TNF-α [42].

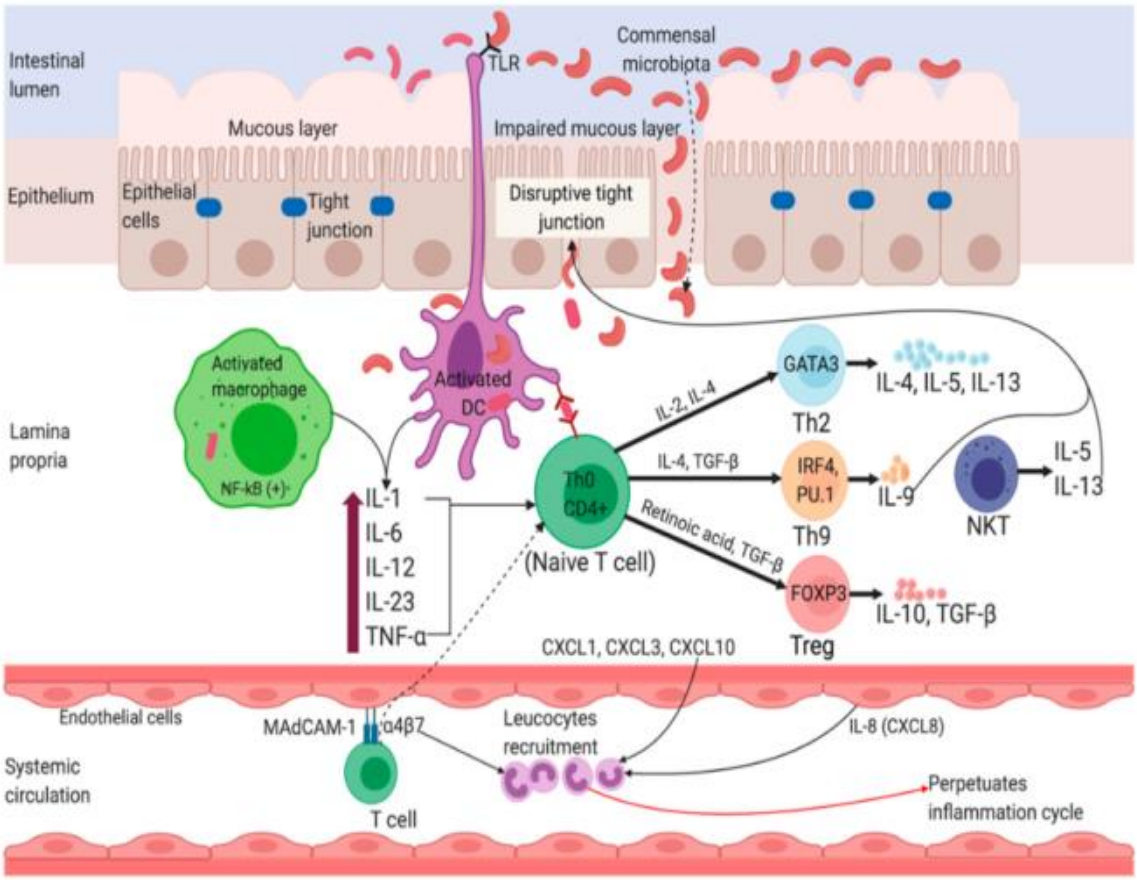

Figure (1): The pathogenesis of IBD [20].

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