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Pathogenesis of Crohn's Disease and Ulcerative Colitis; Systematic Review

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Abstract: **Crohn's disease (CD) and ulcerative colitis (UC) are the two main forms of chronic inflammatory bowel disease (IBD). The aim of this successful updated review study was to overview the pathogenesis of Crohn's disease (CD) and ulcerative colitis, and demonstrate the most updated evidence in this topic, we also aimed to discuss the treatment of both diseases. PubMed and Embase were searched for eligible studies that discussing the pathogenesis background of the most common two inflammatory bowel diseases (CD&UC) up to November 2016, search strategy used MeSH / EMTREE terms and free text words, and included sub-searches related to the index test, target condition, study population and publication type. The etiology is complicated, the most extensively accepted hypothesis purports CD as an immune-mediated condition in genetically vulnerable people, where disease onset is set off by environmental aspects that irritate the mucosal barrier, alter the healthy balance of the gut microbiota, and unusually stimulate gut immune responses. If an individual has a genetic susceptibility to infections, the down guideline of a swelling in the bowel wall does not happen in an appropriate method. This initiates the auto-immune process which is a self-increasing cycle. Extra-intestinal manifestations of IBD are of high significance due to the fact that they cannot just follow intestinal signs, but precede them by years.**

Keywords: **Crohn's disease (CD), ulcerative colitis (UC).**

1. INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are the two main forms of chronic inflammatory bowel disease (IBD). The clinical features, diagnostic assessment, and treatment of these diseases are the topic of this review article [(1,2)]. CD affecting more than 2.5 million individuals in the Western world and has an increasing incidence in the developing world [(3)]. The prevalence of IBD rapidly increased in Europe and North America in the second half of the twentieth century and is becoming more common in the rest of the world as different countries adopt a Western lifestyle (4). Such epidemiologic observations indicate that there are strong environmental influences on IBD: their influence is confirmed by the relatively low concordance rate in identical twins (~50% for Crohn's disease, and ~10% for ulcerative colitis) [(5)].

CD is characterized by mucosal ulceration and inflammation, which may occur anywhere along the gastrointestinal tract but most commonly affect the distal small intestine. Distinguishing features include discontinuous, transmural inflammation involving the whole thickness of the bowel wall, and an inflammatory response associated with lymphoid aggregates and granulomas [(6)].

The clinical features of the disease depend on its localization and often include diarrhea, abdominal pain, fever, clinical signs of subileus or ileus, and/or the passage of blood and mucus per rectum. Patients with Crohn's disease often do not have bloody diarrhea, but rather abdominal pain or nonspecific abdominal symptoms. Patients with left colitis or ulcerative proctitis generally have a milder disease course (Table 1) [(1,7)].

The most widely held hypothesis on the pathogenesis of IBD is that overly aggressive acquired (T cell) immune responses to a subset of commensal enteric bacteria develop in genetically susceptible hosts, and environmental factors precipitate the onset or reactivation of disease [(5,7)].

The aim of this successful updated review study was to overview the pathogenesis of Crohn's disease (CD) and ulcerative colitis, and demonstrate the most updated evidence in this topic, we also aimed to discuss the treatment of both diseases.

Table 1. Differential diagnosis of ulcerative colitis and Crohn's disease (1)

	Ulcerative colitis	Crohn's disease
Epidemiology		
Sex ratio (M:F)	1:1	2:1
Nicotine	Can prevent disease*	Precipitates disease & episodes
Genetic components	Yes, but less than in Crohn's disease	Yes
Clinical manifestations		
Hematochezia	Common	Rare
Blood and mucus per rectum	Common	Rare
Small bowel involvement	No (except in "backwash ileitis")	Yes
Upper GI tract involvement	No	Yes
Abdominal mass	Rare	Sometimes in the right lower quadrant
Extra-intestinal manifestations	Common	Common
Small bowel ileus	Rare	Common
Colonic obstruction	Rare	Common
Perianal fistulae	No	Common
Biochemical findings		
ANCA-positive	Common	Rare
ASCA-positive	Rare	Common
Histopathology		
Transmural mucosal inflammation	No	Yes
Abnormal crypt architecture	Yes	Unusual
Cryptitis and crypt abscesses	Yes	Yes
Granulomata	No	Yes, but rare in mucosal biopsies of the bowel
Fissures or so-called skip lesions	Rare	Common

* But not in the pharmacological sense; therapeutic studies negative.

GI, gastrointestinal; ANCA, anti-neutrophilic cytoplasmic antibodies; ASCA, anti-Saccharomyces cerevisiae antibodies.

2. METHODS

We performed a Systematic review study about pathogenesis of CD&UC.

Data sources and searches:

PubMed and Embase were searched for eligible studies that discussing the pathogenesis background of the most common two inflammatory bowel diseases (CD&UC) up to November 2016, search strategy used MeSH/EMTREE terms and free text words, and included sub-searches related to the index test, target condition, study population and publication type. A methodological filter for the identification of relevant studies was added to increase the specificity of the search. Reference lists of all retrieved concerned studies were checked for additional relevant studies for pathogenies and treatment of these two diseases. Additionally, references were checked of relevant reviews, meta-analyses, guidelines and commentaries identified in PubMed and Embase.

3. RESULTS&DISCUSSION

Common extra-intestinal manifestations:

Patients with Crohn's disease and ulcerative colitis can develop extra-intestinal manifestations. The most common types affect the musculoskeletal system, the skin (**Figure 1**), the eyes, and the hepatobiliary system [11,12]. The occurrence and seriousness of extra-intestinal symptoms might be independent of the medical course of the underlying disease, i.e., some patients may present with an extra-intestinal symptom as their very first sign of the disease while they still have only moderate gastrointestinal symptoms, or none at all. In such scenarios, the clinician ought to always look for proof of Crohn's disease or ulcerative colitis. In case enhancing the medicinal treatment of the underlying intestinal disease fails to improve the extra-intestinal manifestations, these may have to be treated with professional assessment in the medical specialties dealing specifically with the affected organs [11,12].

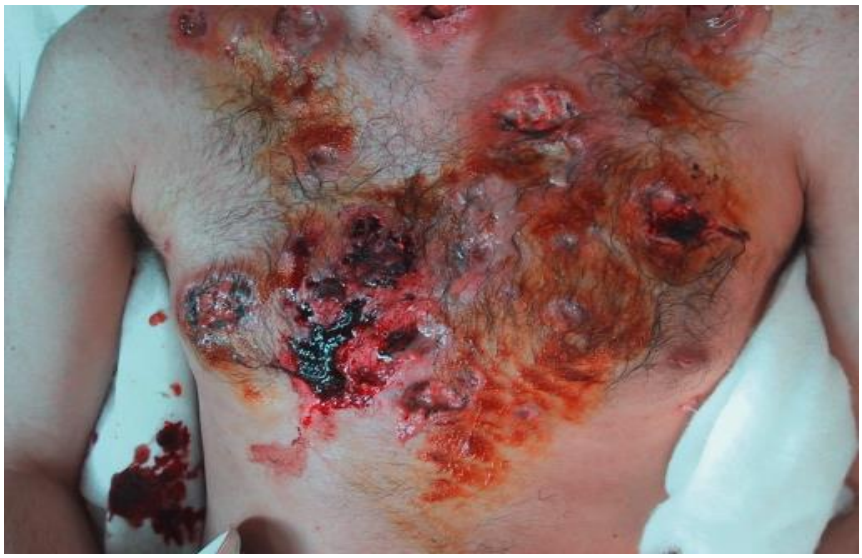

Figure 1: Pyoderma gangrenosum as an extraintestinal manifestation in a patient with ulcerative colitis [11]

Crohn's disease (CD) and Ulcerative Colitis Pathogenesis:

(Genetics Background);

Hereditary factors play an important function in IBD pathogenesis, as evidenced by the increased rates of IBD in Ashkenazi Jews, familial aggregation of IBD, and increased concordance for IBD in monozygotic compared with dizygotic twin sets [8]. Genetic analyses have connected IBD to specific genetic versions, especially CARD15 variants on chromosome 16q12 and the IBD5 haplotype (covering the organic cation transporters, SLC22A4 and SLC22A5, and other genes) on chromosome 5q31 [9]. CD and UC are believed to belong conditions that share some genetic vulnerability loci but vary at others. Concerning the Genetics backgrounds for the pathogenesis of CD we have included three important studies [8,9,10], and those studies revealed the effective genome-wide association studies (GWASs) have actually supplied a logical structure for brand-new mechanistic insights and directions for research study in CD. The most total photo is from the recent meta-analysis of 15 IBD scans (including ulcerative colitis, UC), including a combined overall of more than 75,000 controls and cases [8]. Overall, 163 IBD loci that fulfill genome-wide significance thresholds were found; this is significantly more than other complex diseases. Most genetic associations are shared in between CD and UC (110 loci), and 30 loci were particularly associated with CD (**Figure 2**). These most strongly and regularly implicate styles involving defective intracellular germs killing and natural resistance (CARD15/NOD2, IRGM, IL23R, LRRK2, and ATG16L1) and de-regulated adaptive immune reactions, namely the interleukin-23 (IL-23) and T assistant 17 (Th17) cell pathway (IL23R, IL12B (encoding IL-12p40), STAT3, JAK2, and TYK2) [9]. Dendritic cells (DCs) followed by CD4 T, natural killer (NK), and NKT cells revealed the greatest enrichment of these susceptibility gene sets when evaluated in a panel of immune cell subsets, suggesting a major function for these cells in CD pathogenesis [8]. It is noteworthy that these GWASs were based predominantly on North American and European populations; the International IBD genetics consortium is in the innovative stages of a broadened meta-analysis of association studies involving non-Caucasian populations together with the populations studied in Europe and North America [10].

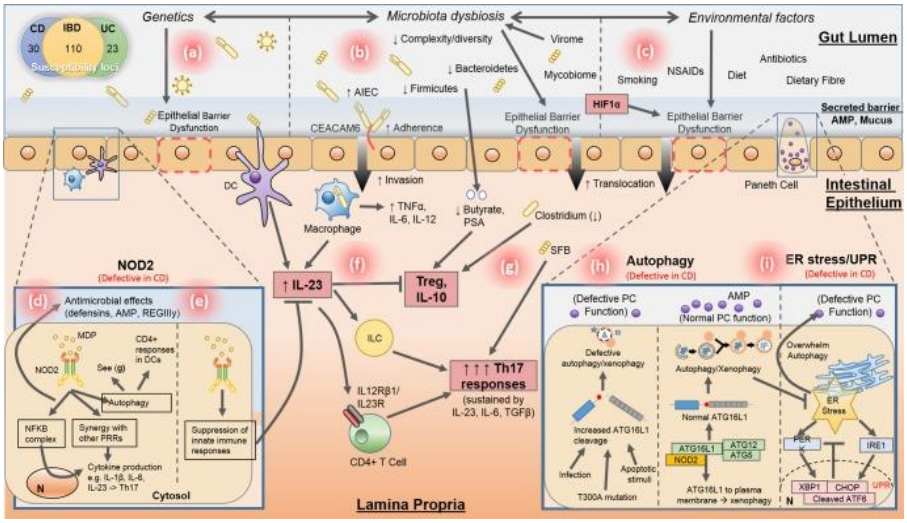

Figure2. Molecular mechanisms in the pathogenesis of Crohn's disease (CD) [10]

30 new signals were identified here beyond those explained in the earlier meta-analysis [13] and other subsequent publications. The brand-new associations were driven mainly by increased power emerging from the expanded sample size rather than enhanced imputation, as more than two-thirds of the unique loci recognized here have great proxies (r2 > 0.8) on both earlier generation varieties (Illumina 300K and Affymetrix 500k Set). Extending this argument beyond the current analysis, it seems likely that much more loci of modest impact size still await discovery [13].

For a lot of the unique loci, associations have been reported formerly in other complicated diseases, making up primarily persistent inflammatory disorders. Such diseases can cluster both within people and families, reflecting shared hereditary threat elements. IBD and ankylosing spondylitis can co-segregate and both are associated with IL23R [14,15] and TNFSF15 [16,17]. The IL10 locus was formerly associated with UC [18] and was determined as a novel CD locus in today study.

Treatment of CD&UC:

The goals of treatment for both ranges of persistent inflammatory bowel disease are the rapid induction of a steroid-free remission and the prevention of issues of the disease itself and its treatment. As a rule, the treatment is picked on the basis of the extent and degree of seriousness of the disease, its responsiveness to previous treatments, and the individual patient scenario [1,12,19].

With respect to the option of drugs and the timing of their use, some of the professional societies prefer a stratified method. The usefulness of a "treatment pyramid" of this type is currently discussed, since there is proof from other specializeds that the early administration of extremely potent drugs such as anti-TNF biological agents might avoid late complications. On the other hand, treatment with immune modulators and biologics confers a cumulative danger of infections, lymphoma, and other types of malignancy, especially in adolescents [20]. It stays to be seen whether early, aggressive treatment can be used successfully in this area of gastroenterology [21].

As in some research studies, Prednisolone or intravenous hydrocortisone are appropriate for initial treatment for serious ileal CD. Azathioprine (AZA) (or mercaptopurine) must be included for those who have relapsed, because it has a corticosteroid sparing effect (NNT 3) and is effective at keeping remission [22]. Methotrexate (MTX) ought to be considered as an appropriate alternative if thiopurines cannot be endured, but has particular contraindications, such as pregnancy [23].

Surgical treatment:

Urgent surgery is suggested for patients with deadly complications, such as intestinal perforation, refractory bleeding, or toxic megacolon, that do not respond to pharmacotherapy [24,25,26]. Optional surgical treatment is suggested for patients with dysplasia or malignancy, a refractory disease course, or intolerance to long-term immunosuppression or other medicinal treatments [25,26]. The most common surgical method utilized to deal with ulcerative colitis is total proctocolectomy with an ileal J-pouch anal anastomosis (IPAA). Particular indicators for surgery in Crohn's disease include the development of fibrotic strictures causing total or partial intestinal blockage, internal complex fistulae, stomach abscesses, and enterovesical, enterovaginal, and enterocutaneous fistulae [27].

4. CONCCLUSION

The etiology is complicated, the most extensively accepted hypothesis purports CD as an immune-mediated condition in genetically vulnerable people, where disease onset is set off by environmental aspects that irritate the mucosal barrier, alter the healthy balance of the gut microbiota, and unusually stimulate gut immune responses. These 3 main aspects (genetics, gut immune reaction, and the microbiota) are influenced by the individual's environmental exposures or triggers (the 'exposome') to engage different sub mechanisms triggering 'Crohn's diseases', a principle which is significantly changing the conventional paradigm of 'Crohn's disease' as a particular clinical entity with one dominant system. If an individual has a genetic susceptibility to infections, the down guideline of a swelling in the bowel wall does not happen in an appropriate method. This initiates the auto-immune process which is a self-increasing cycle. Extra-intestinal manifestations of IBD are of high significance due to the fact that they cannot just follow intestinal signs, but precede them by years. Hepatic and biliary disruptions (primary sclerosing cholangitis), are the most severe issues. Mucocutaneous symptoms can be the first appearance of the main disease (in the mouth). Auto-immune effects (erythema nodosum) or complications triggered even by the treatment can happen.

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