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Review article

Current overview of extrinsic and intrinsic factors in etiology and progression of inflammatory bowel diseases

Marta Sobczak, Adam Fabisiak, Natalia Murawska, Ewelina Wesołowska, Paulina Wierzbicka, Marcin Wlazłowski, Marta Wójcikowska, Hubert Zatorski, Marta Zwolińska, Jakub Fichna *

Department of Biochemistry, Faculty of Medicine, Medical University of Lodz, Łódź, Poland

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ABSTRACT

Inflammatory bowel diseases (IBD) are chronic, relapsing disorders affecting gastrointestinal (GI) tract and associated with intestinal mucosa damage and inflammation. The principal therapeutic goals in IBD include control of the intestinal inflammation and treatment of the major symptoms, mainly abdominal pain and diarrhea. Current therapeutic strategies for IBD rely on the use of non-specific anti-inflammatory agents and immunosuppressive drugs (e.g. aminosalicylates, monoclonal antibodies, and antibiotics), which cause severe side effects, and – in a significant number of patients – do not induce long-term benefits.

In this review, we summarize the epidemiology and the most important risk factors of IBD, including genetic, immunological and environmental. Our main focus is to discuss pharmacological targets for current and future treatments of IBD.

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* Corresponding author.
E-mail address: jakub.fichna@umed.lodz.pl (J. Fichna).

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Introduction

Inflammatory bowel diseases (IBD) are chronic gastrointestinal (GI) disorders characterized by alternating periods of relapses and remissions, with unknown etiology. Several factors are thought to play a role in the pathogenesis of IBD, such as environmental, genetic and inherent [1]. IBD constitute a large group of GI diseases, including collagenous, lymphocytic, eosinophilic and indeterminate colitis, but the most common are Crohn's disease (CD) and ulcerative colitis (UC) [2]. The first symptoms of CD and UC occur between second and fourth decade of life, but the IBD incidence increases with age [3]. Generally, UC diagnosis is more common than CD [4] (Box 1).

CD is characterized by transmural lymphoid aggregates, fissuring and non-necrotic granulomas. It may affect all segments of the GI tract, but most commonly the terminal ileum. Contrary to UC, CD does not involve the whole length of the intestine and the lesions co-localize with healthy areas. Extraintestinal pathological changes in the GI tract, including esophagus, stomach or duodenum, occur in 1–4% of patients [9].

CD can be distinguished into three main phenotypes: inflammatory (most common), fistulizing, and stricturing. The fistulizing phenotype is observed more frequently in Hispanics than in Caucasians or African-Americans [10].

UC, which is characterized by inflammation and ulcerations only in the mucosal and submucosal layers of the colon, mainly involves the rectum, but it may also affect the large intestine. The occupation of the entire colon (pancolitis) occurs in 20–30% of the UC patients. Others (20–30%) have left-sided pancolitis, while in the remaining 40–60% the inflammation is limited to rectosigmoid area [9]. However, in one of the studies the majority of patients (62%) suffered from pancolitis, 27% of the UC patients had left-sided colitis and 11% of them suffered from proctitis and the distribution was similar across all racial groups. Of note, it was assessed that females have a significantly higher risk of left-sided colitis than males [10].

IBD epidemiology

The IBD incidence depends on the geographic region. High incidence of IBD was reported in North Europe and North America, especially in highly developed countries, such as Canada (20.2 and 19.2 per 100,000 persons for CD and UC, respectively), North Europe (24.3 and 10.6 per 100,000 persons in Iceland and United Kingdom, respectively for CD) and Australia (29.3 and 17.4 per 100,000 persons for CD and UC, respectively). In Asia and the Middle East the IBD rates of incidence range from 0.04 to 5.0 per 100,000 persons. Nevertheless, the worldwide incidence of IBD is still increasing, mainly in the developing countries [3].

Similarly, the prevalence of IBD was the highest in Europe (322 per 100,000 persons for CD in Italy and 505 per 100,000 persons for UC in Norway) and Canada (319 and 248 per 100,000 persons for CD and UC, respectively). In Europe, there was no difference in the prevalence between Southern and Northern part [11]. The prevalence of IBD in Asia and Middle East ranges from 4.9 to 168.3 per 100,000 [3].

The diagnosis of IBD is not gender-specific [12]. However, there are reports indicating that women suffer from IBD more frequently than men [13]. Interestingly, Hispanic and African-American males suffer from IBD more frequently in comparison with Asians [14]. Some ethnic differences in the incidence UC and CD in patients have also been observed. IBD morbidity is more common in Caucasian population and UC is diagnosed more frequently than CD in Hispanics and Asians. Furthermore, in the African-American population IBD is diagnosed in younger people in comparison with Asians and CD was more frequently diagnosed than UC [14].

The higher IBD morbidity is reported more frequently in patients with the history of IBD in the family, especially among first-degree relatives (30–100 times more than in the general population). The family history of IBD is documented in 30% of patients diagnosed in young age (before 20 years). For comparison, 13% of patients diagnosed above 40 years have a family member suffering from IBD. These examples confirm the genetic predisposition of IBD inheritance and suggest the involvement of several genes in the IBD development.

Box 1. Disease activity indices play a crucial role in monitoring the progression of IBD, managing the treatment strategy and assessing the effects of drugs on patients.
The first and only index for CD – Crohn's Disease Activity Index (CDAI) was proposed by Best et al. [5]. It included eight variables and the final score reflected the disease activity. Time-consuming calculations are undesirable in such indices, therefore it had to be simplified [6]. A pediatric version of CDAI was designed some time later to better fit CD in children patients [7].
Researchers were not that unanimous developing the index for UC. Around twenty of indices were proposed in the last 60 years and only two of them are being widely used these days: the Mayo Score and the Clinical Activity Index [8]. Both of them have an endoscopic score included.

Pathogenesis of IBD

The etiology of IBD remains poorly established. Many factors may participate in the development of IBD, such as genetic, immunological and environmental, including diet, depression, stress and also influence of free radicals (Fig. 1). There are also some hypotheses that urban living and lack of exposure to pets and vegetable gardens are combined with increased risk of IBD. They all seem to be crucial for the development of IBD, but to a different degree [15].

The studies with monozygotic twins clearly indicate the possibility of the existence of environmental factors in IBD development [16,17]. Another investigation on monozygotic twins revealed that, despite identical genome, they differ in microflora [18]. However, it was also revealed that genetic factors determine the composition of the microflora and are responsible for maintaining homeostasis in the intestine [19].

Genetic factors

One of the most important genes, whose different variants predispose to IBD, is NOD2. It appears that the protein encoded by this gene is responsible for the proper function of Paneth cells, which secrete antimicrobial proteins and cytokines to provide efficient autophagy [20]. It was confirmed in murine models of IBD that NOD2 variants predisposing to CD impair autophagy also in dendritic cells [21].