

Immune Aspects of the Inflammatory Bowel Disease; Correlations with Celiac Disease

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Abstract Inflammatory bowel diseases (IBD) are serious health problems and are connected with increased risk of colitis-associated colorectal carcinoma (CAC). It is the most common cause of death in the patients with Crohn's disease and ulcerative colitis. In this short review, we intend to summarise some aspects of the immunological signalling networks that may be involved in the pathogenesis of CAC patients with the perspectives of treatment of the disease. We also focused on the correlation between celiac disease and IBD.

Keywords: Crohn's disease, ulcerative colitis, colorectal cancer, celiac disease, chronic, inflammation, cytokine, signalling

Cite This Article: Fabian Caja, Pavol Makovicky, and Luca Vannucci, "Immune Aspects of the Inflammatory Bowel Disease; Correlations with Celiac Disease." *International Journal of Celiac Disease*, vol. 4, no. 4 (2016): 130-134. doi: 10.12691/ijcd-4-4-5.

1. Introduction

The Inflammatory Bowel Disease (IBD), including the major types Crohn's disease (CD) and ulcerative colitis (UC), represents a serious health problem in Western countries. The worldwide incidence is currently highest in Europe (UC, 505 per 100,000 persons; CD, 322 per 100,000 persons) and in the North America (UC, 249 per 100,000 persons; CD, 319 per 100,000 persons) [1]. The incidence of CD has an increasing trend in Hungary and Croatia for example, while other countries, including Czech Republic and Slovakia, reported relatively low incidence and prevalence rates [2]. In general, the highest incidence in Europe was observed in Scandinavia and the United Kingdom, while it remains rare in the southern and Eastern Europe [3]. The annual mortality by IBD has increased in the European Union by 8.9% since 1990 and women are killed at a higher rate than men (<http://global-disease-burden.healthgrove.com>). In this minireview, we aim at summarise the general features of IBDs with the focus on molecular immunological processes involved in the pathogenesis of the disease. We also compare IBD with another serious bowel pathology-celiac disease with the therapeutic possibilities in the final part.

2. Exogenous and Endogenous Factors of the IBD

Neither CD nor UC are fatal, but both are significantly decreasing the quality of human's life. The most common symptoms include inflammation of the gut, diarrhoea, vomiting, anaemia, weight loss and rectal bleeding [4].

The proper causes of IBD are not clear so far, but it is considered as a multifactorial disease, resulting from unbalanced relationships between environment, genetic background and innate immunity [5]. The example of genetic background impact is the group of Ashkenazi Jews, who are five to eight times more likely to develop IBD than other non-Jewish groups [6]. Among environmental factors, the Western diet is suspected to induce chronic intestinal inflammation by altering the composition of the microbiome [7]. This is very well reflected in the rising prevalence of IBD worldwide as more newly industrialized countries are adapting to a lifestyle based on a Western diet. An experimental mouse IBD model confirmed that exposure to Western diet induced dysbiosis of the intestinal microbiome, which was followed by disruption of the intestinal barrier function [8]. Moreover, it is well known that specific nutrients may modulate innate immunity towards pro-inflammatory reactions, which influence the composition of intestinal microbiota [9]. The exogenous factors affecting the risk of IBD are still disputed. They include type of childbirth, breastfeeding and exposure to antibiotics in the childhood, but also other factors such as smoking, stress and diet in the adulthood. Crohn's disease but not UC is associated with smoking habits. The main factors increasing the IBD incidence are the low percentage of fibres in the diet, saturated fats, low vitamin D intake, depressions and impaired sleep [10].

Also endogenous factors play important role in the epidemiology of IBD. It is clear that the genetic background is a major endogenous factor that affect the development of IBD. In the past, it was proposed that IBD is caused by the accumulation of genetic mutations in a concrete gene or a few genes. But after few years, genome wide association studies revealed that it is more a combination of gene defects in many genes that causes IBD. De Lange

and Barrett reviewed this phenomenon and summarized all genes included in the IBD epidemiology [4].

3. Relationship between IBD and Celiac Disease

The connection between celiac disease (CeID) and IBD was also studied. As chronic inflammation is a general pattern of CeID, we may suppose that IBD would increase the risk of CeID development. However, recent studies did not find any difference in the prevalence of CeID in patients with IBD diagnosis and the general population [11]. One Hungarian study focused on this association from the opposite view, if the presence of CeID is increasing the risk of IBD development. They found only very small (3.2 %) increase in the prevalence of IBD in celiac patients than in the general population [12]. A very interesting case was reported by Tankova et al., who found one older male patient with a selective IgA deficiency, who developed simultaneous CeID and CD. Celiac disease was moreover located in the upper part of the bowel [13]. Crohn's disease is frequently located in the upper part of the bowel in younger patients, more rarely in the old patients. The authors also hypothesized that the association between CeID and CD may be under-diagnosed due to similar clinical symptoms, and suggested that patients with CD should be also preventively tested for CeID. And what is the association between the colon carcinogenesis and CeID? In general, CeID risk for cancer development is slightly increased, but it is still lower than for IBD. Moreover, recent studies suggest a decrease of CRC occurrence in CeID patients as a consequence of more rapid absorption and excretion of fat and fat-soluble agents that promote colon carcinogenesis and induce changes in the composition of the colon microbiome [14].

4. From Inflammation to Colorectal Cancer

Another very important aspect of IBD is its association with the development of colorectal carcinoma (CRC). Colorectal pathogenesis has been studied for a long time, especially for the connections between the chronic inflammation and the origin of the disease. A special type of CRC, called colitis-associated CRC (CAC), is characterized by the development of CRC under chronic inflammatory conditions, differing from the sporadic form of CRC. For example, patients with UC develop CAC 20 to 30 times more often than the general population. The risk increases with the time after IBD diagnosis [15,16]. Also, malignant potential is higher in CAC, which reduces the therapy possibilities and worsens the survival of CAC patients [17]. The proper mechanisms, increasing the risk of CRC development in IBD patients, are still not clear, but the contribution of the immune system is a potential factor. Generally, all IBD patients have increased production of tumor necrosis factor α (TNF- α) – one of the most important cytokines in the immune system. It regulates the production of pro-inflammatory cytokines interleukin 1 β (IL-1 β) and interleukin 6 (IL-6), production of adhesion molecules, proliferation of fibroblasts and activation of pro-coagulant factors [18]. The main

hallmark of CAC tumours is the development in chronic inflammatory conditions, promoted by various cytokines secreted by immune cells. This includes also activation of essential CAC signalling pathways such as the wingless-related integration site (WNT)- β -catenin, the TNF α -NF κ B and the IL-6-signal transducer and activator of transcription 3 (STAT3) pathways [19,20,21].

5. Interleukin 6 Signalling in IBD

Interleukin 6 signalling was widely studied for its involvement in carcinogenesis of various tissues. Animal CAC models showed that IL-6 activates Janus kinase 2 (JAK2), which activates STAT3 factor. This is a direct promoter of cell proliferation and survival. However, different mechanism was observed in patients with UC [19,22]. Instead of activation of IL-6 signalling, inactivation of the inhibitors of IL-6 signalling, such as suppressor of cytokine signalling 3 (SOCS3), was present [23]. This change in signalling is typically observed in the colonic tissue of UC patients, leading to up-regulation of IL-6 signalling, followed by increased expression of micro RNA 214 (miR-214). It is well known that deregulation of miRNAs is a common hallmark of the carcinogenesis. In this case, miR-214 reduces protein and tensin homolog (PTEN), increases phosphorylation of protein kinase B (AKT) and activates NF- κ B. Accumulation of these signalling changes accelerates the evolution of CRC in UC patients. But the main actor still remains STAT3, which depletion in intestinal epithelial cells prevents progression of the tumour [24]. Immunohistochemical (IHC) analyses showed that in the early stages of CAC, IL-6 is mainly produced by myeloid cells and T-cells with a small contribution of epithelial cells. Different production was observed in IBD patients, with the strong positivity in the epithelial cells. Also the production of SOCS3 is significantly higher in IBD patients than in healthy controls [19,25]. Interestingly, there is a difference between the expression of SOCS3 in UC and CD patients. While UC patients showed significant silencing of SOCS3 expression in the evolutionary process inflammation-dysplasia-carcinoma, CD patients with dysplasia or CRC were lacking those patterns [25]. It was observed that IL-6 in UC patients is activating DNA (cytosine-5-)-methyltransferase (DNMT1), which methylates the promoter region of SOCS3 gene. This is leading to increased STAT3 signalling with its pro-proliferative and anti-apoptotic features [26]. The contribution of another cytokine IL-8 accelerates the development of the colonic cancer as was demonstrated on cancer-initiating cells by Lin et al. [27]. The key pattern accompanying the IL-6 signalling is increased infiltration of activated CD4+ T-cells into the colonic mucosa of the CRC and CAC patients.

6. Signalling Pathways of Other Cytokines

Also other cytokines play important roles in the IBD pathogenesis. The most important include TNF- α , IL-13, IL-17, IL-21, IL-23 and TGF- β 1. All of these cytokines have pleiotropic functions in the immune system, either pro-inflammatory or immunosuppressive. TNF- α is probably

one of the most relevant pro-inflammatory cytokines involved in the IBD pathogenesis. As mentioned above, binding of TNF- α to its receptor is activating mitogen-activated protein kinases (MAPKs), leading to NF- κ B as a final target in the signalling axis. NF- κ B is a master regulator of the expression of pro-inflammatory cytokines, which significantly contribute to colorectal carcinogenesis [19]. Interleukin 13, expressed by activated T-cells and NK cells, also contributes to tumour growth. The expression of IL-13 receptors, IL13R α 1 and IL13R α 2, is significantly increased in UC and CRC patients when compared to controls and CD patients. The signalling from IL-13 receptors is activating MAPK pathway, which is leading to activation of NF- κ B [28]. Recent studies also showed an increased production of Th17 cells, both in UC and CD patients. The differentiation of naïve T-cells into Th17 is maintained mainly by IL-17 and IL-23 cytokines, which were found to be over-expressed in IBD patients [29]. The differentiation is enhanced by IL-6 and TGF- β , which induce expression of IL-23R on the surface of Th17 cells. Interleukin 23 is considered as the stabilisator of Th17 response [30,31]. It is noteworthy to mention, that IL-17 has more protein isoforms, but only IL-17A is associated with the carcinogenesis [32]. The increased production of IL-17A in the tumour microenvironment is leading to increased expression of IL-6, TNF- α and STAT3, which significantly contribute to proliferation of tumour cells. Mice with IL17a knockout showed reduced colorectal carcinogenesis [33]. Interleukin 21 is produced by Th1, Th17 cells and by activated NK cells. Interleukin 21 plays quite important role in the immune system, regulating proliferation of B-cells, T-cells, regulatory T-cells and NK cells. It has similar role in IBD pathogenesis as IL-17A. Patients with UC has increased levels of IL-21 in the mucosa of the colon, positively stimulating Th17 responses [34]. Again, mice IL21 knockout showed decreased number and size of tumours. Moreover, IL21 knockout had reduced expression of STAT3, which is necessary for expression of pro-inflammatory cytokines [35]. One of the most important cytokines in the tumour microenvironment is TGF- β , which plays double role in the carcinogenesis, both pro- and anti-proliferative. In normal conditions, TGF- β is expressed in homeostatic levels, but in IBD patients, its expression is elevated. It is expressed in epithelial cells, tumour-associated fibroblasts and in various inflammatory cells [36]. TGF- β is inducing the expression of L1CAM adhesion molecule in UC and CD patients, which was also confirmed in the murine UC colonic tumour model [37].

In contrast to IBD, patients with CeID have mainly up-regulated expression of IL-15 and interferon γ , which increase the release of tissue transglutaminase 2. It produces deaminated glutamine peptides from gliadin, which bind with high affinity to DQ2 and DQ8 HLA II receptor molecules on the surface of antigen presenting cells. This activates subsequent immune responses with the pathological impact on the patient [38].

7. Genetic Instability as a “side effect” of IBD

The genetic pathways are significantly involved in the IBD pathogenesis. We may mention that UC patients very

frequently display instability in the genetic level, involving inactivation of tumour-suppressor genes, over-expression of oncogenes, loss of heterozygosity and chromosomal and microsatellite instability [39]. These changes are typically observed in CRC patients. Interestingly, genetic instability in UC patients occurs mainly in non-dysplastic tissue. This can be explained by the production of high levels of reactive oxygen species in the inflammatory milieu, accounting for oxidative stress and cellular damage [40]. Except of typically affected genes APC, KRAS and TP53, also mismatch repair gene MutL homolog 1 (MLH1), is frequently inactivated in IBD patients. In this case, an epigenetic mechanism of promoter hypermethylation is involved [41].

8. WNT- β -catenin Signalling Pathway

Among other genetic pathways, WNT- β -catenin is very commonly affected in IBD patients. WNT is a glycoprotein that interacts with the transmembrane receptor Frizzled. This interaction activates various intracellular signalling pathways, which regulate mainly cell proliferation, differentiation, cell polarity and cell migration [42]. It is logical, that deregulation of these processes is fatal and it can contribute to carcinogenesis. The expression of WNT is elevated in IBD to stimulate the proliferation of intestinal cells. It is disputed that it is a response of epithelial cell to inflammation [43]. A possible role of epigenetic mechanisms of WNT-signalling pathway genes was also examined. The promoter hypermethylation of WNT-signalling genes occurs in the early stages of IBD and progressively elevates with the progress of the disease [44].

9. Therapeutic Perspectives-classic vs. Modern

There are also other signalling pathways and molecular mechanisms involved in IBD progression, but are there any treatment possibilities? In fact, there are very limited ways how to manage this disease. There is no direct cure so far and symptoms are now cured by using anti-inflammatory drugs. They are used not only to treat the disease, but also as prevention against CAC. In the case of CAC, surgical approach is preferred with the total proctocolectomy as the gold standard. An extensive resection eliminates all lesions in UC patients and protects them against the development of new lesions. Different approach is used in CD patients, where lesions are segmental and total proctocolectomy is not necessary [45]. New approaches of the treatment occurred in the past years. As TNF- α is one of the main pro-inflammatory cytokines present in IBD patients, anti-TNF- α antibodies are tested. One case-control study showed a reduced risk of CAC development [46]. Anti-IL-6 antibody tocilizumab and anti-VEGF antibody bevacizumab were also tested [47]. Except of the immunotherapy, chemoprevention is still preferred. Thiopurines seem to be associated with decreased neoplasia development in IBD patients [48]. However, new therapeutic approaches depend on the knowledge of the molecular principles of

the IBD, which are still limited. Some new perspectives are going to be opened by the increasing knowledge about the commensal microbiota and the consequent indications for the use of probiotics in prevention and/or treatment of IBDs.

10. Conclusion

In conclusion, IBD represents a serious health problem with limited treatment possibilities. Recent studies did not prove an increased prevalence of celiac disease in IBD patients and vice versa. Among the plethora of signalling pathways, TNF- α -STAT3 and WNT- β -catenin seem to be the predominantly affected in the IBD. The connection between IBD and CRC development is very significant, suggesting how critical is the presence of inflammation in the CRC carcinogenesis. A better understanding of the molecular mechanisms leading to IBD would enhance to develop new and more effective therapeutic strategies.

Statement of Competing Interests

The authors have no competing interests.

Acknowledgements

We acknowledge RVO 61388971 (CZ).

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