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Cent. Eur. J. Biol. • 9(11) • 2014 • 1022-1029
DOI: 10.2478/s11535-014-0345-7

Central European Journal of **Biology**

Current overview of colitis-associated colorectal cancer

Mini-Review

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#Equal contribution

Received 16 December 2013; Accepted 27 April 2014

Abstract: Colitis-associated colorectal cancer (CACRC) constitutes a severe complication of inflammatory bowel diseases (IBD) and occurs in more than one third of IBD patients. In this short review we focus on the mechanisms underlying CACRC pathogenesis, and discuss the approaches for prevention and therapy in CACRC.

Keywords: *Colitis-associated colorectal cancer • Inflammatory bowel diseases • Risk factors • Chemoprevention and chemotherapy*

1. Introduction

Colorectal cancer (CRC) is among the most frequently diagnosed malignant tumors and the second most common malignancy in developed countries. CRC is a significant cause of mortality, established as the fourth cause of death in the world. At least three major forms of CRC have been described, including hereditary, sporadic, and colitis-associated (CACRC) [1]. The major risk factors for CRC development constitute: inflammatory bowel diseases (IBD), hereditary syndromes of familial adenomatous polyposis and the nonpolyposis colorectal cancer syndrome [2].

The first evidence indicating the association between chronic inflammatory state in the colon and cancer development was described by Virchow in 1863 [3] and ever since a cause -effect connection between CACRC and IBD has been investigated. In this review we discuss the mechanisms underlying the pathogenesis of CACRC, with a particular focus on the intrinsic and extrinsic risk factors and relation to IBD. We also give a brief overview on current and future concepts in CACRC chemoprevention and chemotherapy.

The data presented here were collected from electronic scientific databases *e.g.* MEDLINE, SCOPUS, Web of Science, Directory of Open Access Journal, electronic editorial networks, such as BMJ, Elsevier, Karger, Nature Publishing Group, Springer, literature distributors, such as EBSCO, and clinical trials databases, such as CT and EU - CTR. The scientific papers were selected according to the time span ranging mainly from 2000 to present.

2. Epidemiology of CACRC in IBD patients

IBD are idiopathic, relapsing and chronic disorders, which affect the gastrointestinal (GI) system. Within this large group of inflammatory disorders the most common are Crohn's disease (CD) and ulcerative colitis (UC), which are diagnosed in 1-2% of population [4]. IBD occurs between 15-30 and then 50-70 years of age. The major symptoms of IBD include abdominal pain, inflammation, fecal bleeding, diarrhea and weight loss.

Intestinal infections and chronic inflammation may contribute to the development of up to 25% of all diagnosed colorectal tumors. Major studies on CACRC evaluate its risk in UC, rather than CD. Eaden *et al.* [5] presented a wide overview of cancer incidences

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among UC patients, based on 116 studies from several countries. It was revealed that an overall occurrence of CACRC is about 3.7 % and its cumulative risk increases with the duration of UC. Respectively, 10, 20 and 30 years of UC increase the CACRC risk of about 2, 8 and 18%. Regrettably, different inclusion and exclusion criteria and the fact that the studies were performed in several centres negatively affected a clear view on the risk of CACRC in the entire population of UC patients. Lakatos *et al*. [6] confirmed that there is an increased risk of CACRC in IBD patients based on the study with 723 Hungarian subjects. It was also confirmed that the cumulative risk of CACRC in UC increases over the time. Finally, the correlation between carcinogenesis and UC was reported by Jess *et al*. [7], who showed that UC increases the incidence of CRC 2.4-fold.

The incidence of CACRC differs significantly in CD, in comparison with UC patients, what correlates with the specificity of both diseases. Laukoetter *et al*. [8] revealed that the CACRC incidence in CD patients is in fact similar to that in the overall population; however, CD patients developed CACRC at a younger age than control subjects. Of note, it was shown that CD increases the risk of the development of the small intestine cancer, which is 18.5-fold higher in CD patients. These observations were supported by a meta-analysis based on six studies, published in 2005 by Jess *et al*. [9].

The CACRC incidence is higher in male than female IBD patients, suggesting that it may be combined with different hormone levels and turnover, most probably oestrogen production. Using a large population-based cohort (n=7607) of individuals diagnosed with IBD in the Swedish population, it was confirmed that there is a 60% higher risk of CACRC in male than female patients (relative risk=1.6) [10].

3. Risk factors in CACRC

Inflammation is an important tumor promoter and several cytokines involved in inflammatory process, such as TNF-α and IL-1β, alone can promote tumor growth. Site-specific chronic accumulation of activated immune cells, such as neutrophils, macrophages and dendritic cells is also accompanied by the release of reactive nitrogen species (RNS) and reactive oxygen species (ROS), which are known to induce genetic mutations and lead to CRC [11].

The risk factors in the development of advanced neoplasia from dysplastic lesions in the inflamed colon include primary sclerosing cholangitis (PSC), which promotes a change in the bile salt pool and an increased concentration of bile acids in the colon [12]. Lakatos *et al*. [6] revealed that PSC, together with long disease duration, dysplasia, and severe inflammation are important risk factors for CACRC in UC patients.

Jess *et al*. [9] showed that young age at diagnosis of UC predisposes to CACRC. In other studies, young age and the extent of disease at diagnosis were defined as important risk factors for CACRC [13,14].

The localization of inflammatory lesions in the GI tract may also determine the risk of CACRC development. It was revealed that IBD patients with proctitis and proctosigmoiditis are at the lowest risk of CACRC and the higher risk is combined with left-sided colitis and pan-colitis [15,16].

Finally, smoking reduces the risk of CACRC in UC patients by 50%, but increases the risk of CACRC in CD patients 4-fold. This may possibly be due to the opposite effect of nicotine on intestinal inflammation in UC and CD [17].

Factors increasing and decreasing the risk of CACRC are summarized on Figure 1.

4. CACRC from molecular, cellular and systemic point of view

Chronic intestinal inflammation contributes to tumor initiation, the first stage of carcinogenesis, by inducing DNA damage and chromosomal instability, which promote tumor development and progression by enhanced cell proliferation and disturbed apoptosis. Inflammation also stimulates angiogenesis and tissue remodeling, both of which are involved in tumor cell invasion and metastasis [18]. Cancerogenic transformation is thus associated with pathophysiological changes at genomic, cellular and systemic levels (Figure 2).

4.1 Genomic changes

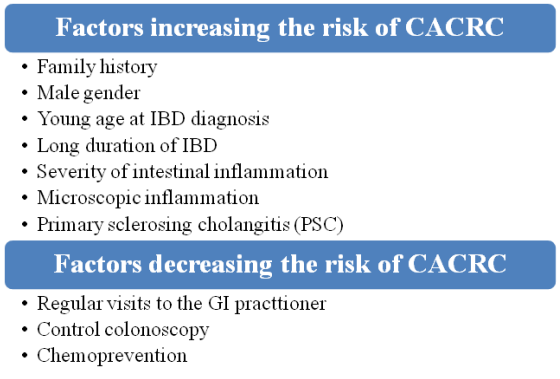

Figure 1. Risk factors in colitis-associated colorectal cancer (CACRC).

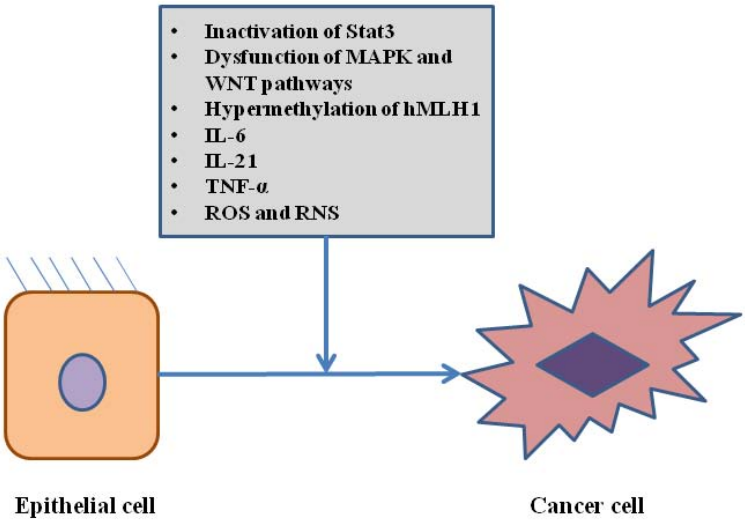

Figure 2. Biomolecular factors stimulating transformation of normal epithelial cell into cancer cell.

In the genome, the major molecular changes underlying CACRC include Loss of Heterozygosity (LOH), Microsatellite Instability (MSI) and CpG Methylator Phenotype (CIMP) [19]. Of note, in CACRC the DNA methylation and MSI tend to function at an early stage, while LOH appears to be a late event in carcinogenesis [19]. MSI occurs because of the defects in mismatch repair (MMR) gene products, including Mut S and Mut L homologs or (hMSH2, hMSH6, hMLH1, hPMS1, hPMS2, and hMLH3) [20].

The methylation status of many genes combined with inflammation, dysplasia and malignant tumors are changed in CACRC, suggesting that epigenetic mechanisms are also crucial in the inflammation-induced carcinogenesis [21]. For example, Dhir *et al*. [22] revealed that the methylation of WNT pathway genes increases due to the inflammation-associated neoplasia. Furthermore, the IBD-associated neoplastic lesions are connected with hypermethylation of *hMLH1*, which is a DNA mismatch repair gene [23].

4.2 Dysregulation of oxidation pathways

Oxidative stress-related pathways are a possible cause of IBD and they also play a major role in the transformation of IBD into CACRC [24]. The amount of phagocytic leukocytes is increased in IBD patients, mainly in UC patients, what results in an enhanced production of pro-oxidant molecules. The oxidative DNA damage increases with disease duration and the ongoing epithelial injuries, caused by the resulting inhibition of protein functions, force a continuous reconstruction. This condition leads to an increased risk of carcinogenesis. In line with this hypothesis, D'Inca recently showed that the maximum level of the oxidative DNA damage can be found in lesions with carcinogenic progression [3,24]. Concurrently, it was shown by Martinez *et al*. [25] that RNS may also induce colon carcinogenesis. The higher expression of the gene encoding 8 oxoguanine DNA glycosylase (OGG1) is also combined with increased risk of CACRC development. OGG1 recognizes oxidative damage within DNA and participates in DNA repair [26].

4.3 Changes in the immune system

At the level of the immune system, one of the important causes for CACRC is the infiltration of macrophages, neutrophils, myeloid derived suppressor cells (MDSC), dendritic cells (DC) and natural killers (NK) cells, and adaptive immune cells, such as T and B lymphocytes into the lamina propria and the colonic mucosa occurring because of chronic inflammatory processes [27]. All these cells impair the balance between pro- and anti-inflammatory cytokines.

The major transcription factors involved in cytokine production and activated during inflammation, NF-κB and STAT3, provide key links between inflammation and cancer. NF-κB is constitutively active in most tumors. NF-κB-targeted gene products include: anti-apoptotic proteins (BCL-2, BCL-XL), inflammatory molecules (TNF-α, IL-6, IL-8, COX-2), effectors of invasion and metastasis (adhesion molecules, MMPs), and angiogenic factors (VEGF) [28]. STAT3 supports carcinogenesis through mechanisms ranging from activation of genes

crucial for proliferation and survival to enhancement of angiogenesis and metastasis.

Among the cytokines significantly involved in inflammation and carcinogenesis is Tumor Necrosis Factor-α (TNF-α) [29,30]. TNF-α was found to increase mucosal infiltration by neutrophils and macrophages [31], while Popivanova *et al*. [32], based on their study on TNF-α receptor p55 knock-out mice and animals treated with anti-TNF-α, reported that TNF-α influences the size and number of tumors and could be one of the major tumor promoters.

Chung and Chang [33] observed an increase in the serum level of IL-6 in patients who underwent resection for local CRC lesions and showed a positive correlation with tumor size, progression and metastasis. Grivennikov *et al*. [34] showed that cytokines involved in the differentiation and function of T helper (Th)-17 lymphocytes, including IL-6, act as tumor promoters in CACRC through increase of intestinal epithelial cell proliferation and inhibition of apoptosis, and thus increase of tumor size in early and late stages of cancer. Also, IL-6 was shown to promote angiogenesis [35]. At the cellular level, the over-expression of IL-6 is associated with the inactivation of Stat3 and its deletion in epithelial cells in the colonic mucosa [36,37].

IL-21 is another cytokine possibly involved in CACRC pathophysiology. It is a pleiotropic cytokine produced by a range of CD4+ Th cells, activated natural killer T (NKT), and T follicular helper cells, which is associated with many immune system-mediated disorders, including IBD, allergy and autoimmunity [38]. IL-21 is over-produced in the colonic mucosa of IBD patients, where it regulates Th-17 cell responses [39,40]. High levels of IL-21 have been observed in the intestine of UC patients with CACRC [41] and therefore it has been defined as a key cytokine for promotion of CACRC [42].

Finally, a selective inhibition of IL-17A, an inflammatory mediator of Th17 cells derived from naive CD4+ cells, in a murine model of CACRC inhibits intestinal inflammation and tumor development [43].

4.4 Other

Several studies demonstrate the role of mitogen activated protein kinases (MAPK) signalling pathway in carcinogenesis. Wakeman *et al*. [44] revealed that the deletion of the enterocyte expression of p38-α MAPK promoted carcinogenesis in mice. Surprisingly, this did not exacerbate inflammation, although it is a factor predisposing to carcinogenesis.

Increased cryptal cell proliferation, changes in crypt cell metabolism, disturbances in bile acid enterohepatic circulation, and alterations in the gut microflora may also contribute to CACRC development. However, their role in the development of CACRC still needs further investigation.

5. Chemoprevention and chemotherapy of CACRC

The most effective methods of CACRC treatment are cytotoxic drugs, radiotherapy or resection of tumor area, which have been discussed in detail elsewhere [45]. In case of pharmacotherapies, low selectivity between cancer and healthy cells and a major risk of side effects are often combined with poor efficacy and the risk of relapse and therefore new therapeutic strategies are currently being developed.

Chemoprevention of cancer may be defined as an introduction of selected natural or synthetic non-toxic substances into the diet for the purpose of reducing cancer development (prevention, or delay). In CACRC there are no recommended or well-established strategies of chemoprevention. Here, we briefly discuss the latest finding in CACRC chemoprevention.

5.1 Nonsteroidal anti-inflammatory drugs (NSAIDs)

The nonsteroidal anti-inflammatory drugs (NSAIDs), in particular mesalamine, constitute a good form of chemoprevention for CACRC in IBD patients [5]. The principal mechanism of NSAID action is the inhibition of COX-2, the major enzyme involved in production of prostaglandins, which influence apoptosis, cell division, angiogenesis and metastasis [46]. It was also evidenced that NSAIDs, such as sulindac and celecoxib, inhibit NF-κB expression in early phase of carcinogenesis [47,48]. Finally, mesalamines scavenge free oxygen and nitrogen radicals and in this manner participate in reduction of DNA single or double strand breaks and replication errors [49].

Some NSAIDs, such as aspirin and indomethacin, were shown to decrease *in vitro* the transcription of the TCF responsive genes and thus the β-catenin/TCF signaling complex, which may suggest the inhibition of the entire pathway [50]. β-catenin plays an important role in cell development, cellular proliferation and differentiation. It has been proposed that elevated level of β-catenin triggers carcinogenesis in CRC, as seen in the mouse colon [51]. Therefore the β-catenin pathway disruption mediated by NSAIDs may lead to efficient CACRC chemoprevention [50].

The intake of NSAIDs may reduce the risk of CACRC development, but their application is limited due to severe adverse effects in the gastrointestinal system, including gastric ulcers [52]. Furthermore, some studies revealed that not all NSAIDs, *e.g*. 5-ASA, are effective in CACRC chemoprevention [53].

5.2 Vitamin D

As shown by Marchiani *et al*. [54], analogs or metabolites of vitamin D possess antiproliferative, pro-apoptotic, and pro-differentiative effects in human colon cancer cells *in vitro*. For example, the vitamin D analog Ro26-2198 inhibited proliferative signals (ERK, c-Myc), decreased pro-inflammatory molecule levels (prostaglandins) and progression to dysplasia in mouse model of CACRC, what suggests its chemopreventive efficacy [55].

5.3 Proton pump inhibitors

The expression of matrix metalloproteinases (MMP)-9 and -11, and membrane-type-1 matrix metalloproteinase MT1-MMP is significantly decreased in mice with CACRC treated with the proton pump inhibitor, omeprazole (10 mg kg^{-1}). Omeprazol is believed to reverse the progression of inflammation-initiated or promoted carcinogenesis through antioxidative, anti-inflammatory, and antimutagenic effect independent of action on gastric acid [56].

5.4 Anti-TNF-α agents

As shown *in vivo* on a mouse model of CACRC, only 16.7% of animals treated intravenously with infliximab at dose 4 mg kg^{-1} for 37 weeks developed tumors *vs*. 75-80% of control mice [57]. This suggests that the early and intensive therapy with infliximab may prevent the development of CACRC in high-risk IBD patients.

5.5 Organic compounds

Recently, a chemoprotective effect on CRC in IBD patients was noted after administration of organomagnesium [58]. Another study on 2578 IBD patients showed a similar effect after treatment with thiopurines [59].

6. Conclusion

There is no doubt that CACRC is in direct correlation with the severity of the inflammation and the extent and duration of the disease. However, as discussed here, the cellular pathways involved in CACRC pathophysiology have not been fully elucidated, what hampers the development of effective therapeutic strategies.

The discovery of the drug with anti-inflammatory and antitumor activity in the GI system may thus limit time and costs of treatment and possible hospitalization of IBD and CACRC patients. Moreover, an improved therapy of IBD and CACRC may influence patient quality of life and comfort, which are significantly decreased during the course of disease. Further continuation of the studies on CACRC pathophysiology and possible treatment are thus warranted.

Conflict of interests

The authors have no conflict of interest to disclose.

Acknowledgments

Supported by the Iuventus Plus program of the Polish Ministry of Science and Higher Education (IP2012 010772 to JF) and the Medical University of Lodz (502-03/1-156-02/502-14-141 to M Sobczak, 502-03/1-156-02/502-14-140 to M Sałaga).

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