Chronic Inflammation in Colorectal Carcinogenesis: Role of Inflammatory Mediators, Intestinal Microbes, and Chemoprevention Potency

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ABSTRACT

Colorectal carcinogenesis is a multi-factorial process which involves accumulation of genetic defect, protein modification, and cell interaction with matrix in colonic epithelial cells. Chronic inflammation is suspected to play role in carcinogenesis by inhibiting apoptosis, impairing DNA, and chronically stimulating mucosal proliferation. Alteration in intestinal microbes' population, either in one particular species or in overall composition, may also cause chronic inflammation which increase the risk of developing adenoma or carcinoma.

Inflammatory mediators and intestinal microbes have diverse effect in colorectal carcinogenesis. Several may increase host anti-tumor immunity, while the others may increase tumor growth. Various ways of interactions have just started to be partially understood. In addition, colorectal cancer chemoprevention is a promising and important knowledge due to limited success of current available therapy. Chemopreventive agents are currently being studied and have different success rate.

Keywords: *inflammation, microbes, chemoprevention, carcinogenesis, colorectal cancer*

ABSTRAK

Karsinogenesis kolorektal adalah proses multifaktorial yang melibatkan akumulasi dari defek genetik, modifikasi protein dan interaksi sel dengan matriks pada sel epitel kolon. Inflamasi kronik diduga berperan pada karsinogenesis dengan menghambat apoptosis, merusak DNA, dan menstimulasi proliferasi mukosa secara kronik. Perubahan pada populasi mikroba usus, baik pada spesies tertentu ataupun pada komposisinya secara keseluruhan, mungkin juga dapat menyebabkan inflamasi kronik yang meningkatkan risiko perkembangan menjadi adenoma dan karsinoma.

Mediator inflamasi dan mikrobiota usus memiliki efek yang beragam pada karsinogenesis kolorektal. Beberapa dapat meningkatkan imunitas anti-tumor pejamu, sementara lainnya dapat meningkatkan pertumbuhan tumor. Berbagai cara proses tersebut berinteraksi baru dipahami sebagian. Kemoprevensi kanker kolorektal merupakan ilmu yang menjanjikan dan penting dikarenakan terbatasnya keberhasilan terapi. Agen kemopreventif kanker saat ini masih banyak diteliti dan memiliki tingkat keberhasilan yang berbeda-beda.

Kata kunci: *inflamasi, mikrobiota, kemoprevensi, karsinogenesis, kanker kolorektal*

INTRODUCTION

In United States, incidence of colorectal cancer (CRC) is 160,000 cases, from which 57,000 die of the disease every year. This incidence decreased as much as 3% between 1998-2005, as efforts in screening and surveillance were increased, however CRC is now still the second leading cause of death from cancer among adults.[1] Indonesian Study Group of Colorectal Adenocarcinoma stated that the incidence of CRC in Indonesia was 1.8 per 100,000 population.[2] CRC starts from a benign adenomatous polyp, which develops into advance adenoma with high level of dysplasia and further develops into invasive adenocarcinoma.[3] This is a multi-factorial process through complex interaction between genetic and environmental factors.[4] Chronic inflammation condition, depending on the duration and severity of inflammation, is often associated with increased risk of developing malignancy. Chronic inflammation is suspected to play role in carcinogenesis by inhibiting apoptosis, impairing DNA, and chronically stimulating mucosal proliferation. This chronic inflammation condition is often found in patients with inflammatory bowel disease (IBD), or in patients with particular bacterial infection.[5,6]

CRC is a serious problem which accompanies IBD patients and causes 10-15% death in IBD patients.[7] Crohn and Rosenberg have recognized the increase risk of CRC in ulcerative colitis (UC) patients since 1925. Cumulative risk for CRC after 20 years diagnosis of UC varies between 1-34%.[5,8-10] This variation is caused by age difference at diagnosis, sex, extend and duration of disease, and the availability of referral hospital. A meta-analysis predicts CRC risk in UC patients is increased, as much as 2% after 10 years, 8% after 20 years, and 18% after 30 years being diagnosed with UC.[11] Similarly, Crohn Disease (CD) increases the risk for CRC as much as 2.9% after 10 years, 5.6% after 20 years, and 8.3% after 30 years from the initial onset of the disease.[12] The risk of CRC increases in line with the duration of the disease and the extent of colorectal involvement. Latest study has also supported the severity of microscopic inflammation as a risk factor.[13] Patients with UC and CD are at an increased risk of developing CRC through variety mechanism which has not been fully understood.

This review article will discuss on chronic inflammation aspect; several inflammatory mediators and intestinal microbes, which influence the development of CRC. Also, it will discuss on the potential target which can give opportunity to the development of therapeutic intervention and even chemoprevention, which could be proved to be effective in inhibiting the progression of colitis-associated cancer (CAC).

ROLE OF INFLAMMATORY MEDIATORS IN COLORECTAL CARCINOGENESIS

Oxidative Stress

Tumor protein 53-induced nuclear protein 1 (TP53INP1) is an antiproliferative and proapoptotic protein which is involved in cell response to stress. A study demonstrated that oxidative stress, which was increased in TP53INP1-deficient mice, produced more severe colitis and supported its development to CRC.[14]

A group of researcher reported an increased incidence of adenocarcinoma in the colon in UC animal model without administration of carcinogenic substances. They succeed in inducing neoplasia in mice which did not have 8-oxoguanine glycosylase (Ogg1) enzyme.[15] This study revealed that Ogg1 was an important enzyme to repair DNA in colitis and probably play a significant role in preventing dysplastic changes in the inflamed epithelium. Interestingly, this researcher group also reported CRC inhibition by inositol compounds might be associated with its function on the modulation of macrophage-mediated inflammation and oxidative stress.[16] Generally, this finding showed that oxidative stress response in the inflamed gut might contribute in the promotion and progression of CRC.[5]

Cyclooxygenase-2 (COX-2)

Two isoforms of cyclooxygenase (COX) enzyme are COX-1 dan COX-2. COX-1 is expressed in normal tissue and plays important role in tissue homeostasis, while COX-2 is an inducible enzyme, which is expressed abundantly in the location of inflammation and colorectal neoplasm. COX-2 catalyzes the synthesis of prostaglandins (PGs) from arachidonic acid. COX-2 expression is activated by a number of proinflammatory cytokines, including interleukin (IL)-1 α, IL-1 β, and tumor necrosis factor-α (TNF-α).[5]

COX-2 is induced in colonic epithelium of patients with active IBD and in inflamed tissues of IL-10-deficient mice. COX-2 is expressed very early in the pathogenesis of CRC. In its association with human cancer, COX-2 is over-expressed in about 80% CRC and 40% colorectal adenoma when compared with normal mucosa.[17]

Many evidences have showed that the pro-inflammatory and tumor-promoting effects of COX-2

are mediated by prostaglandin E2 (PGE2). COX-2 increases enterocyte proliferation, positively regulates angiogenesis, and stimulates cell migration and invasion through PGE2 molecule. PGE2 may directly regulate colon carcinogenesis by regulating Wingless and INT (WNT) signaling pathway, which has a crucial role in colon carcinogenesis.[5]

Tumor Necrosis Factor-α (TNF-α)

TNF-α is a cytokine member of TNF and is a key molecule which control inflammation and host defense. Activation of TNF p55 dan p75 receptor causes intracellular proteins recruitment, which later activate several particular signal transduction pathways, such as: nuclear factor-κB (NF-κB).[18] TNF-α involves in DNA damage through the formation of reactive oxygen species. However, antioxidants may significantly reduce TNF-α-induced genetic damage in these cells.[19] TNF-α treatment in cultured cell causes increasing of gene mutation, gene amplification, micronuclei formation and chromosomal instability. Furthermore, TNF-Rp55 gene ablation and TNF antagonist administration reduces COX-2 expression and tumor angiogenesis in colitis-associated cancer (CAC) animal models.[20] Therefore, TNF-α may also increase tumor angiogenesis by inducing the infiltration of COX-2 expressing macrophages and neutrophils. Combination of these results shows that inhibition of TNF-α may diminish progression of colon carcinoma by reducing COX-2 expression and also indirectly inhibiting the WNT signaling pathway.[5]

This cytokine levels are increased in the blood and colonic mucosa of UC and CD patients. The use of anti-TNF-α antibodies, which has been proven to be effective in IBD, is the most recent development. However, the implications to human's CRC are unknown yet.[5] This is interesting to be waited for, whether this anticytokine therapy will influence CRC development in IBD patients.

Nuclear Factor-κB (NF-κB)

Nuclear factor-κB (NF-κB) has been considered to be important in the process between inflammation and carcinogenesis. NF-κB is a transcription factor which has function to increase proliferation and survival. TNF-α and other pro-inflammatory cytokines, which are: interleukin (IL)-1, toll-like receptors (TLR) can activate NF-κB signaling pathway.[5] Activation of NF-κB is needed for the expression of a range of proinflammatory molecules, including cytokines and adhesion molecules.[21] Results of study performed by Greten et al. explained that signal for survival, which was produced by NF-κB, played important role in the initiation of CRC.[22]

Sulfasalazine and methotrexate are widely used in acute phase of IBD treatment, by inhibiting NF-κB activity. Other agents, such as: curcumin and ginseng extract, may also inhibit NF-κB activity.[23-25]

Interleukin-6 (IL-6)

Recent studies stressed on the role of IL-6 in the development of IBD and its progression to CRC.[5] Mouse model have shown that IL-6 stimulate survival, proliferation, and progression to cancer from intestinal epithelial cells. Furthermore, level of IL-6 is increased in the serum of colon cancer patients, and can be induced by TNF-α.[5] Latest study in human showed that patients with active UC, dysplasia and cancer had significantly higher level of IL-6 compared with inactive UC patients and control.[26] Becker et al, also succeed to demonstrate that inhibition of IL-6 with antibody to IL-6 might decrease tumor size.[27]

Interleukin-10 (IL-10)

IL-10 has anti-inflammatory activities.[5] Mice whose IL-10 activity was eliminated might experience severe intestinal inflammation due to intestinal normal flora, which further developed into colitis and CRC.[28]

ROLE OF INFECTION IN COLORECTAL CARCINOGENESIS

Lately, knowledge about microbes as one of malignancy causes due to chronic inflammation is developing. As an example, *Helicobacter pylori* (*H. pylori*) in gastric cancer and human papilloma virus (HPV) in cervical cancer.[6]

In normal colon, microbes maintain colonic mucosa in physiologic mild inflammation condition, and stimulate the release of pro-inflammatory cytokines. Alteration in colon microbes has significant effect in the development of colon neoplasia, possibly through the production of heterocyclic aromatic amino acid and superoxide components. Some studies have shown the presence of several microbes which can increase this process, while some other microbes may overcome this destructive effect. Currently, it was suspected that changes in intestinal microbes population, either in particular species or in overall composition, may cause chronic inflammation which then increase the risk of developing adenoma or carcinoma.[29]

Some microbes which have been studied are:[30]

- ***Lactobacillus salivarius***
  Studies in mice showed that *Lactobacillus salivarius* might reduce the intensity of inflammation in intestinal mucosa, reduce the incidence of colon cancer from 50% to 10%, and reduce the population of enterococcus and *Clostridium perfringens*.
- ***Streptococcus bovis***
  Association between colon malignancies with endocarditis due to *Streptococcus bovis* (*S. bovis)* was first reported in a case report in 1951. *S. bovis* was thought as a risk factor of colorectal neoplasia, possibly induce oncogenesis through host immune response. Currently, screening colonoscopy is recommended for all patients who have history of bacteremia or endocarditis due to *S. bovis*.
- ***Helicobacter pylori***
  The association of *Helicobacter pylori* (*H. pylori)* with colorectal cancer has not been widely known. Hypergastrinemia, which is related to *H. pylori* colonization, is suspected as a mechanism which causes colorectal carcinogenesis. Hypergastrinemia has trophy effect in intestinal mucosa.
- ***Escherichia coli***
  Escherichia coli (E. coli) is a normal flora in human digestive tract; however the species which is attached to the mucosa can possibly cause neoplasia. Several studies showed that *E. coli* which is present in mucosa or intraepithelial, is often found in colon mucosa of patients with colon adenocarcinoma, but not found in normal control. This mechanism may be caused by intimin protein which is produced by enteropathogenic *E. coli*. This protein may decrease the DNA repair process in vitro, thus increase the possibility of colon epithelial cells to develop into malignant tumor.
- ***Clostridium septicum***
  Clostridium septicum (C. septicum) has been correlated to several hematologic malignancies, particularly leukemia. However, some case reports also reported the association between *C. septicum* infection and colorectal cancer, particularly in diabetic patients. There is no evidence that *C. septicum* has effect in colorectal tumorigenesis. It was suspected that disturbed intestinal mucosa in CRC is the port de entry of this organism to the blood stream.
- ***Enterococcus faecalis***
  Enterococcus faecalis is part of human intestinal microbes which produce oxygen free radicals, including extracellular superoxide, which can impair colonic epithelial cells DNA, either in vitro or in vivo. However, there is no study which reveals the association of intestinal colonization by this bacteria and colorectal cancer development.

Some types of virus, such as: human papiloma virus (HPV), John Cunningham virus (JCV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), also has been studied for their association with CRC incidence and still showed inconclusive results.[29]

COLORECTAL CANCER CHEMOPREVENTION POTENCY

Early screening of CRC is the most important and as a key for management in most patients. In addition, CRC chemoprevention is a promising and important knowledge, as there is still limited success of current available therapy. Nowadays, cancer chemopreventive agents have diverse success rate.

COX-2 Inhibitor

COX-2 inhibitor has been known to suppress sporadic CRC, however it is still unknown whether COX-2 inhibitor also has preventive effect to colitis associated CRC. Non-steroid anti-inflammation drugs (NSAIDs) "sulindac" is an effective chemopreventive agent in sporadic CRC; yet the benefit potency in colitis associated CRC is still need to be investigated.[30-32]

COX-2 inhibitor has been found to induce apoptosis in tumor cells and to inhibit tumor growth in animal models and in humans.[5] Mukawa et al explored the effect of etodolac, a selective COX-2 inhibitor, to tumorigenesis in CAC model of p53-deficient mice which received DSS. It was found that etodolac could decrease the occurrence of neoplasia significantly.[33] Etodolac might also decrease the occurrence of aberrant crypt foci and tumors in rats.[34] PC-407 (4-[5-naphthyl-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide), a celecoxib derivates, was found to downregulate COX-2 mRNA, protein level and PGE2 production significantly in conjunction with tumor growth inhibition.[35]

5-aminosalicylic Acid

Chemopreventive ability of 5-aminosalicylic acid (5-ASA) can be associated with 5 different pathways, which are: interference with cell cycle progression, scavenging of reactive oxygen- or nitrogen derived metabolites, TNF-α signaling, WNT/β-catenin signaling, and antibacterial activity.[5] Study in animal support the role of 5-ASA in inhibiting CRC development in mice during or

after the induction of inflammation. 5-ASA is only effective if administered during and/or after intestinal inflammation. Interestingly, 5-ASA decrease proliferation of epithelial cells in colitis associated CRC but not in sporadic CRC.[36] Results from several observational study supported the protective role between 5-ASA and colitis associated CRC. Study by Eaden et al, revealed that mesalamine was effective in decreasing cancer risk as much as 81% and that mesalamine had greater protective effect compared to sulfasalazine.[37,38] However, latest clinical study in long term UC patients failed to show the preventive role of mesalamine in progression of flat low-grade dysplasia to advance neoplasia.[39]

Folic Acid

Folate maintains the normal DNA methylation process and steady-state condition of DNA precursors. This role indicate that folate has potential as chemopreventive agent.[5] Recent study suggests that in IBD patients with normal homocysteine level, the increase in carcinogenic risk is negligible. Different with patients with hyper-homocysteinemia, folate deficiency may be associated with increased risk of colitis associated CRC.[40] Depressed red blood cell folate is related to increased risk of dysplasia and cancer in UC patients and may play role as a risk factor for neoplastic transformation. Case control studies have shown that folate may be protective against CAC. Lashner et al, examined the effect of folate supplementation in 98 UC patients (minimal for 8 years of duration) and exhibited dose-response effect, also supported the role of folate in CRC prevention.[41] Therefore, daily folate supplementation may protect against CRC development in UC patients.

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) has shown effectiveness as colon cancer chemopreventive agents in variety pre-clinical studies.[5] Deoxycholic acid (DCA) has been linked with colonic carcinogenesis through effect mediated by protein kinase C activation. UDCA inhibits DCA-induced translocation of protein kinase C. This mechanism make UDCA has chemopreventive effect to colon carcinogenesis.[42] UDCA administration in mouse model of colitis decrease the expression of TNF-α in colonic mucosa.[43] Pardi et al, evaluated the effect of UDCA in colorectal neoplasia in a group of UC patients and obtained result that UDCA significantly decreased the risk to develop colorectal dysplasia or CRC in that population.[44]

CONCLUSION

Inflammatory mediators and intestinal microbes have diverse effect in colorectal carcinogenesis. Interleukin-10 may increase host antitumor immunity, while the others: COX-2, TNF-α, NF-κB, and interleukin-6, may increase development of CRC. *L. salivarius* may decrease CRC incidence, while *S. bovis,* and *H. pylori* were suspected as risk factors of CRC. As an addition, 5-ASA, folic acid, and ursodeoxycholic acid are CRC chemopreventive agents, which are promising and important, as there is still limited success with current available therapy. Further studies on genetic, epigenetic, and immunologic mechanism which modulate a range of inflammatory mediators and intestinal microbes which play role in the progression from physiologic into pathologic inflammation and CRC neoplasia are still needed.

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