World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i6.663

World J Gastroenterol 2010 February 14; 16(6): 663-672
ISSN 1007-9327 (print)

EDITORIAL

Iron: An emerging factor in colorectal carcinogenesis

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Author contributions: Chua ACG and Klopcic B contributed equally to this work; Chua ACG, Klopcic B and Trinder D organised the Editorial; Chua ACG and Klopcic B wrote the Editorial; Trinder D, Lawrance IC and Olynyk JK revised the article.
Supported by Grants from the Cancer Council of Western Australia and Fremantle Hospital Medical Research Foundation
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Received: November 2, 2009 Revised: November 26, 2009
Accepted: December 3, 2009
Published online: February 14, 2010

Abstract

The carcinogenic potential of iron in colorectal cancer (CRC) is not fully understood. Iron is able to undergo reduction and oxidation, making it important in many physiological processes. This inherent redox property of iron, however, also renders it toxic when it is present in excess. Iron-mediated generation of reactive oxygen species *via* the Fenton reaction, if uncontrolled, may lead to cell damage as a result of lipid peroxidation and oxidative DNA and protein damage. This may promote carcinogenesis through increased genomic instability, chromosomal rearrangements as well as mutations of proto-oncogenes and tumour suppressor genes. Carcinogenesis is also affected by inflammation which is exacerbated by iron. Population studies indicate an association between high dietary iron intake and CRC risk. In this editorial, we examine the link between iron-induced oxidative stress and inflammation on the pathogenesis of CRC.

Key words: Iron; Haem; Colorectal cancer; Oxidative stress; Inflammation; Haemochromatosis

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Chua ACG, Klopcic B, Lawrance IC, Olynyk JK, Trinder D. Iron: An emerging factor in colorectal carcinogenesis. *World J Gastroenterol* 2010; 16(6): 663-672 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i6/663.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i6.663

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in developed countries. Apart from genetic mutations, environmental factors appear to play a role in intestinal carcinogenesis. Results from numerous population studies support the idea that dietary iron and/or elevated iron levels increase the risk of cancers including CRC, hepatocellular carcinoma (HCC) and lung cancer[1-6]. HCC occurs at a higher incidence in hereditary haemochromatosis (HH) patients with hepatic iron overload than in the normal population[7] and recently, an increased risk for CRC and breast cancer development in patients with HH has also been demonstrated[8,9]. Further support for a role of iron in carcinogenesis comes from animal studies. Multiple injections of iron compounds, such as iron dextran complex, ferric nitriloacetate and ferric saccharate in rodents result in the formation of sarcomas, renal cell carcinoma and mesothelioma, respectively[10-12]. Iron has also been implicated in intestinal carcinogenesis in rodent models of CRC[13,14].

Iron, whilst indispensable for life, can cause tissue injury through the formation of reactive oxygen species (ROS) and the high oxidative potential of iron and its

participation in oxidative stress-related carcinogenesis have been reviewed in detail elsewhere[15-17]. The excessive generation of oxidative stress can lead to carcinogenic events, and this has been the premise for the hypothesis that high iron levels may potentiate the risk of cancer. In addition, iron is a source of sustenance for cancer cell growth and proliferation. Cancer cell growth is enhanced by iron administration and has been shown to be retarded by both dietary iron deprivation[18] and treatment with iron chelators[19-21]. It is thought that genetic modifications and continual activation of the signalling pathways of cell proliferation by ROS synergistically promote carcinogenesis[16,22]. Chronic inflammation also induces cell oxidative stress, which promotes the onset of dysplasia[23] and is accompanied by a dysregulation in iron metabolism[24]. Nonetheless, the mechanistic link among iron, oxidative stress, inflammation and colorectal carcinogenesis remains to be elucidated.

CRC

The incidence of CRC varies among countries and this has been mainly attributed to environmental factors, although genetic factors are also important. Environmental risk factors for colorectal carcinogenesis include many dietary factors such as high red meat and alcohol consumption as well as low fibre and vegetable intake[25,26].

The majority of CRCs originate from pre-existing adenomatous polyps of the colonic mucosa[27]. These are defined as well demarcated masses of epithelial mucosa with increased crypt proliferation. Eventually, neoplastic cells migrate through the muscularis mucosa and it is once the basement membrane surrounding these cells is breached that the lesions are classified as malignant. These morphological and histopathological changes are accompanied by sequential dysregulation of key molecular pathways of cell division and tissue homeostasis[28]. Several syndromes have been described in families with a history of CRC, which involve mutations in components of these pathways[29]. Affected persons with familial adenomatous polyposis (FAP) develop hundreds of adenomatous polyps throughout their lifetime, some of which inevitably progress to malignancy. Genetic studies in subjects with FAP led to the discovery of the adenomatous polyposis coli (*APC*) gene, a key gene in the regulation of mucosal epithelial maturation *via* the Wnt signalling pathway[30,31]. In contrast, hereditary non-polyposis colorectal cancer (HNPCC) is characterised by an increased risk for developing CRC in the absence of a germ line mutation in the *APC* gene and is typically accompanied by the loss of DNA mismatch repair genes which impacts on other signalling pathways[32,33]. Although there is currently no evidence that iron plays a role in the pathology of these syndromes, it is interesting to note that iron can increase Wnt signalling in the absence of APC[34] and that mutations in the haemochromatosis gene (*HFE*) act as a genetic modifier of HNPCC disease expression[35].

Although there is a strong role for genes in the pathogenesis of CRC in the above-mentioned risk groups, environmental factors seem to play a more significant role. Population based studies have shown that in immigrant groups, the incidence of CRC changes towards that observed in the host country[36,37]. Another indication of the importance of environmental factors is that in Japan, a country with a traditionally low incidence of CRC, the rate has rapidly increased in recent years, a circumstance that has been primarily attributed to changes in life-style in the recent decades[29]. It is also interesting to note, that one of the highest incidences of CRC in the United States can be found in Japanese Hawaiians, highlighting the significance of environment *vs* genes[38].

Of the environmental risk factors, the diet is of particular interest since it impacts on the composition of the intestinal luminal contents, which are in direct contact with the colonic mucosa. Diets between countries vary significantly in their iron content and iron-rich food components, suggesting that iron intake could be one of the factors influencing CRC incidence in different populations. Dietary iron as an environmental modifier of CRC has been examined in population-based studies and there is evidence that both dietary iron[4,5,39] and/or increased body iron stores[1,2,40] enhance the risk of CRC.

IRON METABOLISM

Iron is a vital trace element participating in numerous biological and cellular processes such as electron transfer, oxygen transport and DNA synthesis as well as cell cycle progression and growth[41]. Iron absorption from the diet occurs mainly in the duodenum by a tightly regulated process. Most of the absorbed iron is utilized for erythropoiesis and any excessive iron is stored mainly in the liver[42]. Dietary iron occurs in two forms, haem iron from red meat and non-haem iron from plants and dairy products. Both forms of iron are taken up from the intestinal lumen into the enterocyte by different pathways. Haem iron is taken up as an intact metalloporphyrin by a haem transporter, the identity of which has yet to be confirmed. After entering the enterocyte, haem is broken down by haem oxygenase into free iron, biliverdin that is rapidly converted to bilirubin and carbon monoxide[43,44]. In contrast, non-haem ferric iron is reduced to ferrous iron by a ferrireductase and is then taken up by divalent metal transporter 1 at the apical surface of enterocytes. The iron from both sources enters a common intracellular iron pool and is stored as ferritin or transferred across the basolateral membrane of the enterocyte into the circulation by ferroportin. Upon release, iron is oxidised by hephaestin and binds to plasma transferrin. Transferrin-bound iron is taken up by cells *via* transferrin receptors. Iron absorption is inversely regulated by body iron levels, increasing during iron deficiency and decreasing in conditions of iron excess. Iron metabolism is regulated by the hepatic hormone, hepcidin, and its expression is controlled by many factors including iron stores, hypoxia, inflammation, anaemia and erythropoiesis[45,46]. The regulation of cellular iron metabolism has been extensively reviewed elsewhere[42,47-49].

Iron and CRC risk

The association between dietary iron and CRC risk has been examined in many population-based studies. A meta-analysis of studies investigating dietary iron intake, body iron stores and CRC demonstrated a positive correlation between iron in the diet and CRC risk[50]. Notably, two large prospective cohort studies have found that high iron intake and CRC risk were associated with other factors such as a high fat diet or bile acids[4,5] and at least three other case control studies have corroborated the positive correlation between dietary iron and CRC[39,51,52]. Of the studies analysing body iron stores and CRC, one large cohort study observed an association between transferrin saturation and CRC risk[2] whilst three case control studies found a positive correlation between serum ferritin levels and the formation of colorectal adenomatous polyps[1,40,53]. Other studies, however, reported inverse correlations between transferrin saturation[54] or ferritin levels[5] and CRC risk. The role of body iron stores in CRC appears more complex than that of dietary iron and the influence of genetic factors on body iron stores will be discussed in more detail below.

The effect of high red meat consumption, as a dietary source of iron, on the pathogenesis of CRC has been of considerable interest. Red meat is a major component of the human diet in some societies and contains a high amount of myoglobin and haemoglobin. Both contain haem, a porphyrin structure that contains a central iron atom and it has been suggested that the haem content in red meat promotes colorectal carcinogenesis[55,56]. A meta-analysis of 48 studies specifically addressing red meat consumption showed a significantly increased risk of developing CRC in people with a high intake of red meat as well as processed meat in most of the studies[57]. Of interest is a recent very large prospective cohort study investigating nutrition and disease that described an increased risk of CRC in people who consumed red meat rich in haem, whilst no increased risk was identified for poultry and an inverse correlation was observed for fish, both of which have a lower haem content[58]. Another two prospective cohort studies also reported that haem iron was associated with a higher risk of CRC especially in those who consumed alcohol[59] or those with a low intake of chlorophyll[26]. It is, however, unclear whether the effects of red meat on colorectal carcinogenesis are due to haem, the iron bound to haem, or a combination of both.

HH is a common disorder of iron metabolism that usually results from a homozygous C282Y mutation in the *HFE* gene. HFE protein is a key regulator of hepcidin, and in HH, the HFE-mediated regulation of hepcidin is impaired resulting in excessive absorption of iron and increased deposition of iron primarily in the liver[47,60]. As mentioned earlier, these individuals have an increased risk of developing CRC. This is exemplified by the recent findings that patients homozygous for the C282Y mutation have a 2.4-fold increased risk of developing CRC[9]. This is of particular significance considering that the C282Y mutation is one of the most abundant autosomal mutations in some Western societies with homozygosity rates ranging from 1/102 in Northern Ireland to less than 1/100 000 in Greece[61]. The homozygosity rate of 1/385 in the United States of America calculates as an estimated number of 718 000 affected individuals with an increased risk of CRC[61]. Another study describing a 7.7-fold increased risk of developing CRC in patients with homozygous mutations in both *HFE* and *TFR1* genes, further implicates a dysregulation in iron metabolism as a possible mechanism contributing to colorectal carcinogenesis[62]. An increased risk for CRC has also been described for compound C282Y/H63D heterozygotes, single C282Y or H63D heterozygotes and H63D homozygotes[35,63-65], but not all studies detected a significant correlation between *HFE* mutations and CRC[65-73]. Knekt *et al*[2], however, reported a 3-fold increased risk for CRC that was associated with a transferrin saturation level exceeding 60% in a large cohort from Finland, which may include subjects with mutations in the *HFE* gene. Furthermore, systemic iron reduction by phlebotomy decreases visceral malignancies and mortality in patients with peripheral arterial disease[74] and in blood donors the number of non-haematological malignancies is significantly reduced[75] indicating that reduction of iron levels might decrease CRC risk. The availability of mouse models of HH enables future studies to investigate the interaction of dietary iron, regulation of body iron stores and colorectal carcinogenesis.

Role of luminal iron in colorectal carcinogenesis

There is evidence suggesting that significant iron absorption may occur in the colon[76,77]. Increased iron intake results in higher levels of iron in colonic epithelial cells in rats[78], and although divalent metal transporter 1, ferroportin and hephaestin mRNA expression is highest in the duodenum and decreases along with the length of the small intestine[79], their expression is still relatively high in the colon, especially hephaestin and ferroportin. These findings suggest that there may be significant colonic iron transport, which impacts on cell proliferation and cancer development. In a recent study, it was shown that there was increased iron staining in human colorectal tumours[80]. The expression of proteins involved in cellular iron uptake such as divalent metal transporter 1 and transferrin receptor 1 was also upregulated. The expression of the iron exporter, ferroportin, was increased but it was located intracellularly whilst hephaestin expression was decreased, suggesting decreased release of iron from the cells. These results suggest that the retention of iron by tumours may facilitate cell proliferation.

Further support for the concept of iron as a risk factor for CRC has been demonstrated in animal studies. Elevated dietary iron levels increased the incidence of tumours in rodent models of CRC induced by inflammatory or carcinogenic agents[13,14]. In these experiments, however, iron was supplemented with inorganic carbonyl iron, a form that does not constitute a major component of natural diets. Interestingly, in the inflammatory model, Seril and colleagues demonstrated that systemic iron supplementation did not increase tumour incidence. This

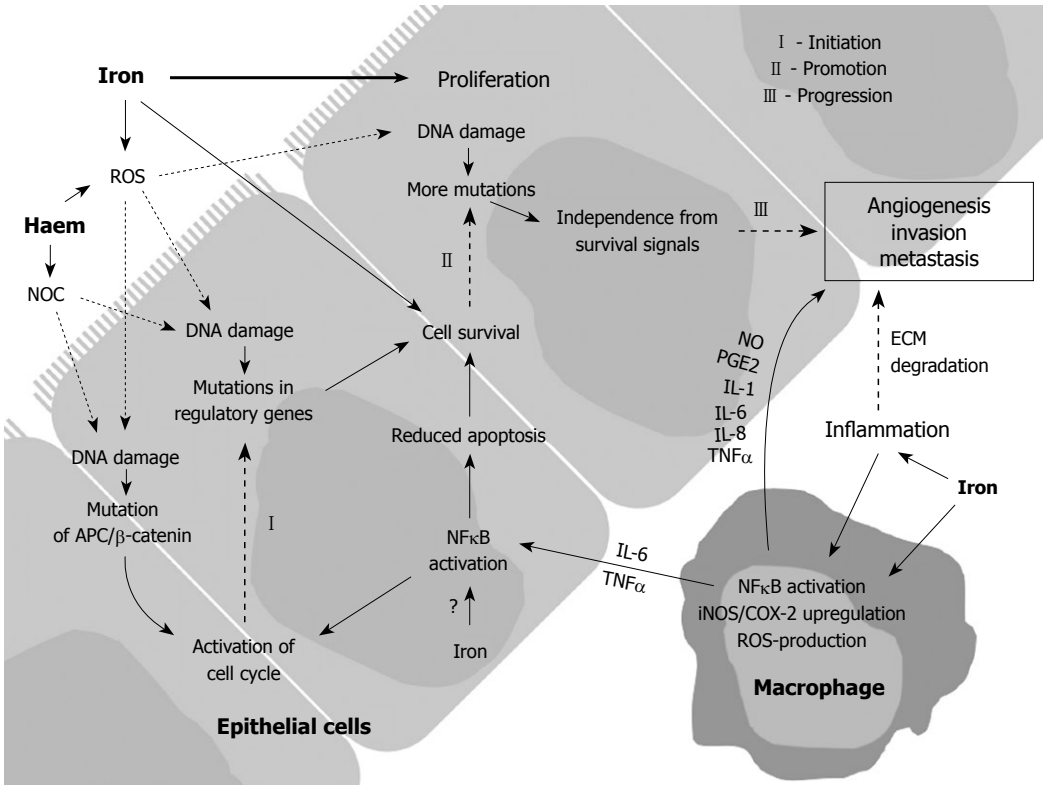

Figure 1 Potential roles of iron in the development of colorectal cancer. Luminal iron may cause DNA damage through the generation of reactive oxygen species (ROS) *via* the Fenton reaction. Haem may also stimulate the production of N-nitroso compounds (NOC) in the colon which are mutagenic. (Ⅰ) In the initiation phase of tumorigenesis, DNA damage leads to mutations in key genes regulating cell proliferation and survival such as APC or β-catenin of the Wnt pathway; (Ⅱ) In the promotion phase, the increase in cell proliferation and survival due to the deleterious effects of NOC and ROS leads to further genetic instability and an accumulation of more mutations. Iron is an important nutrient required for proliferation during this phase. Iron also increases intestinal inflammation and the pro-inflammatory cytokines, TNFα and IL-6 released from inflammatory cells increase cell survival through inhibition of apoptosis *via* the activation of NFκB; (Ⅲ) In the progression phase, tumour cells gain independence from survival signals and progress towards a malignant phenotype. Iron has been shown to activate NFκB increasing inducible nitric oxide synthase (iNOS) and cyclo-oxygenase (COX)-2 expression in macrophages. Activated macrophages produce more ROS, increase infiltration through degradation of the extracellular matrix (ECM) and promote angiogenesis by release of nitric oxide (NO), prostaglandin E2 (PGE2), IL-1, -6 and -8 as well as TNFα, ultimately leading to tissue invasion and metastasis.

suggests that increased luminal iron but not systemic iron levels increase colorectal carcinogenesis in an inflammatory model of CRC[81]. In a carcinogen-induced CRC model, the number of preneoplastic lesions increased with the amount of haem in the diet[82]. Haem iron is more bioavailable than non-haem iron and has been shown to increase mucosal proliferation and cytotoxicity, indicating that haem may have a greater propensity for inducing malignancy compared with other forms of dietary iron[55,56]. Haem has been shown to stimulate the production of endogenous N-nitroso compounds in the large intestine after red meat ingestion, many of which are pro-carcinogenic[83]. The genotoxic effect of haem has also been demonstrated in human colonic cells, where DNA damage was induced by haemoglobin and haemin[84]. The exact mechanism by which luminal iron (haem and/or non-haem), iron transport, systemic iron levels and their regulation impact the pathogenesis of CRC, however, remains to be elucidated.

Iron and molecular pathways of colorectal carcinogenesis

Colorectal carcinogenesis is a multi-step process involving the formation of adenomatous polyps and their subsequent progression to malignancy. At the molecular level, this process is reflected by sequential events of gene mutation and activation of key molecular pathways[85,86]. Some of these pathways may be altered by iron and iron-mediated generation of ROS (Figure 1). The *APC* gene was initially identified in patients with FAP and subsequently shown to be mutated in > 80% of human colorectal neoplasia[85]. *APC* mutations involved in carcinogenesis led to nuclear accumulation of β-catenin and constitutive activation of the wnt/β-catenin/T cell factor (TCF) signalling pathway. In rodent models of azoxymethane-induced CRC, the majority of colonic tumours harbour mutations in *APC* and/or *β-catenin* genes[87,88]. Activation of the wnt/β-catenin/TCF pathway results in increased expression of cyclin D1 and c-myc, both of which are positive regulators of cell proliferation[89,90]. Iron has been implicated in *APC* loss[34] and iron chelators decrease the expression of cyclin D1 and c-myc[41].

The molecular pathogenesis of ulcerative colitis-associated colorectal carcinogenesis has been extensively studied[91]. Events such as chromosomal and microsatellite instability and alterations in tumour suppressor genes (*p53* and *APC* mutations) and DNA mismatch repair genes have been documented[92,93]. The inhibitor of NFκB kinase

(IKKβ)/nuclear factor kappa B (NFκB) signalling pathway constitutes a key molecular link between inflammation and carcinogenesis. NFκB is activated in colorectal carcinogenesis and is influenced by both inflammation and oxidative stress[94]. NFκB targets the genes that control cell proliferation, apoptosis, angiogenesis and metastasis[94,95]. A direct stimulatory effect of iron on NFκB signalling has also been demonstrated in hepatic macrophages[96,97].

Other pathways involved in colorectal carcinogenesis include cyclo-oxygenase (COX)-2 mediated prostaglandin E2 synthesis and inducible nitric oxide synthase (iNOS)-mediated generation of nitric oxide[98]. Prostaglandin E2 is involved in regulating angiogenesis and inhibiting apoptosis[99] whilst iNOS activity induces DNA damage and promotes microvascularisation[100]. Both COX-2 and iNOS are frequently over-expressed in human CRC[101,102] and inhibition of their activity has been shown to decrease tumorigenesis in rodent models of CRC[103,104]. Furthermore, iNOS is a target of the wnt/β-catenin/TCF pathway and its production of ROS through nitric oxide is catalysed by iron[105].

OXIDATIVE STRESS AND COLORECTAL CARCINOGENESIS

Oxidative stress occurs when the body or cell is unable to combat the deleterious effects of overproduction of oxidants or free radicals due to decreased anti-oxidant activity to counterbalance or eliminate them. Oxidative stress is related to many pathological conditions such as infection, inflammation, iron and other transition metal overload. It has also been implicated in carcinogenesis[15,106,107]. Although many reactive species and free radicals such as reactive nitrogen species contribute to oxidative stress, the role of ROS in colorectal carcinogenesis will mainly be discussed here. ROS is generated through the partial reduction of oxygen which results in superoxide anion, singlet oxygen, hydrogen peroxide and hydroxyl radical formation. ROS plays a dual role in biological systems. When the balance between oxidant and anti-oxidant activity is maintained, ROS can participate as secondary messengers in intracellular signal transduction cascades, whilst the presence of excessive ROS induces tissue damage.

Iron is a strong oxidant and when present at high levels, it generates ROS *via* the Haber-Weiss-Fenton reaction. Iron-mediated generation of ROS can cause oxidative damage to lipids, nucleic acids or proteins[86]. Oxidative damage to proteins and lipids can generate reactive intermediates that can couple to DNA bases resulting in DNA lesions[86]. DNA damage as a consequence of prolonged oxidative stress can result in mutation of proto-oncogenes and tumour suppressor genes, microsatellite instability and chromosomal rearrangements as well as a dysregulation in transcription, signal transduction and replication, all of which are associated with carcinogenesis[15,86,108]. Haem is also an oxidant[109], and despite being essential for many biological processes and enzyme systems, excessive free haem catalyses ROS production, resulting in oxidative stress[110]. The degradation of haem by haem oxygenase-1 alleviates oxidative stress[111] and bilirubin, a by-product of haem breakdown, is anti-oxidative and has been shown to scavenge peroxyl radicals in plasma[112,113]. In mice lacking copper-and zinc-containing superoxide dismutase, oxidative damage is pervasive and the rate of liver cancer development is increased later in life[114] whilst, mice with decreased manganese-containing superoxide dismutase activity have an increased risk for lymphoma and adenocarcinoma[115]. These results suggest that reduced anti-oxidant activity can lead to cancer.

Oxidative stress is enhanced in neoplastic tissue from the colonic mucosa of CRC patients[116,117]. In these patients, lipid peroxidation is increased in colonic tumours compared with normal mucosa[116]. In addition, there is a greater extent of DNA strand breakage in colonic mucosal cells isolated from neoplastic tissues compared with normal tissues from cancer patients[117]. Oxidative damage is also more evident in the earlier stages of CRC than in the more advanced stages of cancer. The accumulation of iron in a human colon cancer cell line has been shown to correlate with increased oxidative protein and DNA damage[118]. In rodent studies, mice and rats fed a diet high in iron[119-122] and haem[82] exhibited greater lipid peroxidation activity in the colon and increased colonic aberrant crypt foci, which are pre-neoplastic lesions[82,123,124]. Oxidative damage markers are increased in the colons of *Hfe* knockout mice[125], indicating an increased presence of ROS in these iron-loaded mice. Oxidative stress due to high iron and/or haem levels may, therefore, be instrumental in mediating colorectal carcinogenesis.

INFLAMMATION AND CRC

The relationship between inflammation and tumour development has been a major focus in recent cancer research. Persistent inflammation as a result of infection promotes carcinogenesis; for example, infection with hepatitis B and C and human papilloma viruses are associated with HCC and cervical cancer, respectively, whilst *Helicobacter pylori* infection is linked to gastric cancer[126]. Furthermore, subjects with inflammatory bowel disease such as ulcerative colitis and Crohn's disease suffer from recurring inflammation in the colonic mucosa and are at an increased risk of developing CRC[127].

Chronic inflammation and metabolites from phagocytic processes result in formation of excessive ROS and nitric oxide[98,128], which as mentioned above, can directly cause damage to DNA, protein or lipids. Inflammatory cells active in chronic inflammation are also present within a tumour and its surrounding tissue. This suggests that the presence of oxidative stress and the network of inflammatory cytokines and chemokines in a tumour microenvironment may perpetuate carcinogenesis by promoting genotoxicity, proliferation and survival as well as angiogenesis, cell invasion and metastasis[129]. Cytokines that are frequently associated with carcinogenesis include TNFα and IL-6, which promote cell proliferation and

survival[130]. Angiogenesis, invasion and metastasis are influenced by the cytokines, TNFα, IL-1, -6 and -8[129].

CRC occurs in approximately 4% of patients with ulcerative colitis[131] where the risk for CRC has been reported to be approximately 10-fold higher than in the normal population[127,132]. The risk for cancer increases with longer duration and the extent of colon affected by this disease, and how well the inflammation is controlled, indicating that it is the prolonged inflammatory stimulus that directly affects the pathogenesis of CRC in these patients. In addition to the blood loss and iron deficiency due to the chronic intestinal inflammation, patients with ulcerative colitis and Crohn's disease may also develop iron deficiency anaemia secondary to inflammation and reduced mobilization of bone marrow iron and are frequently treated with oral iron supplementation. Hence, the effects of iron on colitis-associated colorectal carcinogenesis have also been examined. Chronic inflammation induced in mice treated with dextran sodium sulphate resulted in colorectal tumorigenesis which became worse with dietary iron supplementation, indicating the tumour-promoting role of iron when inflammation was present[13]. This was accompanied by the increased presence of enhanced nitrotyrosine and iNOS expression, which implicates a role for oxidative stress in inflammation-associated carcinogenesis. Further evidence comes from experimental models where colitis is attenuated when anti-oxidant activity is increased[133,134]. In addition, the formation of pro-oxidants due to increased activity of phagocytic leukocytes in the colons of ulcerative colitis patients has been reported[135]. These findings suggest that oxidative stress induced by both inflammation and iron plays a major role in inflammation-associated colorectal carcinogenesis.

Better understanding about the relationship between inflammation and iron metabolism has been achieved since the identification of hepcidin. Inflammation affects iron homeostasis by inducing hepcidin through an IL-6-mediated pathway[45]. Increased hepcidin levels caused decreased iron absorption[136,137] as well as iron retention by reticulo-endothelial macrophages, which may result in hypoferraemia (low serum iron concentration)[138]. Hypoferraemia is associated with the anaemia of chronic disease, also known as anaemia of inflammation. Haem, like iron, is pro-inflammatory and increases the expression of inflammatory adhesion molecules in endothelial cells[109]. Haem oxygenase 1 knockout mice suffer from anaemia, tissue iron loading and severe inflammation, having enlarged spleens and lymph nodes, vasculitis and inflammatory cell infiltrates in the liver[139]. Carbon monoxide, a by-product of haem degradation, ameliorates inflammation in a mouse model of colitis[140]. High dietary iron and/or haem levels are likely to contribute to the pathogenesis of inflammation-associated colorectal carcinogenesis.

FUTURE PERSPECTIVES

Population-based studies as well as animal studies point to a role for dietary and/or systemic body iron levels in colorectal carcinogenesis. The effect of high iron levels on regulatory pathways of iron metabolism through HFE and hepcidin as well as the increased production of ROS in the presence of iron provide potential mechanisms. The interference of high iron levels with ROS and/or inflammation and their effects on pathways involved in colorectal carcinogenesis remains poorly understood. Future studies in mouse models of HH, dietary iron overload and colorectal carcinogenesis will provide valuable insights into this fascinating aspect of iron biology and CRC.

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