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Abstract

Excessive gut luminal iron has been shown to contribute to the initiation and progression of colorectal cancer. However, emerging evidence suggests that reduced iron intake and low systemic iron levels are also associated with the pathogenesis of colorectal cancer. This is of significance due to colorectal cancer patients often presenting with iron deficiency. Iron is necessary for appropriate immunological functions; hence, iron deficiency may hinder cancer immunosurveillance and potentially modify the tumour immune microenvironment. Both of which may assist in cancer development. This is supported by studies showing that colorectal cancer patients with iron deficiency have inferior outcomes and reduced response to therapy. Here, we provide an overview of the immunological consequences of iron deficiency and suggest ensuring adequate iron therapy to limit these outcomes.

Introduction

Colorectal cancer is the third most common cancer diagnosed globally and is the second leading cause of cancer mortality. Geographical variability exists within the prevalence of colorectal cancer, most often associated with a western lifestyle. Obesity, poor diet and a decline in physical activity are all known contributors to colorectal cancer development.[1, 2] However, an emerging dietary contributor that has been linked to colorectal cancer is iron.

Iron is a vital micronutrient that is central to many major biological functions, for instance, its role in the transport of oxygen within the iron-containing haemoglobin complex.[3] Irons capacity to be utilised in multiple biochemical reactions is through its

ability to transition through multiple oxidation states, within the cell the most commonly found being ferrous (Fe2+) and ferric (Fe3+) forms.[4] In normal physiology iron is necessary for cellular proliferation. For instance, DNA synthesis requires the iron-dependent enzyme ribonucleotide reductase, which catalyses the rate-limiting step of DNA synthesis. Likewise, iron contributes to cell cycle progression, as it forms an essential part of the electron transport chain, providing energy production for cell cycling. As these processes which are necessary for cellular proliferation are dependent on iron, this allows the potential for iron to be utilised in pathological conditions such as cancer. Iron has been implicated in multiple tumour types, with the most notable being colorectal cancer.[5]

Excessive intestinal iron within the gastrointestinal (GI) tract has been shown to have a role in increasing the risk of developing colorectal cancer.[6] This is through its utility in cancer cell proliferation, contributing to oxidative stress-induced colonic damage, as well as amplifying oncogenic signalling.[7, 8] In contrast, evidence to suggest a role for iron deficit in the pathogenesis of colorectal cancer is less well defined. This is of particular focus for investigation, due to iron deficiency being common in colorectal cancer patients. Iron deficiency can result in the clinical manifestation of anaemia within these patients, through limiting haematopoiesis.[9, 10] As haematopoiesis produces all immune cells, along with iron being required for immune cell function, this leaves the potential for iron deficiency to cause an attenuated immune response.[11, 12] If this is occurring in colorectal cancer patients this may lead to a reduced immunosurveillance response and altered tumour immune microenvironment, which has the potential to contribute to cancer progression.[13]

Hence, this review will address the consequences of iron deficiency on immune function and provide an insight into iron therapy in order to limit these outcomes.

Iron Metabolism

Before we can expand upon the role of iron in colorectal cancer, we first need to appreciate how iron is absorbed and regulated within the body. As iron is necessary for homeostasis its concentration is normally tightly controlled within the body.[14] This occurs through being complexed to proteins that facilitate its absorption, transportation, storage and utilisation (Figure 1).[4] Iron is present within the body by two means, through absorption or recycling.[15] Dietary iron can be consumed in the form of haem iron (Fe^{2+}) and non-haem iron (Fe^{3+}).[16] Initially, dietary iron is absorbed through the apical surface of enterocytes predominantly of the duodenum and upper jejunum, this is facilitated by both divalent metal transporter-1 (DMT-1) and haem carrier protein 1 (HCP-1).[17, 18] Non-haem iron is reduced by duodenal cytochrome B (Dcytb) to Fe^{2+} before it can be transported by DMT-1 into the enterocyte. Likewise, HCP-1 absorbs haem iron before being internalised into the intestinal enterocytes. Once intracellular the enzyme haem oxygenase-1 (HO-1) releases iron from its haem complex.[19] These mechanisms collectively contribute to the intracellular iron pool; iron then has one of two fates dependent on the body's requirements for iron. If there is no iron requirement within the body, then the iron remains inert bound to the intracellular storage protein ferritin.[18] This may be carried out by the chaperone protein poly binding protein 1 (PCBP1) which facilitates the loading of iron onto ferritin.[20] In contrast, if iron is required by the body it will transverse the basolateral surface, by the efflux protein ferroportin (FPN), passing into the circulation.[18] The second mechanism by which iron is released is through the mononuclear phagocytic

system (MPS) which regulates iron recycling. MPS is central for iron homeostasis; specialized macrophages recycle iron through engulfment of senescent erythrocytes.[15] These two mechanisms, recycling and absorption, regulate the input of iron into the circulation. Circulating iron is found associated with the plasma protein transferrin in order to maintain it in a redox inert state. Transferrin functions to deliver iron to all tissues, including the bone marrow for erythropoiesis, through binding to the cells surface transferrin receptor.[17]

The absorption of iron is regulated by local iron levels, along with systemic factors. At the local level, iron concentration regulates the iron regulatory protein RNA binding activity, which in turn alters the levels of DMT-1 and FPN.[18] Systemic signals regulating the body's iron requirements are sensed by the liver, which in turn alters the expression of the iron regulatory hormone hepcidin. Hepcidin binds to the FPN leading to internalisation and degradation, which in turn limits the absorption of iron in the small intestine. Similarly, hepcidin regulates iron MPS recycling by causing sequestration of iron into macrophages.[21] Factors influencing the liver's production of hepcidin include the iron stores, erythropoiesis rate, hypoxia and inflammation (Figure 1). During inflammation, the cytokine IL-6 is necessary for the induction of hepcidin. This is seen during infection when pathogenic macromolecules such as lipopolysaccharides act on macrophages, such as the hepatic Kupffer cells, to induce production of IL-6 which in turn acts on hepatocytes to cause hepcidin mRNA production.[22]

Excess and Deficit of Iron in Colorectal Cancer

Only 10% of iron consumed in a typical diet is absorbed in the small intestine, this leaves the remnant iron residing within the GI tract.[23] Excessive iron within the GI tract may contribute to increased proliferation and neoplastic conversion of colonic cells. Rodent studies have revealed increased dietary iron enhances proliferation of colonic crypt cells and amplifies colorectal tumour development.[24, 25] This may be through irons utility in cellular proliferation, along with its ability to switch between oxidation states, which is tremendously toxic due to the production of reactive oxygen species from the Fenton's reaction.[4] Reactive oxygen species increase oxidative stress within the GI tract that contributes to DNA damage, modification of proteins and lipid peroxification. Oxidative stress-induced damage to DNA may lead to genomic instability that can contribute to carcinogenesis.[7] Similarly, excess iron-induced oxidative stress can contribute to colonic inflammation.[26] Chronic inflammation of the colon can contribute to colorectal cancer through the production of growth factors and cytokines that can support tumour growth, disrupt differentiation and promote cancer cell survival.[27, 28]

The mechanisms linking excessive iron and colorectal cancer are further supported through the tumour suppressor gene adenomatous polyposis coli (APC). APC is recurrently mutated in sporadic and hereditary colorectal cancer.[29] *In vitro* studies have shown that excessive iron in a background of APC mutation leads to an increase in signalling through the major oncogenic signalling pathway, Wnt.[8] Iron/APC-driven colorectal carcinogenesis has also been supported through an APC-deficient murine model, where luminal iron depletion resulted in a reduction in tumour development, whereas, an increase in luminal iron promoted tumorigenesis.[30] These studies suggest an association between iron and colorectal

cancer, through increasing oxidative stress, inducing carcinogens and amplifying oncogenic signalling.

The association between high iron and the risk of colorectal cancer has been well established. However, a study by *Bird et al*[31] assessed 965 men and women aged 50-75 to determine iron intake as a risk for development of adenomatous polyps, a precursor lesion to colorectal cancer. They found a U-shaped association between iron intake and colorectal polyps, showing that individuals that consume high iron (>27.3 mg/day) as well as low iron (<11.6 mg/day) had increased risk, compared to those consuming an adequate amount of iron (11.6-13.6 mg/day).[31] This suggests that a deficit of iron could equally contribute to the pathogenesis of colorectal cancer as high iron does. A similar study by *Cross et al*[32] supports this, showing an inverse association between serum iron levels and the risk of colon cancer.[32] This may indicate that the level of iron within the blood may be contributing to cancer development when in shortage, in a similar way that excessive iron within the gut lumen contributes to tumour formation. The mechanism supporting iron deficiency and colorectal cancer development is not fully understood. However, it may involve cellular functions requirement for iron, which when deficient may hinder immune cells ability to protect against cancer.[13]

Dietary Iron and Colorectal Cancer

Many dietary components, frequently associated with iron, have been shown to contribute to or have protective roles against colorectal cancer. For instance, phytates are anti-nutrients that form complexes with dietary minerals including iron, leading to a reduction in bioavailability.[33] Phytates are inhibitors of iron-induced

production of hydroxyl radicals, a potent oxidant that can contribute to cancer development.[34] Likewise, vitamin C has been suggested to have a protective role against cancer through regulating iron. Vitamin C chelates iron, leading to greatly enhanced absorption of iron from the diet.[35, 36] Vitamin C limits free radical damage through the quenching of reactive oxygen species and has been shown to modulate cancer cell survival.[37, 38] This has been supported in a large population study showing that dietary intake of vitamin C is associated with a lower risk of colorectal cancer.[39]

Dietary iron is present in two forms, haem iron from animal sources such as red meat and non-haem iron from seeds, nuts, grains and dark green leafy vegetables.[40, 41] Red meat including beef and lamb is characterised by a high myoglobin content which consists of increased levels of haem iron relative to white meat such as chicken.[42] Dietary components of meat have been shown to contribute to colorectal cancer, for instance, *N*-nitroso compounds are mutagenic and are potent carcinogens.[43, 44] Likewise, haem iron has also been shown to contribute to colorectal cancer via the Fenton's reaction. Hydroxyl radicals produced by the Fenton's reaction can alter DNA leading to oxidative base damage.[45] Furthermore, haem iron has been shown to contribute cancer through inducing colonic hyperproliferation through modulation of the intestinal microbiota and inducing mutations through DNA adducts.[46, 47] Haem iron also leads to the raised formation of lipid peroxyl radicals, such as malondialdehyde and 4-hydroxynonenal, which are potent carcinogens.[3] This provides a strong association between haem iron and colorectal cancer, however, no evidence is available to link a mechanism of non-haem iron and colorectal cancer.

This is supported in a study by *Luo et al*[48] which assessed the different forms of iron and their association with colorectal cancer. They determined that haem iron was positively associated with colorectal cancer, whereas, non-haem iron showed no positive association. Supporting the role of excessive dietary haem iron, but not non-haem iron, in the pathogenesis of colorectal cancer. Interestingly, along with excessive dietary haem iron, this study also determined that a lower intake of non-haem iron was also associated with colorectal cancer.[48] This supports previous studies by *Bird et al*[31] and *Cross et al*[32] showing that low iron is associated with cancer risk, however, this study expands upon this suggesting a reduction of non-haem iron is responsible.

Iron Deficiency Anaemia

Colorectal cancer is commonly associated with the development of iron deficiency, which is prevalent in approximately 60% of colorectal cancer patients. Iron deficiency can then lead to the clinical manifestation of iron deficiency anaemia (IDA).[9] Causative mechanisms of colorectal cancer-associated IDA comprises chronic tumour-induced blood loss, reduced luminal absorption of iron and impairment of iron homeostasis prompted by chronic inflammatory disease.[49] IDA induced through chronic GI bleeding results in a depletion of iron stores which leads to absolute iron deficiency (AID). Whereas, reduced uptake of iron, along with sequestration to the MPS, causes a decline in biologically available iron resulting in functional iron deficiency (FID).[50] The clinical relevance of the distinction between AID and FID relates to the administration of iron therapy to treat anaemia. AID requires iron

therapy irrespective of actual haemoglobin levels, whereas, in FID iron therapy is only recommended if anaemia induced symptoms occur.[49]

Haematopoiesis is sensitive to iron deficiency, leading to the manifestation of anaemia in iron-deficient colorectal cancer patients.[10, 49, 51] Haematopoiesis produces erythrocytes as well as immune cells such as T-cells, macrophages, dendritic cells and natural killer cells. Hence, this suggests that the effects of iron deficiency may not be restricted to the erythroid lineage and may influence the development and function of immune cells.[11, 51] With iron deficiency being so prevalent within colorectal cancer, this review will address the implication of iron deficiency anaemia on immune function and how this may contribute to the pathogenesis of colorectal cancer.

Iron Deficiency, Immune system and Infection

Depletion of biologically available iron within the body due to iron deficiency results in the clinical manifestation of anaemia. However, iron is essential for all cells to function.[52] Iron is critical in maintaining the immune system through regulating growth and differentiation of immune cells.[12] Additionally, iron is essential for components of peroxide and nitrous oxide generating enzymes required for adequate enzymatic functionality of immune cells.[53] Therefore, iron deficiency results in impaired cellular immunity, notably leading to defective T-cell maturation[54], halting of macrophage differentiation[55] and impaired natural killer cells activity.[56] The association between iron deficiency and impairment of immune function has been confirmed, as patients with IDA have increased morbidity from infectious disease.[57]

Iron Deficiency and Immunosurveillance

The immune system is essential to prevent infection; however, it is also required to detect and eliminate potentially transformed cells before they manifest into a malignancy. Transformed cells begin to express foreign antigen that can be recognised by the immune system. Immune cells act to survey the body for these cancerous or precancerous cells and eliminate them in a process called immunosurveillance.[58] Hence, in order for cancer cells to survive they need to evade immune destruction, which is a hallmark of cancer.[59] Iron plays an essential role in immunosurveillance, through its utilisation in growth and differentiation of immune cells, as well as influencing cell-mediated immune response and cytokines activities.[60] Therefore, iron deficiency provides the potential for a suppressed immunosurveillance response, which may contribute to tumour immune cell evasion and inadequate tumour cell destruction.[61] How iron deficiency alters the major immune cells and cytokines involved in the immune surveillance response are discussed below.

Dendritic Cells

Dendritic cells are the most potent antigen-presenting cells that bridge the innate and adaptive immune systems and are required for activation of the antitumor T cells.[62] Iron plays a key role in the differentiation of dendritic cells through supporting the induction of the cyclin-dependent kinase inhibitor p21. Iron deprivation of dendritic cells results in an undifferentiated phenotype, with absent or blunted dendritic processes, that are unable to stimulate T cells. Depletion of iron leads to an increase in the cell surface localisation of transferrin receptors on dendritic cells, suggesting that these cells are attempting to acquire iron. Hence, in IDA there may be a

reduction in the activation of antitumor T cell response, through impaired dendritic cell function.[63]

T-Cells

T cells are critical to immunosurveillance through their various subtypes. Cytotoxic T cells are major effector cells in the immune response against cancer, through their T cell receptors ability to recognise tumour associated antigens on cancer cells.[64] Cytotoxic T cells then induce apoptosis of tumour cells through perforin and granzyme mediated cell lysis.[65] Helper T cells act to support this mechanism through aiding dendritic cells in activating cytotoxic T cells, along with producing cytokines such as IL-2 and IFN-gamma to recruit and activate T cells and natural killer cells.[66] However, in IDA these mechanisms are suboptimal.

Iron deficiency has been shown to cause a reduction of circulating T cells through a limitation of T cell proliferation.[67] Similarly, iron deficiency also leads to a reduction in T cell motility through inhibiting protein kinase C.[13] The overlying mechanism that results in these iron deficiency-induced T cell dysfunction may be through increased oxidative stress, due to an increase in oxidant levels along with a decrease in antioxidant enzymatic activity associated with iron deficit. This increase in oxidative stress caused by IDA induces DNA damage in lymphocytes; this was confirmed in a study by *Aslan et al*[68] which showed that lymphocyte DNA damage was significantly increased in patients with IDA. Lymphocyte DNA damage may result in a defective T cell population, contributing to an impaired immune response.[68, 69] T cells act as the key cells in immunosurveillance, which if repressed create a favourable condition for the development and progression of cancer.[13]

Natural Killer Cells

Natural killer cells are specialised cytotoxic cells that play a pivotal role in immunosurveillance through perforin and granzyme mediated tumour cell destruction.[70] Stress associated ligands are present on tumour cells, such as HSP70 and MICA/B. These stimulate natural killer cells through activating receptors, NKG2D and NKp46, allowing natural killer cells to detect cancer cells. However, IDA can lead to an impairment of natural killer cells antitumor activity through the induction of hypoxia. Hypoxia leads to a downregulation of natural killer cell-activating receptors, NKG2D and NKp46, as well as decreasing the presence of stress associated ligands HSP70 and MICA/B on cancer cells.[71, 72] Hypoxia also leads to a degradation of natural killer cell-derived granzyme B that is required for the elimination of cancerous cells.[73] Hence, IDA patients may have reduced immunosurveillance abilities of natural killer cells, which have the potential to allow evasion of cancer cell destruction by the immune system.[13]

IL-2

IL-2 is an essential cytokine regulating immunosurveillance. IL-2 is produced by lymphocytes and is critical for the proliferation of naïve T cells and their differentiation into antitumoral effector T cells.[74] Release of IL-2 is also vital in the communication between T cells and natural killer cells.[75] Furthermore, IL-2 is required to stimulate the growth and activity of natural killer cells, in order for them to exert their antitumor responses. Therefore, IL-2 plays a pivotal role in regulating the immunosurveillance cellular response to cancer. However, *in vitro* studies have assessed the implications of iron deficiency on immune cell cytokine production. Demonstrating a significant reduction in IL-2 production in response to iron deficit.

This may lead to a reduced antitumoral immune response in patients with IDA, as IL-2 may be required by the immune system to control cancer.[74] This has been supported in colorectal cancer mouse models, where increased IL-2 expression was associated with inhibited tumour formation and growth.[76] Therefore, a reduction in IL-2 production associated with iron deficiency creates a dampened immunological environment that may be more passive to cancer development.

IFN-gamma

IFN-gamma is a cytokine released by T helper cells, which acts to aid the immunosurveillance antitumor response through helping to recruit and activate natural killer cells.[77, 78] Hence, IFN-gamma acting on natural killer cells acts to limit tumour growth and metastasis.[79] However, iron deficiency leads to a reduction in IFN-gamma secretion.[80] IFN-gamma is a pleiotropic cytokine that has anti-proliferative, pro-apoptotic and general antitumor effects. Hence a decrease in IFN-gamma in IDA may lead to a hindering of natural killer cell function and creating a protumorigenic cytokine environment.[81] Supporting evidence implicates a decline in IFN-gamma in the pathogenesis of colorectal cancer, as a decline in IFN-gamma contributes to the proliferation of APC mutant cells through altering EGF and Wnt-mediated signalling.[82] Further supportive evidence has shown that colorectal cancer patients with lower levels of IFN-gamma, present with significantly worse survival.[83] This data suggests that IFN-gamma has a protective role against colorectal cancer, which is dampened through iron deficiency.

Iron Deficiency and Tumour Microenvironment

IDA may alter immune cell function leading to an insufficient immunosurveillance ability of the immune system, which could aid in tumour development. Additionally,

iron deficiency may also alter immune cells within the tumour microenvironment, causing them to exert a protumourgenic response.

Macrophages

Red blood cell haem degradation contributes to iron recycling in the MPS. Spleen and liver macrophages are responsible for this by converting haem to ferrous iron through the expression of high levels of the enzyme HO-1. Tumour-associated macrophages (TAMs) are present in the tumour microenvironment and dependent on their polarization phenotype contribute to tumour development or regression, in part through regulating iron availability for use in cancer cell proliferation. M1 classically activated macrophages are pro-inflammatory, express high intracellular levels of ferritin that sequesters iron and promote tumour regression. Whereas, M2 macrophages favour tumour growth in part through upregulation of HO-1 mediated iron generation and increased iron export to the tumour microenvironment. HO-1 is expressed in residential macrophages and recruited monocytes within the tumour stroma, hence iron recycling in the tumour microenvironment is dependent heavily on the TAM activity.[84, 85] *In vitro* studies have shown that depending on TAM polarisation there are different tumour responses, through HO-1-induced iron production and export to the tumour microenvironment. Conditioned media from M2 macrophages lead to more effective stimulation of cancer cell proliferation than that of M1 macrophages. This was dampened by iron chelation, suggesting that increased iron export to the tumour microenvironment by M2 macrophages is responsible for enhanced cellular proliferation.[86]

Therefore, in individuals with IDA, there may be the potential for there to be a decrease in the iron-sequestering M1 macrophages and an increase in the iron-

374 releasing M2 macrophages. This has been supported *in vitro* were bone marrow-
375 derived macrophages treated with iron showed an increase in M1 polarisation
376 phenotype, while decreasing M2 phenotype.[87] Hence, in individuals with iron
377 deficiency there may be a reduction in M1 polarisation and a loss of inhibition of M2
378 polarisation. Similarly, research into the effects of iron therapy on immune function
379 against cancer has revealed that iron-loaded TAMs induced through injection of iron
380 oxide nanoparticle lead to reduced tumour size within *in vivo* models. This occurs
381 through the iron treatment leading to repolarization of TAMs to exert an antitumor
382 effect.[88]
383
384 Previously discussed is the role of IFN-gamma deficit induced by iron deficiency
385 driving colorectal cancer. This is further supported in a study using APC deficient
386 multiple intestinal neoplasia mice that lack IFN-gamma signalling. This lack of IFN-
387 gamma signalling led to an accumulation of TAMs which were more prone to M2
388 polarisation.[81]

389 Regulatory T-cells

390 Regulatory T-cells (T-Regs) have an indispensable function in peripheral tolerance,
391 preventing detrimental immunopathological responses against self and unharmful
392 foreign antigens.[89] The risk of developing cancer increases as a result of unregulated
393 immunological responses, as seen in patients with inflammatory bowel disease who
394 have increased risk of developing colorectal cancer. This occurs through multiple
395 mechanisms, for instance, persistent activation of the immune system in chronic
396 inflammation can contribute tumour promoting growth factors and cytokines. Anti-
397 inflammatory CD4+ T-Regs act to reinstate immune homeostasis during chronic
398 inflammation.[90, 91] However, *in vitro* studies have assessed the implications of iron

deficiency on T-Regs. Iron chelation resulted in impaired T-Reg activation and proliferation.[92] This suggests that iron deficiency may lead to the loss of the immunosuppressive effects of T-Regs in the tumour microenvironment, which may contribute to chronic inflammation which is associated with colorectal cancer.

Implications of Iron Deficiency on Colorectal Cancer

The consequence of iron deficiency anaemia on the immune system's ability to prevent cancer

A 2015 population study conducted by *Hung et al*[93] evaluated the risk of cancer in patients with IDA. They determined that there was a significantly increased risk of developing cancer in patients with IDA, irrespective of age or gender.[93] A similar study by *Ioannou et al*[94] assessed explicitly GI malignancies, with their findings revealing GI tumours to be more prevalent in men and postmenopausal women with IDA compared to those with normal iron levels. However, this was not seen in premenopausal women.[94] These studies suggest an association between IDA and the development of cancer. Which may be due to an impairment of immune function, allowing tumour cell evasion through diminished immunosurveillance or due to a switch to protumorigenic immune cell function within the tumour microenvironment. Further supporting this, in animal studies oral carcinogen lead to earlier cancer development in iron-deficient rats, compared to those with normal iron levels.[95]

Iron deficiency anaemia exacerbates colorectal cancer

Patients with IDA have been shown to have an increased risk of developing tumours. However, IDA is commonly present in patients with predating colorectal cancer. Hence, impairment of immune function by iron deficiency may exacerbate the

patients' pre-existing cancer. This may be through limiting the immune system's ability to limit tumour growth, hindering responses to therapy and restricting the immune system's response to circulating tumour cells which may develop into distant metastasis.[96] This has been assessed in clinical studies which showed that colorectal cancer patients with IDA have inferior outcomes than those without IDA, presenting with worse tumour staging and lower disease-free survival.[97]

Iron deficiency anaemia and response to therapy

IDA may also lead to a reduced response to therapies, such as surgery and chemotherapy. Preoperative anaemia in colorectal cancer patients, usually induced through iron deficiency, leads to a decreased survival following surgery.[98] This may be due to the immune's systems requirements to prevent dissemination of cancer cells following surgery. IDA may impair immune function allowing circulating tumour cells induced through surgery to be undetected and to form metastasis. Similar evidence has supported the fact that anaemia leads to inferior patient outcomes following treatment, a study by *An et al*[99] showed that patients with preoperative anaemia treated with adjuvant FOLFOX chemotherapy presented with a worse prognosis, than those without anaemia.[99]

Iron Therapy

Oral iron therapy is the current standard treatment for IDA.[100] However, this has been shown to increase the concentration of luminal iron within the GI tract, which increases oxidative stress and inflammation that may contribute to the progression of colorectal cancer.[101] In contrast, studies assessing preoperative IDA in colorectal cancer patients have shown that intravenous iron therapy replenishes iron stores

and treats iron deficiency more effectively than oral iron, without contributing to gut iron concentration.[102] This is further supported in patients with FID that have reduced luminal iron absorption, therefore oral iron is poorly absorbed in the duodenum of these patients and can contribute to gut iron concentration. Whereas, intravenous iron is more effective at treating iron deficiency in FID patients.[49, 50]

Oral iron supplementation has been shown to have a variety of GI side-effects including abdominal pain, dyspepsia, constipation and diarrhoea. Leading to non-compliance as a result of these side-effects. In contrast, intravenous iron has been shown to be better tolerated, with fewer GI side-effects.[103] Furthermore, many studies have been conducted to support the efficacy and safety of intravenous iron therapy preoperatively in colorectal patients with IDA. A 2020 study by *Kam et al*[104], showed that colorectal cancer patients with IDA who received intravenous iron therapy had significantly increased haemoglobin levels prior to surgery, as well as requiring less red blood cell transfusions, compared to patients not treated with intravenous iron. This study also supported the safety of intravenous iron, stating that they observed no iron-related adverse events following treatment.[104]

This suggests that intravenous iron may provide a more adequate therapy to treat IDA in colorectal cancer patients, compared to oral iron supplementation. Intravenous iron may be a more beneficial therapy by providing optimum repletion of iron stores, in order to ensure normal immune function.

Conclusion

Multiple studies have shown that excessive gut luminal iron contributes to colorectal carcinogenesis, through increasing oxidative stress, contributing to inflammation and providing iron for cancer cell proliferation. However, the implication of iron deficiency on colorectal cancer has not been fully assessed. This is of prominent need for investigation due to colorectal cancer patients often presenting with IDA. Iron is necessary for correct immunological function. Hence, iron deficiency may result in a dampened immunosurveillance response, most notably leading to impairments of dendritic cells, T-cells and natural killer cells. Along with this, iron deficiency can modify macrophage polarization and alter T-reg populations, promoting a procarcinogenic tumour immune microenvironment. Collectively these mechanisms may link why patients with IDA have significantly increased risk of developing cancer, have worse colorectal cancer tumour staging, reduced disease-free survival, and reduced response to therapy (Figure 2). Therefore, in order to limits these outcomes, adequate iron therapy is necessary. Oral iron is typically given to colorectal cancer patients with IDA; however, this increases gut luminal iron concentration and does not provide optimum replenishment of iron stores. Studies assessing iron therapy in colorectal cancer patients with IDA have shown that intravenous iron was more effective at replenishing iron stores and treating iron deficiency anaemia than oral iron supplements. This suggests that intravenous iron therapy may be more beneficial in supporting cancer immunosurveillance and limiting pro-tumorigenic microenvironment, without the oncogenic consequences of increasing gut luminal iron.

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Figure 1: Schematic representation of systemic iron regulation.

Figure 2: Summary of how colorectal cancer causes iron deficiency anaemia leading to altered immune function that contributes to cancer progression.