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REVIEW

Roles of Hormones and Signaling Molecules in Describing the Relationship Between Obesity and Colon cancer

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Abstract Colon cancer represents a highly prevalent disease in the Western world. While dietary and lifestyle recommendations remain important factors in disease prevention and treatment, epidemiological data have made it clear that obesity and excess body weight remain significant risk factors for the disease. A number of potential direct and indirect relationships exist between obesity and increased risk of colon cancer. Several mechanisms which appear promising and warrant further investigation are discussed here, specifically the modifying role of insulin and insulin-like growth factors, leptin, adipose-tissue induced changes in estrogens and androgens, and inflammatory molecules. A brief review of these hormones and signaling molecules and their action in colon cancer development is described. A thorough integration and understanding of the mechanisms of action these systems exert on colonic epithelia will be important in designing studies and experiments aimed at elucidating disease etiology for prevention and treatment.

Keywords Colon cancer · Inflammation · Insulin · Leptin · Obesity

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Introduction

Colon cancer is the third most prevalent form of cancer in the occidental world for both men and women, and accounts for 10% of new cancer cases and 10% of cancer deaths [1-3]. Despite dietary and lifestyle recommendations, as well as increased public awareness and education, the incidence of the disease has not declined [1]. As with most cancers, the interaction of environmental effects and genetics play an important role in colonic carcinogenesis. There is convincing evidence that among environmental factors, diet, and specifically high fruit and vegetable consumption, may reduce risk of the disease [4]. Contrastingly, increased body fatness and BMI are associated with increased risk of colon cancer in numerous epidemiological studies [5-12]. In vivo studies in rats further support the notion that increases in body mass may lead to colonic cancer [13, 14].

Potential Links Between Obesity and Colon Cancer

Environmental factors and metabolic state clearly play a role in leading to molecular changes which may modify risk of colon cancer. Epidemiological observations suggest that diet, drugs (namely non-steroid anti-inflammatory drugs), antioxidants, and calcium can delay colorectal cancer onset or cause regression of its precursor adenoma, thus suggesting that environment can constitute an important protective effect against colon cancer [15-18]. Similarly, odds ratios suggest that increasing BMI from 20 to 25 may increase risk by 50% and increasing BMI to 30 or more may double the risk of colon cancer [7]. Overall, obesity may contribute indirectly

to a number of neoplastic conditions and increased mutagenic risk, through inappropriate stimulation of the immune response, release of reactive oxygen species and other free radicals, all of which can be inducing enhanced DNA damage in turn leading to critical mutations [19].

Specific to colon cancer, obesity and its downstream effects may lead to a number of changes that increase risk for the disease. To date, several mechanisms have been proposed to explain the molecular association between obesity and colon cancer. Specifically, this review will summarize the role of the following hormones and signaling molecules whose changes in obesity may lead to increased colon cancer risk. These include: 1) insulin and insulin-like growth factors, 2) leptin, 3) adipose tissue-induced changes of estrogens and androgens and 4) inflammatory molecules.

Insulin Insulin is a polypeptide hormone with a broad variety of functions and influences in a large number of intermediary metabolic processes. Insulin plasma concentrations are typically higher in obese than in lean individuals regardless of diabetic status, potentially due to the stronger need for fuel utilization and energy regulation [20]. Physical inactivity and diets high in refined sugars and low in fiber are associated with obesity and insulin resistance, conditions known as causes to hyperinsulinaemia [21]. To add, insulin is responsible for and critically involved in short-term regulation of metabolism and insulin plasma concentrations are typically higher in obese than in lean individuals regardless of diabetic status [20, 22, 23].

It has been demonstrated that increasing systemic levels of insulin can result in increased insulin-like growth factor 1 (IGF-1) levels [24]. Similarly, increased levels of both free and bioavailable IGF-1 have been reported in obese subjects [25]. Furthermore, as reported by Renehan et al [26]., increased adiposity, measured by BMI, correlates with blood circulating insulin levels in non-diabetic individuals, as does free IGF-1.

It is often hypothesized that high insulin and IGF levels observed in obese individuals may increase the risk of tumorigenesis by stimulating certain signaling pathways favoring pro-carcinogenic processes (such as induction of proliferation and angiogenesis and suppression of apoptosis) either directly via the MAPK pathway or indirectly by increasing IGF-1 levels [20, 22, 27, 28]. Both of these regulatory actions result in increased levels of epithelial cell proliferation and reduced levels of apoptosis (main effects shown through in vitro studies), thus, increasing the risk of colon cancer [20, 22]. Compared to insulin, however, IGF exerts a definitively longer-term integrating effect on mammalian development and growth [29].

IGF-1 potently inhibits apoptosis and is required for cell cycle progression [28]. Most of the IGF-1 (>90%) circulating in the plasma is bound to Insulin Growth Factor Binding Protein-3 (IGFBP-3). IGFBP-3 yields IGF-1 unavailable to its receptors, thus, the bound form of IGF-1 becomes inactivated. However, IGFBP-3 can still exert a direct inhibitory effect on the cells targeted by IGF-1 as evidenced by in vitro studies [28, 30, 31]. Both IGF-1 and IGFBP-3 are produced and released by the liver. The IGFBP-3/IGF-1 complex can be resolved by IGFBP proteases which cleave IGFBP thus releasing IGF-1 which, once released, is in its active form [28, 32].

Both normal colonocytes and cultured colonic adenocarcinoma cells express the IGF-1 receptor in vitro. Binding of IGF-1 to the colonocyte receptor inhibits apoptosis and promotes progression via the cell cycle regardless of whether the cells are of normal or adenocarcinoma origin (exertion of a universal effect) [28, 32-37]. This suggests that IGF-1 can modulate growth along the normal-tumorigenic continuum [28, 38]. Furthermore, IGF-1 has been reported to induce the production of the angiogenic endothelial growth factor in vitro, promoting angiogenesis, a necessary step for cancer development [28, 39]. In addition, transformed cells over-express IGF-1, suggesting that IGF-1 is linked to the process of their transformation [28].

Insulin also promotes proliferation of both normal colonocytes and cultured colonic adenocarcinoma in vitro [28, 34, 36, 37]. Adenocarcinoma-derived colonocytes express receptors for both insulin and IGF-1. Significant evidence suggests that insulin influences proliferation via complexing with the IGF-1 receptor [28]. Further, studies have described the close relationship between apoptosis and IGF [40, 41]. Increases in insulin can also indirectly regulate IGF-1 by increasing the number of hepatic growth hormone receptors, hence extending an indirect regulatory effect on effectiveness and ultimate result of IGF-1 action [28, 38]. Insulin also reduces the production of IGFBP-1 and IGFBP-2 (which bind to IGF-1 and inactive it) thus resulting in higher levels of free (active) IGF-1 in the plasma [22, 28].

Mechanistically, the activation of ras protein mediates the insulin and IGF-1 signaling pathway, signaling the increase of proliferation and the decrease of apoptosis [28, 42, 43]. Mutations which lead to the over-expression (activation) of ras protein are very commonly observed in colon cancer and induce transformation of adenomas into malignant highly invasive tumors [28]. Insulin-induced farnesylation of ras constitutes yet another mechanism via which insulin influences mutagenesis. Farnesylation is the modification of ras carboxyl termini with C15-prenyl (farnesyl) groups that is necessary for ras to transfer its oncogenic signals from membrane receptors [28, 44].

Insulin increases the levels of farnesylated ras protein, hence inducing the ras-mediated response to growth factors in cells (this includes both IGF-1 and epithelial growth factor) [45, 46].

Leptin Leptin is a hormone and a cytokine produced mainly by the adipose tissue and acts as a satiety regulator by repressing the sense of hunger via binding to leptin receptors in the brain [47]. Since obese individuals have increased adipose tissue mass, they generally produce more leptin compared to lean individuals and thus exhibit significantly higher plasma leptin concentrations [48]. As Stattin et al. report [49], circulating leptin levels are closely related to the percentage and amount of adipose tissue (correlations of body mass index, BMI). According to Jaffe and Schwartz [50], leptin serum levels are about five times higher in obese people than in normal individuals.

There are several mechanisms that have been proposed in support of a link between leptin and cancer [51]. Leptin has been shown to be a mitogen for some colonic adenocarcinoma cell lines, exerting its mitogenic effect via the stimulation of MAPK and NF-κB signaling pathways [49, 51]. In addition, leptin has been shown to both suppress apoptosis and stimulate proliferation of colonic epithelial cells In vivo [49, 51]. Leptin has also been reported to induce angiogenesis in vitro [52, 53], and to function as a growth factor by stimulating the invasive capacity of the cells at early stages of neoplasia, thus inducing their potential metastatic properties [54]. In addition to stimulating the growth of colon cancer cells [54], leptin binding sites have been also identified along the entire length of the gastrointestinal tract from the tongue to the rectum in animal models [55]. Furthermore, leptin signaling via the STAT pathway has been demonstrated to occur in the various regions of the mouse gastrointestinal tract (both small intestine and colon) [54]. It has been proposed that leptin may also exert effects inductive of carcinogenesis via a variety of signaling pathways involving a series of signaling molecules as JAK2 tyrosine kinase, phosphoinositide PI3 kinase, mTOR kinase and protein kinase C (PKC). More specifically, Attoub et al [54]. reported that leptin potently (EC50 = 10 − 30 ng/ml) induces the invasion of collagen gels by premalignant familial adenomatous colonic cells PC/AA/C1 and non-tumorigenic MDCK kidney epithelial cells, their src-transformed counterparts, and the human adenocarcinoma colonic cells LoVo and HCT-8/S11. Attoub et al. also demonstrated that leptin induces transient elevation of the PI3′-kinase lipid products in JAK2 immunoprecipitates prepared from parental MDCK cells, while the leptin effect on invasion can be potentiated by the activated form of the small GTPase RhoA and abrogated by dominant negative mutants of RhoA, Rac1, and the p110alpha of PI3′-K. Jaffe and Schwartz [50] demonstrated that leptin in the colonic cell lines LS174T and HM7, activated the mitogen-activated protein kinase pathway, induced invasion of colonic cells and concomitantly increased the formation of lamellipodial structures. Jaffe and Schwartz [50] concluded that leptin demonstrates a direct and dose- and time-dependent activation of RhoA, Cdc42 and Rac1 in these colon cancer cell lines, potentially leading to increased cell proliferation.

Estrogens and Androgens Risk factors for colon cancer may also in part be modified by hormones. For example, one study demonstrated that estrogen-negative women (postmenopausal women not taking hormone replacement therapy) are at increased risk of colon cancer independent of BMI [56]. However, estrogen positive women demonstrated a greater than a two-fold increased risk for colon cancer at BMI >30. Mechanistically, estrogen may prevent tumor growth by competitively preventing IGF from binding to its receptors. Estrogen positive women exhibit high levels of circulating estrogen regardless of body size, which can up-regulate IGF and insulin receptors and sensitivity; specifically, IGF receptors which are necessary for tumor formation and rich in colonic tissue [57-59]. While estrogen becomes protective by binding IGF receptors, high levels of circulating insulin induced by excess adipose tissue may bind to the increased insulin receptors and increase colon cancer risk [56]. In contrast, estrogen negative women exhibit lower levels of estrogen, IGF and insulin receptors such that estrogen's protective effect is lost and small changes in circulating estrogen derived from excess adipose tissue has little effect on risk or colon cancer. Similarly, androgens in men may exert likewise effects on the insulin pathways and modify colon cancer risk [60].

Other studies have shown that human colon cancer derived Caco-2 cells are responsive to estradiol, which rapidly induces a number of important cell signaling intermediates that lead to increased cell proliferation, namely through several c-src-related tyrosine kinases [61]. Activation of human c-src has been observed in human colon carcinomas [62-64]. More recent studies demonstrate that tyrosine phosphoyrlation of villin by c-scr kinase leads to enhanced intestinal cell spreading and cell migration [65]. In addition, estradiol has also been shown to activate MAP kinase, inhibition of which has been shown to block colon cancer growth [66] and whose hyperactivation has been reported in a number of human cancers including the adenoma to carcinoma sequence in colon cancer [67]. While excess adipose tissue may result in increased estrogen, it remains unclear whether this increase will lead to biologically significant increases in estradiol so as to recapitulate some of the effects described herein, however,

estrogenic effects induced by adipose tissue provide an additional mechanism whereby obesity exerts colonic cancer promoting effects.

Inflammatory Markers Adipose tissue has been recognized as an active organ which secretes a number of signals and proteins, including cytokines and other hormone-like factors. Obesity has been shown to be associated with a low-grade chronic inflammation, and increased levels of adipose tissue can lead to increases in a variety of pro-inflammatory agents (adipokines–cytokines) which includes adiponectin, tumor necrosis factor-alpha (*TNF-α*), the interleukin family of agents IL-1b, IL-6, IL-8, IL-10, monocyte chemoattractant protein-1 (MCP-1), macrophage migration inhibitory factor, nerve growth factor, vascular endothelial growth factor, plasminogen activator inhibitor-1, haptoglobin and leptin [68-70]. These compounds are all involved in the induction of inflammation via several different mechanisms and signaling pathways [71].

Overall, obesity and insulin resistance are associated with chronic, low-grade systemic inflammation [40, 41]. Further, the expression and release of inflammation-related adipokines typically increases as adipose tissue mass expands with increased obesity [72]. According to a bulk of epidemiological data, chronic bowel inflammation predisposes persons to malignancy in cases of inflammatory bowel disease and colon cancer [40, 41]. Furthermore, several risk factors for colorectal cancer, including a sedentary lifestyle, have been associated to the evidence of systemic inflammation as indicated by circulating levels of C-reactive protein (CRP) [40, 41]. Additionally, it has been reported that in an inflammatory state, local cell-mediated immunity is attenuated and angiogenesis is increased along with a variety of other growth factors. When present long-term (chronic state), the aforementioned condition fosters an ideal environment for mutated cells to be nurtured and not be subjected to immune control [40]. It is noteworthy that, according to the epidemiology of colon cancer, this entire process still appears to require approximately two or three decades in order to be manifested as malignancy, as suggested by the close association between chronic ulcerative colitis and colon cancer over time, thus indicating the additive nature of the phenomenon. A potential role of the pro-inflammatory leukotriene D4 (LTD4) in this process has also been proposed, since LTD4 has been demonstrated to be signaling increased proliferation and suppression of apoptosis in several lines of non-transformed intestinal epithelial cells [73].

NF-κB is considered a master transcriptional regulator of the immune system as it directly stimulates approximately 150 relevant genes [74]. It is activated by inflammatory cytokines such as *TNF-α* and interleukin-1 (IL-1), which are both released by nearby cells in response to infection or inflammation. In addition to infection and inflammation, NF-κB can also be activated by other stressful situations, such as ionizing radiation or agents which induce cellular toxicity. NF-κB can directly activate oncogenes [71, 75]. As obesity is considered a condition of chronic inflammation, higher activation of cytokines and NF-κB may lead to increased risk of cancer in general and potentially colon cancer in particular, although more specific studies are needed to detect such an effect.

Lastly, the low physical activity levels observed in many obese individuals can also change the levels of prostaglandins [76]. Increased prostaglandin production by tumors has been associated with aggressive tumor behavior [77]. Additionally, individuals with colorectal polyps or cancer have been shown to have higher levels of colonic mucosal prostaglandin E_2 (PGE_2) versus controls. Concentrations of prostaglandins decrease due to reduced physical activity, which in turn results in the reduction of gastrointestinal motility and stimulation of cell proliferation, both of which effects increase the risk of colon cancer [78]. Low physical activity increases the concentration of PGE_2 which can lead directly to the induction of cell proliferation. Additionally, low levels of physical activity increase the number and activity of macrophages and are suspected to also increase mitogen-induced proliferation [76].

Conclusions

Colorectal cancer constitutes an important disease with a high prevalence. There is a significant body of epidemiological data linking the obese phenotype with increased risk

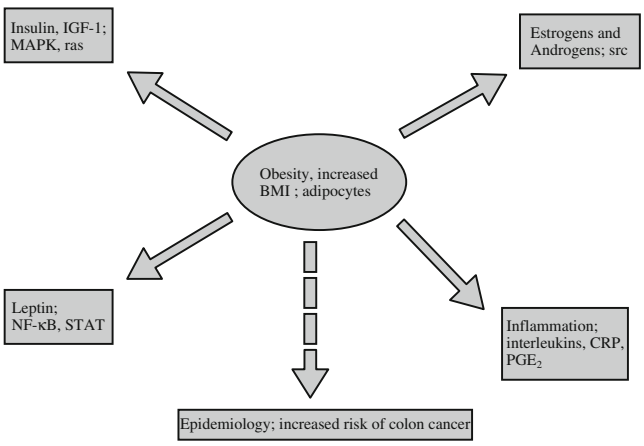

Fig. 1 Obesity, which is epidemiologically linked to colon cancer, and increased adipocytes, can lead to a number of changes in hormones and signaling molecules which in turn modify colon cancer risk

of colon cancer. This association however has not yet been definitely proven as causal. Nevertheless, a variety of potential mechanisms have been proposed and to some extent examined as potential explanations describing this relationship which has been confirmed through epidemiology (Fig. 1). The mechanisms discussed here refer to the modifying capability of obesity, and specifically signals released by adipocytes, to increase colon cancer pathways and overall risk. Specific agents such as insulin and insulin-like growth factor induce signaling cascades resulting in induced proliferation, angiogenesis and reduced apoptosis. Increases in serum leptin can lead to changes in colonic epithelia resulting in increased cancer risk. Androgens and estrogens appear to play a role as modifying hormones that can lead to increased risk of obesity depending on life stage. Finally, chronic inflammation can result in a background environment in which damaging signals and cell insults can lead to cell proliferation and eventual carcinoma. As research describing the potential relationship of obesity and colon cancer advances, it will be important to consider the effects of hormones and signaling molecules as powerful modifiers of the epithelial environment and overall disease process.

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