Review Article

Role of Obesity in the Tumorigenesis of Gastric Cancer

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Abstract

Gastric cancer as a common cancer is a multi-factorial disease that is dependent on parallel effects of environment and genetics. Endogenous and host factors, including gender and several genetic backgrounds are known risk factors also many environmental factors, including smoking, diet, infection and increasing body weight and body mass index (BMI) are associated with the gastric cancer. Epidemiological data have consistently demonstrated a positive relation between obesity and gastric cancer, whereas mechanistic studies have sought to uncover obesity related carcinogenic pathways. Biological mechanisms and the relationship between obesity and cancer are complex and not well understood. Different effective factors include obesity-related hormones and adipokines, growth factors, modulation of energy balance and calorie restriction, inflammatory processes and multiple signaling pathways that affect cancer cell promotion and progression. In this review, we will discuss the recent advances in the understanding of the association of obesity changes in the gastric cancer.

Keywords: *Adipokine, cytokine, gastric cancer, inflammation, obesity*

Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer death worldwide,[1] with a wide variation in incidence rates across different geographical areas.[2] Gastric cancer is a multi-factorial disease that is dependent to parallel effects of environment and genetics. Endogenous and host factors, including those related to male gender, and several genetic backgrounds are known risk factors to a lesser extent.[3]

Many environmental factors, including smoking, high salt intake and a diet with an insufficient level of antioxidants are involved in the pathogenesis of gastric cancer.[4] Several epidemiological studies have investigated the effects of increasing body weight and body mass index (BMI) on the risk of gastric cancer.[5,6]

Obesity is closely linked to an increase adipose tissue with dysfunction. The results of these changes are chronic inflammation and adverse interplay of sex steroids, endocrine hormones and various adipokines. Epidemiological data have consistently demonstrated a positive relation between obesity and gastric cancer, whereas mechanistic studies have sought to uncover obesity related carcinogenic pathways.[7]

In this review, we will discuss the recent advances in the understanding of the obesity changes and association of chronic inflammation and adverse interplay of sex steroids, endocrine hormones and various adipokines with gastric cancer.

Obesity and Cancer

Obesity is an important public health problem worldwide. Based on the World Health Organization (WHO) criteria, overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. Body mass index (BMI) is commonly used to classify overweight and obesity in adults. The WHO definition is a BMI greater than or equal to 25 is overweight and a BMI greater than or equal to 30 is obese.

According to the WHO report in 2014, more than 1.9 billion adults aged 18 years and older were overweight. The worldwide prevalence of obesity more than doubled between 1980 and 2014. Overall, 11% of men and 15% of women were obese.[8]

Epidemiological studies have demonstrated that obesity is associated with increased risk of several cancer types, including gastric, colon, endometrium, pancreas,

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postmenopausal breast, esophagus, gallbladder, kidney, liver, and hematological malignancy.[9] Also, obesity is associated with an increase in cancer mortality. Among patients with a BMI ≥40 kg/m^2 compared with patients with a normal BMI, mortality from all causes of cancer was found to be 52% higher in men and 62% higher in women.[10]

Biological mechanisms and the relationship between obesity and cancer are complex and not well understood. Different effective factors include obesity-related hormones and adipokines, growth factors, modulation of energy balance and calorie restriction, inflammatory processes and multiple signaling pathways that, affect cancer cell promotion and progression.[6,11] Understanding of mechanisms which obesity may induce cancer development is important for prevention of cancer, also to improve outcomes for obese cancer patients.

Possible mechanisms linking obesity with gastric cancer may include obesity associated insulin resistance and an abnormally increased blood level of insulin like growth factor (IGF) and altered levels of adipokines such as adiponectin, leptin, resistin and visfatin.[12] It has been established that obesity is associated with higher levels of proinflammatory cytokines, including Tumor necrosis factor α (TNF-α), Interleukine-6 (IL-6) and C-reactive protein (CRP). Inflammation may stimulate cancer development by activation of Nuclear factor-κB (NF-κB) complex pathway.[11,13] Also, steroid hormones, including estrogen, androgens, progesterone, and adrenal steroids are associated with energy balance and progression of several types of cancer.[14]

Factors involved in obesity associated gastric cancer and their mechanisms

Insulin and Insulin like growth factor (IGF)

Obesity is accompanied by increased insulin independently of type 2 diabetes, presumably due to increased need for metabolic processes energy.[15] According to the findings of several studies, insulin contributes to increased cancer risk. Insulin as a mitogenic hormone in muscle, liver and adipose tissue can increase tissue mass, augment glucose uptake, and finally synthesize nutrients. These anabolic effects are not directly related to carcinogenesis unclear, but could involve the activation of IGF system which is mitogenic under conditions of hyperglycemia or hyperinsulinemia, independently of type 2 diabetes, and alter levels of IGF binding protein-1 (IGFBP1) and -2 (IGFBP2) which accompanied by increased bioavailability of IGFs.[16]

In the obese patients, have been reported higher circulating levels of IGF-I than non-obese patients with hyperinsulinemia.[17] Insulin like growth factor-1 (IGF-1) is a mitogenic and anti-apoptotic factor, mainly produced by the liver, inhibits apoptosis and stimulates cell division therefore could contribute to the development of cancer.[18] Insulin and IGF-1 through the phosphatidylinositol 3-kinase (PI3K)/Akt target of rapamycin (mTOR) pathway and Ras-raf-MAPK signaling which alter the expression of genes involved in cell growth and proliferation[19,20] Figure 1. In addition, IGFs and insulin like growth factor-1 receptors (IGF-1R) and insulin are over expressed in various cancer tissues.[21] IGF-1Rs have tyrosine kinase activity and after binding of theirs ligands, these receptors activate and promote cell migration and redistribution of a- and b-catenins and E-cadherin from adherent junctions into the cytoplasm and promote tumorigenesis.[16,22]

Epidemiological data have consistently demonstrated a positive relation between type 2 diabetes mellitus and gastric cancer. The molecular basis for this association is unclear but could involve IGF-I signaling, which is mitogenic under conditions of hyperglycemia or hyperinsulinemia.[23]

Adipokines

The adipose tissue is a complex endocrine organ. In obesity, adipose tissues have a state of low grade chronic inflammation and presence inflammatory cells (e.g. macrophages and lymphocytes). In fact, adipose tissue involved in carcinogenesis via dysregulated secretion of various adipokines, which are produced by white adipose tissue.[24,25] These adipokines have been implicated in cancer development through effects on various inflammatory pathways, insulin resistance and lipolysis.[26]

More than 15 adipokines have been reported in the literatures to be associated with cancers.[27] Among these

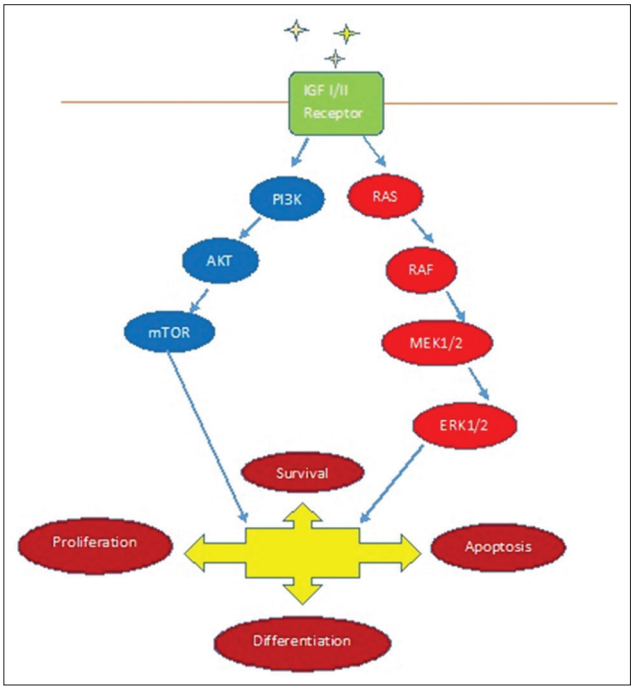

Figure 1: IGF associated gastric cancer and its mechanisms: By binding with IGFs and IGF receptors activate signaling pathways such as RAS/MAPK and PI-3K/AKT, thus resulting in the functions of proliferation, survival, apoptosis and differentiation in cancer cells

adipokines some adipokines such as adiponectin are protective against tumourigenesis and its serum levels are usually decreased in the patients with cancer while the circulating levels of majority of pro-inflammatory adipokine levels, such as leptin, resistin, and visfatin increase in cancers.[24] In continues, refers to a series of these adipokines that act as circulating hormones in gastric.

Resistin

Resistin is a member of family of cysteine-rich proteins called "Resistin-like molecules" (RELMs). Its gene, called Retn mapping to the p13.3 band of chromosome,[28] encoded a encoded a 12.5-kDa protein.[29] It is expressed at very low levels, in human adipose cells, whereas high levels of resistin are expressed in mononuclear leukocytes, macrophages, spleen, and bone marrow cells.[30,31]

Resistin has identified as an important mediator in inflammation associated cancers. Few studies, in human, have been investigating the association of resistin and RELMs with gastric cancer. Zheng *et al*. reported a higher expression of RELMb in intestinal type compared to diffuse type gastric carcinomas. In addition, RELMb correlated positively with tumor differentiation and inversely with tumor infiltration, lymph node metastasis and heparanase expression.[32] About resistin in gastric cancer, Nakajima *et al*. showed that resistin correlate significantly with stage progression and suggested its use as a biomarker for gastric cancer progression.[12] In a previous study, we showed that resistin doesn't express by gastric cancer cell and exogenously by paracrine pathway causes gastric cancer progression.[33] In another study, we showed that exogenous resistin induces gastric cancer cell proliferation by increases human telomerase reverse transcriptase (hTERT) gene expression.[34]

Hesieh *et al*. showed that resistin induced stromal cell-derived factor-1 (SDF-1) upregulation by activation of Toll-like receptor 4 (TLR4), P38 mitogen-activated protein kinases (p38 MARK) and nuclear factor NF-κB. SDF-1 is involved in the carcinogenesis of human gastric cancer, where it stimulates angiogenesis and favors metastasis of tumor cells to distant organs.[35]

Visfatin

Visfatin, a novel adipocyte derived adipokine, is highly enriched in the visceral fat and its plasma levels increase during the development of obesity.[36] Visfatin is also known as pre-B cell enhancing factor (PBEF), a growth factor for early B cell proliferation,[37] and it is the secretory form of nicotinamide phosphoribosyl-transferase (Nampt),[38] the rate-limiting enzyme of mammalian nicotinamide adenine dinucleotide (NAD) biosynthesis.

As yet visfatin receptor has not been identified but in studies on diabetes had indicated that visfatin can significantly regulate insulin secretion. Presumably visfatin with use of insulin receptor and intracellular signaling can regulate insulin secretion from pancreatic beta cells and affects a variety of metabolic and stress responses.[39,40]

Visfatin have three major functions: Growth Factor, cytokine and nicotinamide phosphoribosyl transferase, therefore increasing of visfatin have several effects. Recent studies have shown that over-expression of visfatin is important in the carcinogenesis in several types of cancers.[41,42] several studies have shown visfatin is over-expressed in human gastric cancer tissues and established gastric cancer cells[33,43] also reported that high plasma visfatin levels gradually increase with stage progression of gastric cancer.[12]

Visfatin by up regulation of cyclin D1 and cdk2 expression activates G1-S phase cell cycle progression. Visfatin also increases the expression of matrix metalloproteinases 2, matrix metalloproteinases 9, and vascular endothelial growth factor genes, therefore induces metastasis and angiogenesis of cancer.[41,44] In several studies have shown, visfatin can regulate a variety of different signaling pathways such as Signal transducer and activator of transcription 3 (STAT3), PI3K/Akt and extracellular signal-regulated protein kinases 1 and 2 (ERK1/2).[45,46]

These findings about visfatin show its role in carcinogenesis and cancer progression. Few studies, in human, have been investigated the association of visfatin with gastric cancer, in a previous study, we showed that visfatin expresses by gastric cancer cell and endogenously causes gastric cancer progression.[33] In another study, we showed that visfatin upregulation of human telomerase reverse transcriptase (hTERT) gene expression can cause gastric cancer progression.[47]

Leptin

Leptin gene is located on chromosome 7 in humans and encodes a 16 kDa protein with 167 amino acids.[48] Leptin is produced primarily in the adipocytes of white and brown adipose tissue, placenta, ovaries, bone marrow, skeletal muscle, mammary epithelial cells, pituitary, liver, gastric chief cells and P/D1 cells.[49,50] In obese individuals, there is a higher circulating concentration of leptin than normal weight individuals. Leptin reduces appetite as a circulating signal, but obese individuals show resistance to leptin.[51]

Leptin stimulates the proliferation, migration, and invasion of tumor cells. Several studies have investigated the expression of the leptin in normal and malignant gastric tissue[52-60] and have shown there is a positive correlation between expression of leptin and its receptor.[52] Also, high leptin and its receptor expression were associated with aggressiveness of tumor.[52,57,58] In fact, it is a key player in the obesity and cancer link.

In vitro studies have shown leptin causes increased cell proliferation in gastric carcinoma cell lines AGS,[54] MKN-28,[55,56] MKN-74[55] and HS746T,[56] via activating a

number of signaling pathways, JAK2/STAT3 and STAT5, IRS/PI3K, SHP2/MAPK, and AMPK/ACC.[55,56,61-63]

Adiponectin

Adiponectin is an adipose tissue derived hormone, which is down regulated in obesity. Circulating concentrations of adiponectin are 3 to 30 ng/mL that is expressed in differentiated adipocytes.[64,65]

Adiponectin has an inverse association with total body fat mass and displays, protective actions on the development of various obesity related diseases such as cancer.[66] Epidemiologic studies show that low level of adiponectin has an inverse association with cancer progression as well as advanced disease.[67,68] Lower plasma adiponectin levels have also been found in patients with gastric cancer, especially in upper gastric cancer, compared with healthy control subjects, and were inversely correlated with tumor size, depth of invasion, and metastasis stage (76). This inverse correlation is due to anti-inflammatory, antitumor, and antiangiogenic effects of adiponectin (75). The anti-inflammatory effects of adiponectin are supported by an observed inverse correlation between plasma levels of adiponectin and C-reactive protein.[69] The antitumor and anti-angiogenic effects of adiponectin are supported by an observed induction of apoptosis and inhibits the proliferation of gastric cancer cell lines through adiponectin receptors AdipoR1 and AdipoR2 (78).

Inflammatory cytokines

Obesity is associated with chronic low-grade inflammation (or meta-inflammation), characterized by increased inflammatory signaling, abnormal cytokine production and immune activation. The connection between inflammation and cancer has been studied for years, and chronic inflammation is thought to be a key contributor to tumor development.[70]

Inflammatory cytokines and chemokines, including TNF-α, IL-6, and CRP are more deregulated in the gastric cancer. In continues, refers to a series of these inflammatory cytokines that act as contributor to tumor development.

Tumor necrosis factor α

Tumor necrosis factor α is a 26-kDa transmembrane protein and a powerful inflammatory cytokine. TNF-α, first identified as an antitumor agent, but now also is recognized as a tumor promoting cytokine that links inflammation and cancer.[71] Recent studies have indicated that TNF-alpha overexpression in adipose tissue is a common feature in human and animal models of obesity and plays an important role in mediating the insulin resistance by over-expression in fat tissue.[72,73]

In fact, TNF-α contributes to the deregulation of the insulin signaling pathway, including serine phosphorylation of insulin-receptor substrate (IRS) proteins by c-jun N terminal kinase (JNK) and an inhibitor of nuclear factor-κB kinase (IKK)[74,75] and induce inhibitory serine 307 (Ser307) phosphorylation of IRS-1 which decreases activation of insulin mediated Akt/PI3K/mTOR pathway.[76,77] Zhao *et al*. investigated link between over-expression of CXCR4 and an obvious involvement in gastric cancer metastasis. They showed that H. pylori upregulates CXCR4 expression in gastric cancer through TNF-alpha.[78] Oshima *et al*. investigated the role of TNF-α in gastric tumorigenesis and indicated that TNF-α signaling through Tumor necrosis factor receptor 1 (TNFR1) is important for gastric tumor development. They suggested that the activation of TNF-α/TNFR1 signaling in the tumor promotes gastric cancer and development through induction of Nicotinamide adenine dinucleotide phosphate oxidase organizer 1 (Noxo1) and G Protein Subunit Alpha 14 (Gna14), contribute to maintaining the tumor cells in an undifferentiated state.[79]

Interleukin 6

IL-6 is produced by a variety of different cell types such as fibroblasts, endothelial cells, macrophages, T cells and myocytes. In obesity, adipose tissue, increase in adipocyte size, number and fat mass that is associated with recruitment and activation of T lymphocytes and macrophages in this tissue with the production of IL-6.[80,81]

The principal signaling mechanism of IL-6 involves activation of the transducer and activator of transcription 3 (STAT3) transcription factor and subsequent regulation of gene transcription. Other signaling pathways activated by IL-6 include PI3K and AMPK signaling pathways.

It has been suggested that IL-6 play a potential role in the pathogenesis and growth of malignancies. Production of IL-6 by gastric cancer cell lines has been reported and act in a paracrine and autocrine manner in tumor cells. It has also been shown that IL-6 levels correlated with clinicopathological features of gastric cancer.[82,83]

C-reactive protein (CRP)

C-reactive protein is a marker of systemic inflammation produced mainly by the liver under the stimulation of adipocyte derived proinflammatory cytokines and elevated in obesity.[84] Serum CRP elevates in many malignancies, and it is a prognostic indicator of malignant potential. However, the prognostic value of CRP in gastric cancer remains uncertain, but in many studies have been shown that the serum CRP level is abnormally elevated in gastric cancer patients and might be a potential prognostic factor.[85] Recently, Chen *et al*. evaluated the significance of serum CRP as a biomarker of long term survival in patients with advanced gastric cancer. They showed that elevated serum CRP baseline levels before chemotherapy were associated with reduced survival in patients with advanced gastric cancer. The rate of CRP

declining was also associated with survival. The CRP baseline concentration before and after chemotherapy may be used as predictive markers of advanced gastric cancer.[86]

Sex hormones

Epidemiologic studies suggest differences in complications from obesity in men vs women, which determines differences in plasma levels of sex hormones.[65] Endogenous sex hormones are active in tumor cell growth and directly mediate the effect of obesity on cancer.

Data from studies have been shown that gastric cancer for most populations in both high and low incidence regions, in men is approximately double that of women. These differences cannot be explained by variations in environmental factors or *Helicobacter pylori* (H. pylori) infection, therefore female sex hormones have been proposed to be protective.

Constanza Camargo *et al*. performed a meta-analysis to examine associations of gastric cancer risk in women with sex hormone. Their analysis showed that longer exposure to estrogen effects of either ovarian or exogenous origin may decrease risk of gastric cancer.[1]

There is evidence that estrogens regulate the insulin receptor substrate-1 (IRS-1) expression and induce free radical mediated DNA damage and gene mutations in cells.[87] Also, has been shown that estrogen contribute to the decreasing insulin sensitivity, regulation of body adiposity and increasing leptin signaling pathways.[88] In women, leptin levels during the menstrual cycle correlate directly with the estrogen levels. Regulation of leptin levels with estrogen in women may play a protective role, although a high level of leptin is considered to be a risk factor for males to cancer development.[89] Overall, estrogen may prevent gastric cancer, but additional studies are warranted.

Genetic factors

In recent years, several new genes have been discovered to be associated with gastric cancer. For example, Immune response-related genes, Gastric mucosal protective genes, Metabolic enzyme genes, DNA repair genes, Tumor suppressor genes, transforming growth factor b (TGF-b), and Vascular endothelial growth-factor (VEGF).[90] According to the epidemiological studies, about 65-80% of the variation in BMI is determined by genetic factors.[91] Obesity is associated with a risk of at least 20 different cancers.[92]

Genome-wide association studies in colorectal cancer have described altered macrophage-enriched metabolic network genes.[93] The single-nucleotide polymorphism associated with obesity is the fat mass and obesity related (FTO) gene, which may function through nutrient sensing but with no relation to gastrointestinal cancers.[65,94]

Discussion

In this review, we attempted to summarize and discuss available data in order to better understand the association of obesity changes such as chronic inflammation and adverse interplay of sex steroids, endocrine hormones and various adipokines with the gastric cancers.

Several epidemiological studies have investigated the effect of increasing body weight and obesity on the risk of gastric cancer. Obesity is an inflammatory disease that leads to the onset of metabolic syndrome and cancer. Possible mechanisms linking obesity with gastric cancer may include obesity associated insulin resistance and an abnormally increased blood level of insulin like growth factor (IGF) and altered levels of adipokines such as adiponectin, leptin, resistin and visfatin.[12] It has been established that obesity is associated with higher levels of pro-inflammatory cytokines, including TNF-α, IL-6 and CRP are infiltrating the inflamed tissues and trigger pathways of activation of NF-κB complex pathway.[11,13] On the other hand, changes in sex steroids, including estrogen, androgens, progesterone, and adrenal steroids are associated with energy balance and progression of several types of cancer.[14]

In conclusion, characterization of the relationship between obesity and gastric cancers could help in the establishment of new preventive strategies and also in identification of new specific targets for cancer therapy, for improving life quality of patients and the quality of health services.

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Conflicts of interest

There are no conflicts of interest.

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