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An IL-6 link between obesity and cancer

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1. ABSTRACT

Obesity is a growing epidemic all over the world that by virtue of inducation of a chronic, low-grade, and systemic inflammation leads to an increased risk of a number of diseases, including cancer. IL-6 an important cytokine in the increased risk to cancer in obese patients mainly because of its pro-inflammatory activitiy. Some data suggest that IL-6 might increase the risk of certain cancers such as those that originate from breast, liver, prostate, colon, and esophagus. A better understanding of the regulation and role of IL-6 in obesity-associated cancer is required to develop effective therapeutic approaches.

2. INTRODUCTION

Obesity is one of the foremost health threats throughout the world as the prevalence of obesity among children, adolescents, and adults has been dramatically increasing over the past few decades (1). The World Health Organization (WHO) estimates that there are currently more than 1.6 billion overweight adults and at least 400 million of these are obese. Moreover, they predict that by 2015 approximately 2.3 billion adults will be overweight and more than 700 million will be obese. Thus, obesity is acquiring the characteristics of a pandemic and has been recognized as a major global health threat. Obesity is linked

Table 1. IL-6 and obesity-related cancers.

Obesity related cancers	IL-6 related cancers
Colorectal Cancer	Colorectal Cancer
Breast cancer (Postmenopausal)	Breast cancer (Postmenopausal)
Prostate cancer (advanced)	Prostate cancer
Cancer of gastric cardia	Gastric cancer
Liver cancer	Liver cancer
Esophageal cancer	Esophageal cancer
Pancreatic cancer	Pancreatic cancer
Renal cell carcinoma	Renal cell carcinoma
Ovarian cancer	Ovarian cancer
Gallbladder cancer	Lymphoma
Endometrial cancer	Multiple Myeloma

Both Obesity and IL-6 have been implicated in the initiation and progression of a multitude of cancers. Many of the cancers over-lap between obesity-related and IL-6-related cancers. This and the knowledge that obesity is characterized by low-grade chronic inflammation lead to concept that IL-6 is one of the major players in obesity-related cancers

to several types of common diseases including cardiovascular disease, type 2 diabetes mellitus, hypertension, dyslipidemia, liver disease, as well as various types of cancer (2). Therefore, the health consequences of obesity are huge and varied, ranging from an increased risk of premature death to several non-fatal but debilitating diseases that have adverse effects on the quality of life. Obesity and physical inactivity may account for 25 to 30 percent of several major cancers (3) (Table 1). A recent study that used NCI Surveillance, Epidemiology, and End Results (SEER) data, estimated that in 2007, in the United States, about 34,000 new cases of cancer in men (4 percent) and 50,500 in women (7 percent) were due to obesity (NCI factsheet). Another recent report estimated that, in the United States, 14 percent of cancer-related deaths in men and 20 percent in women were due to weight and obesity (4). Obesity is closely associated with chronic low-grade inflammation characterized by abnormal production of cytokines and acute phase proteins (5,6). Mature adipocytes and non-fat stromal cells act as an endocrine and paracrine organ and through a network of tissue, the sympathetic nervous system, and the brain can influence appetite, energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism and homeostasis. Adipocytes, through their production of a number of adipokines, contribute to the pro-inflammatory state in obesity, which promotes tumor development and has been established as a hallmark of cancer. A number of cytokines are also produced and secreted by adipose tissue, which play a significant role in tumor development as well. One of the primary cytokines produced by adipose tissue, interleukin-6 (IL-6), is strongly related to obesity. IL-6 has been linked to number of diseases including cardiovascular disease, diabetes, and various cancers (Table 1). On the other hand, IL-6 is secreted by muscle tissue as a myokine during exercise suggesting a beneficial role for IL-6. Therefore, to separate the adverse effect of IL-6 from its beneficial role, it is necessary to understand the fundamental mechanism in a disease state, which in turn will lead to the development of therapies against IL-6 dependent cancer.

3. IL-6-AN OVERVIEW

IL-6 is an interleukin that acts as both a pro-inflammatory and anti-inflammatory cytokine and modulates the immune response, inflammation, as well as the nervous, hematopoietic, and endocrine systems (7). It regulates humoral and cellular responses and plays a central role in inflammation and tissue injury. Its signaling in cells is mediated through a hetero-trimeric receptor complex consisiting of one IL-6 subunit and two gp-130 subunits. In the last decade, IL-6 has been intensely investigated and implicated as a major player in the regulation of metabolic disease states. This cytokine plays an important role in the pathogenesis of coronary heart disease, as well as Type 1 and Type 2 diabetes. Additionally, IL-6 has been implicated in the development of various types of cancers. Although IL-6 is characterized as both a pro- and anti-inflammatory cytokine, it is well recognized as a mediator of the low-grade chronic inflammatory state of obesity (8). However, data regarding the function of IL-6 in both obesity and insulin resistance are controversial and unresolved (9,10). Numerous studies have shown that IL-6 levels are greatly elevated in obese humans and strongly correlated with increased body mass index (BMI) and waist circumference (11,12). IL-6 has also been implicated as a marker for visceral adipose tissue (13,14) because visceral adipose tissue releases more IL-6 than subcutaneous adipose tissue (15,16). Conversely, one of the most striking observations highlighting the anti-obesogenic effects of IL-6 was that knockout mice (IL-6$^{-/-}$) developed mature onset obesity, hypertriglyceridemia, and glucose intolerance (17). However, these age-related obesity and metabolic syndrome phenotypes were not observed in other IL-6 deficient mice (18). Overall, the fact that IL-6 is released from adipose tissue into systemic circulation and can positively correlate with obesity and body fat implicates a possible role for IL-6 in regulating body weight and lipid metabolism. Although IL-6 has widespread tissue distribution, previous reports have indicated that 30% of circulating IL-6 originates from the adipose tissue (15,19,20). Therefore, IL-6 is also considered as adipokine or adipocytokine. Consistent with these reports, plasma IL-6 levels are markedly elevated in obese subjects (21). Mature adipocytes in adipose tissue produce and secrete only a fraction of adipose tissue IL-6 (15), and it is well established that other cell types in adipose tissue are capable of IL-6 production (16,22). The production of IL-6 is well documented in different adipose tissues and adipocyte models (16,23,24,25,26,27). Recent documentation of IL-6 knockout mouse model in attenuating obesity-induced liver carcinogenesis has further strengthened the direct link between obesity-induced cancer development through IL-6 (28). The main objective of this review is to understand the connection between fat cells and IL-6 and its implication on different types of cancers. We will also comprehensively discuss the regulatory mechanisms that lead to the variable expression level of IL-6, which may shed some light on the intervention of IL-6-mediated development of cancer.

4. OBESITY, INFLAMMATION AND CANCER

4.1. Obesity and Inflammation

One of the most important realizations in the field of metabolic disease over the last decade is that obesity is associated with a state of chronic, low-grade,

systemic inflammation. This has been suggested to have an important role in the pathogenesis of severe disorders such as insulin resistance, atherosclerosis, and cancer (6,29,30). Adipose tissue is comprised not only of adipocytes but also a stromalvascular cell fraction (SVF). This SVF consists of a variety of cellular populations such as, lymphocytes, fibroblasts, endothelial cells, stromal cells and preadipocytes. Non-fat cells serve as a rich source of cytokines and adipokines (31). Therefore, adipose tissue can be considered an immune organ and, in this capacity, is the primary *in vivo* site of inflammation in obesity. Expression of positive regulators of inflammation is increased in subcutaneous adipose tissue from obese humans and mice, whereas calorie restriction causes reversion of the adipose tissue transcriptome toward one more similar to lean subjects with a downregulation of pro-inflammatory cytokines (32). Adding to its complexity of functions, different anatomic depots of adipose tissue manifest distinct metabolic properties. Although excess subcutaneous adipose tissue (SAT) imparts risk, excess visceral adipose tissue (VAT) is even more strongly predictive of obesity-related co-morbidities and long-term mortality (33). Aberrant expression of a wide range of cytokines and adipokines is a central feature of the inflammatory process within adipose tissue in obesity. The expanding white adipose tissue (WAT) makes a substantial contribution to the development of obesity-linked inflammation via dysregulated secretion (from both by adipocytes and the non-adipocyte fraction) of; pro-inflammatory cytokines Interleukin (IL)-6 and 1 and tumor necrosis factor alpha (TNF-α); chemokines (monocyte chemotactic protein 1, MCP-1); adipokines (haptoglobin, PAI-1, leptin, visfatin, resistin and vascular endothelial growth factor, VEGF); and the reduction of anti-inflammatory adipokines (e.g. adiponectin, IL-10, antagonist IL-1) (31).

The precise role of these inflammatory components in carcinogenesis is not completely understood and therefore continues to be an appealing avenue of research. A leading hypothesis implicates adipose tissue hypoxia in the origin of inflammation (34), which was confirmed in murine obesity and reversed with weight loss. The possible reason of hypoxia-mediated inflammatory response is that adipose hypoxia may induce cell necrosis, which releases cellular byproducts. This in turn recruits macrophages and other phagocytic cells and induces the inflammatory response. Adipose tissue-associated macrophages in obese mice and humans induce near necrotic adipocytes and the surviving hypoxic adipocytes to upregulate hypoxia inducible genes, including hypoxia-inducible factor-1 (HIF-1). In turn, this enhances expression of inflammatory cytokines through activation of NFkappaB. In addition, hypoxia may contribute to oxidative stress and related abnormalities in the endoplasmic reticulum mechanisms that have been implicated in the genesis of inflammation in adipocytes. Recent findings indicate that obesity leads to adipose tissue fibrosis, whereby extracellular matrix proteins (ECM) are deposited in the fat depots (35,36). Adipose tissue fibrosis is also associated with an excess amount of cytokines (35). It is predicted that the cytokines are responsible for the excess production of ECMs in the fibroblasts. Our unpublished data indicates that surplus ECM may also contribute to the excessive production of cytokines, including IL-6 and IL-8, by modifying the physical parameters of the tissue environment, which may create a vicious cycle.

4.2. Inflammation and cancer

It is well recognized that inflammation is involved in the promotion and progression of cancer (37,38), and tumor-promoting inflammation has finally been recognized as one of the hallmarks of cancer (39). Carcinogenesis is a multistage process, and, in the classical sequence of chemical carcinogenesis, tumor initiation is followed by tumor promotion (40). Tumor-promoting inflammation may precede tumor initiation, creating a favorable microenvironment in which cells with cancer-causing mutations thrive. Human epidemiology and animal model studies indicate that chronic, smoldering inflammation may be a far more widespread ground for cancer development than previously thought, and NF-κB activation, as one of the pillars of inflammation, may have a promoting role in most cancers.

Inflammation is one prerequisite needed for tumour cells to invade and seed at distant sites, where inflammatory mechanisms will probably further support their engraftment and growth (41). Angiogenesis and EMT are important steps in tumour progression (42), and genes necessary for angiogenesis are direct targets of NF-κB and/or STAT3—including VEGF, HIF1α, CXCL1 and CXCL8. Key molecules in EMT such as E-cadherin, Twist and Snail are also targets of NF-κB (43,44). Furthermore, the expression of MMP2 and MMP9—which are essential for tumour cell invasion—is controlled by NF-κB and STAT3. Tumour necrosis and intrinsic signaling events lead to the recruitment of bone-marrow-derived cells which secrete cytokines and chemokines that favor tumour progression. IL-1α and HMGB1, which are capable of activating NF-κB in inflammatory cells thereby inducing the secretion of pro-inflammatory cytokines (45,46), are typically released by dying tumour cells. In addition to immune cells, cancer-associated fibroblasts (CAFs) have an important role during tumour progression, as they can be a main source of IL-6, VEGF, TGFβ (47) and the pro-invasive factors MMP3 and IL-8, the latter of which is released in a TNFα/NF-κB-dependent manner (48). CAFs have been shown to exhibit robust IκBα phosphorylation and NF-κB activation in human colorectal liver metastases (49). Another mechanism by which cancer cells create a pro-metastatic environment is the secretion of extracellular proteins. For example, lung cancer cells secrete high amounts of versican, which induces TNFα and IL-6 production in myeloid cells through its binding to TLR2. The blockade of TNFα synthesis through the deletion of *Tlr2* or *Tnf* markedly suppresses the metastatic growth of versican-producing tumour cells (50).

4.3. Obesity and cancer

Energy imbalance is associated with obesity and different studies have observed a relationship between obesity and cancer (51,52,53). The relationship between

dysregulated metabolism and carcinogenesis was first enunciated by Otto Warburg (54). In 2002, the International Agency for Research on Cancer (IARC) expert panel evaluated the link between weight and cancer and concluded that avoiding weight gain could prevent some cancers. Since the IARC report, many observational and epidemiological studies have further investigated the association between adiposity and cancer, suggesting that obesity is associated with a significantly increased risk of developing several cancer types including those of colon (55), esophagus, breast (in postmenopausal women) (56), endometrium, kidney, liver, gallbladder, and pancreas (53,56,57,58,59). Obesity management is an opportunity for cancer prevention (60), and adipose tissue has been suggested as a target organ in the treatment of hormone-dependent breast cancer and other types of cancer. A number of epidemiological studies have also provided sufficient evidence of a positive association between obesity and the incidence of cancer, particularly of hormone-dependent and gastrointestinal cancers. Modulation of energy balance, through increased physical activity, reduced the risk of many cancers, including cancers of the colon, breast and endometrium. In this context, it has been shown that weight loss by dietary and physical activity interventions partially reverses metabolic, endocrinal, inflammatory, and renal alterations associated with obesity (61).

In the following section we will discuss a number of obesity-related cancers and the role of IL-6 in the development of those cancers.

4.3.1. Obesity, IL-6 and breast cancer

Breast cancer is the second most common cancer in the world and the most common neoplasia among women. The association between indicators of body size and risk of breast cancer has been examined in numerous studies (62,63,64). Several hypotheses for this link have been proposed including alterations in sex hormones, growth factors and cytokines (58). Interestingly, several studies established that the association between body size and the risk of breast cancer differed according to menopausal status (65,66). In fact, BMI and body weight have been found to be positively related to the risk of breast cancer among postmenopausal women whereas some studies found inverse associations (58). Furthermore, abdominal adiposity has been found to be positively associated with a higher risk of breast cancer in postmenopausal women; this relationship being stronger among non-hormone replacement therapy users than hormone replacement therapy users (67,68). Obesity increases breast cancer risk in postmenopausal women by around 50%, most likely by increasing serum concentrations of free estradiol (62,63,69). Estradiol level is enhanced in the local site of breast tissue and in circulation by the increased level of aromatase enzyme, which converts androgen to estrogen. It is known that IL-6, secreted by the tumor cells, are able to stimulate aromatase production in adipose stromal cells *in vitro* and *in vivo*, thereby stimulating estrogen biosynthesis (70) and contributing to hormone-dependent breast cancer progression.

However, the mechanisms that underlie the association between obesity and breast cancer risk are not completely understood. IL-6 has a complex role in breast cancer. It is documented that IL-6 has an inhibitory role in the early stage breast cancer, since high serum levels of IL-6 has been associated with poor outcome in advanced metastatic breast cancer (71). On the other hand, elevated levels of local and systemic IL-6 level is linked with increased metastasis. The up-regulation of IL-6 in breast cancer is mediated by NFkappaB and AP-1 transcription factors (72). It was reported that this regulation is particularly important in mammary cancer cell lines with enhanced metastatic potential. The expression of IL-6 in mammary cancer was also enhanced by aryl hydrocarbon receptor activation (73), in addition to treatment with IL-1beta or phorbol ester. For this reason, aryl hydrocarbon receptor could be considered a potential target for modulation of IL-6 expression. Patient data demonstrated that circulating IL-6 levels predict worse survival in metastatic breast cancer (74). High levels of serum IL-6 have independent prognostic value. Breast cancer cells have the ability to produce IL-6 and autocrine cytokine loops have been reported (75). Although, under certain conditions, IL-6 may inhibit growth of estrogen receptor-positive tumor cells, growth-stimulatory autocrine and paracrine regulations have been documented (76,77). IL-6 signals may be potentiated by interaction between the IL-6 receptor and tyrosine kinase receptors (77), which may result in synergistic biological responses. Stromal cells are a rich source of IL-6 in the breast and our previous finding indicate that the cytokine produced by them is implicated in regulation of migration and invasion (78). IL-6 production in those cells depends on the pathway of cofilin-1, a regulator of actin dynamics. There is considerable evidence linking the activation of STAT3 by IL-6 to the regulation of cellular events in breast tumor models. Constitutive STAT3 activity detected in a breast cancer cell line is responsible for tumor cell migration (79). Additionally, in T47D cells the IL-6/STAT axis leads to stimulation of migration (77). The effects of STAT3 are, in part, mediated by Twist, which is required for hypoxia induced angiogenesis and migration (80). In concordance with these *in vitro* observations, there was a strong correlation between activated STAT3 and Twist expression in patients' tissues. Involvement of IL-6 in breast tumorigenesis is also evident by the regulation of psoriasin in breast tumors, a molecule whose expression is associated with tumor aggressiveness (81). Importantly, epithelial-to-mesenchymal transition (EMT), a process characterized with reduced expression of E-cadherin and increased expression of markers such as vimentin or N-cadherin, is induced in breast cancer cells by IL-6 (82). Involvement of the trans-membrane receptor Notch and its ligand, Jagged-1, in mammary carcinogenesis upon stimulation with IL-6 was also demonstrated (83). In concordance with all those findings, it has been demonstrated that IL-6 is a mediator of multidrug resistance in breast cancer (84).

4.3.2. Obesity, IL-6 and gastric cancer

Growing evidence suggests that increasing body weight is associated with an increased risk for gastric-cardia cancer (85,86,87,88) but not for gastric non-cardia

cancer (86,88). A systematic review of four published US and European studies that evaluated the association between body mass index (BMI) and risk of gastric cardia adenocarcinoma reported that overweight (BMI ≥25 to <30 kg/m^2) or obesity (BMI ≥30 kg/m^2) was significantly associated with a 1.5-fold increase in risk of gastric cardia adenocarcinoma (85). Three recent studies also found a positive association between BMI and risk for gastric cardia cancer (88,89,90). A recent meta-analysis indicates that, overall, overweight and obesity are associated with an increased risk of gastric cancer (91). The strength of the association also increases with increasing BMI. A Study reveals that there is a positive association between excess body weight and gastric cancer among non-Asians, but not among Asians. IL-6 seems to be involved in gastric oncogenesis because serum levels of IL-6 were reportedly increased in gastrointestinal cells and in the mucosa of patients suffering from gastric cancer (GC) (92). The IL-6 level was elevated in patients with *helicobaterium pylori* (HP)-induced gastritis, and after treatment the concentration of this cytokine in serum was decreased in almost all cases (93). These observations allow us to establish the IL-6 serum level as a prognostic factor for gastritis and GC, but do not explain the particular role of this cytokine in carcinogenesis, given that dual functions of IL-6 confuse and often restrict the evaluation of its effect in a particular case.

4.3.3. Obesity, IL-6 and colon cancer

Colorectal cancer is the third most common cancer in the world. Incidence rates are approximately 10-fold higher in developed than in developing countries (94). A possible association between an excess of body weight and risk of colon cancer has been examined in many epidemiological and cohort studies; these studies have concluded that obesity is related to a higher risk of colorectal cancer (52,95,96). Different studies have suggested that waist circumference and the waist/hip ratio are also strongly related to a higher risk of colorectal cancer and large adenomas in men, as supported by European Prospective Investigation into Cancer and Nutrition (EPIC),whereas body weight and BMI are associated with higher colon cancer risk in men but not women (97,98). The reasons for this gender difference are speculative. One hypothesis is that abdominal adiposity, more common in men than in women, is a stronger predictor of colon cancer risk than peripheral adiposity (99). However, the mechanisms involved in the association between abdominal obesity and increased colon cancer risk remains unclear. Another possible explanation is the protective role of exogenous estrogens on the risk of colorectal cancer.

Elevated expression of IL-6, which can be detected in patient serum, is linked to increased risk of development of colorectal adenomas (100). In general, expression of IL-6 in serum or tissue samples of patients with cancer or tumour-bearing animals correlates with poor prognosis (75,101,102). Recent studies have established the role of IL-6 and STAT3 in colitis associated colon cancer (CAC) (103). Chronic colitis has been associated with carcinogenesis, however the mechanisms underlying the development of cancer are not completely understood (104). Regulation of STAT3 phosphorylation by IL-6 and SOCS-3 was demonstrated in colitis and cancer (105). A High percentage of SOCS-3-positive cells were found in ulcerative colitis cells. The percentage of cells in which SOCS-3 is expressed decreased during colon cancer progression, and SOCS-3 itself may be involved in regulation of proliferation and apoptosis, as described in prostate cancer. SOCS-3 was shown to limit damage-induced crypt hyperproliferation and tumorigenesis (106). These observations correlate with data showing that persistent activation of STAT3 leads to colon cancer growth (107). Corvinus and associates showed that a dominant-negative STAT3 mutant has an inhibitory effect on proliferation of those cells. Similar to prostate cancer, it was demonstrated that IL-6 trans-signaling promotes *in vivo* tumor progression (108). Thus, this tumor trans-signaling may be even more important than signaling through the membrane receptor in late stages of carcinogenesis. Genetic ablation of IL-6 in mice reduced both the multiplicity and size of colonic adenomas in mice subjected to the azoxymethane and dextran sulphate-mediated colitis associated colon cancer induction protocol (109). Inhibition of IL-6 signaling by administration of a soluble gp130-Fc fusion protein (gp130 is the signal transducing subunit of the IL-6 receptor) into mice bearing established CAC tumors led to a reduction in tumor size, indicating inhibition of tumor growth (109) (110). Attenuation of IL-6 signaling during tumor induction resulted in a decrease in both tumor multiplicity and growth (109,111). In a recent report, Fenton and Birmingham demonstrated that adiponectin plays an important role in attenuating the IL-6 mediated proliferation of the murine colon cancer cell lines by reducing STAT phosphorylation (112). This result further strengthens the notion that reduced expression of adiponectin in the circulation of obese individuals may lead to a congenial environment for IL-6 stimulated cancer development.

4.3.4. Obesity, IL-6 and prostate cancer

Prostate cancer is the most frequently diagnosed cancer in men in Europe (113). More than 40 studies, including prospective and case–control studies, examining the association between obesity and risk of prostate cancer have provided conflicting results (114). However, a recent meta-analysis has suggested a weakly significant positive association with an estimated increase in prostate cancer risk (5% excess risk per 5 unit increment of BMI) (115). A recent prospective study on prostate cancer clearly shows that obese men are more likely to die from prostate cancer than men of normal weight, though no more likely to actually develop the disease (116). The association between waist circumference or waist/hip-ratio and risk of prostate cancer has been examined in only a very few studies with most studies reporting no significant associations (88,117). IL-6 is involved in regulation of immune reaction, cell growth and differentiation. IL-6 is expressed mainly by prostate stromal cells, although both stroma and epithelium express the IL-6 receptor. Levels of both IL-6 and its receptor increase during the process of carcinogenesis in prostate tissue. Activation of the JAK/STAT (Janus kinase/signal transducer and activator of transcription), MAPK and PI3K/AKT signaling pathways has been reported in various prostate cancer cell lines in response to IL-6 (118) (Figure 1). IL-6 promotes growth of most

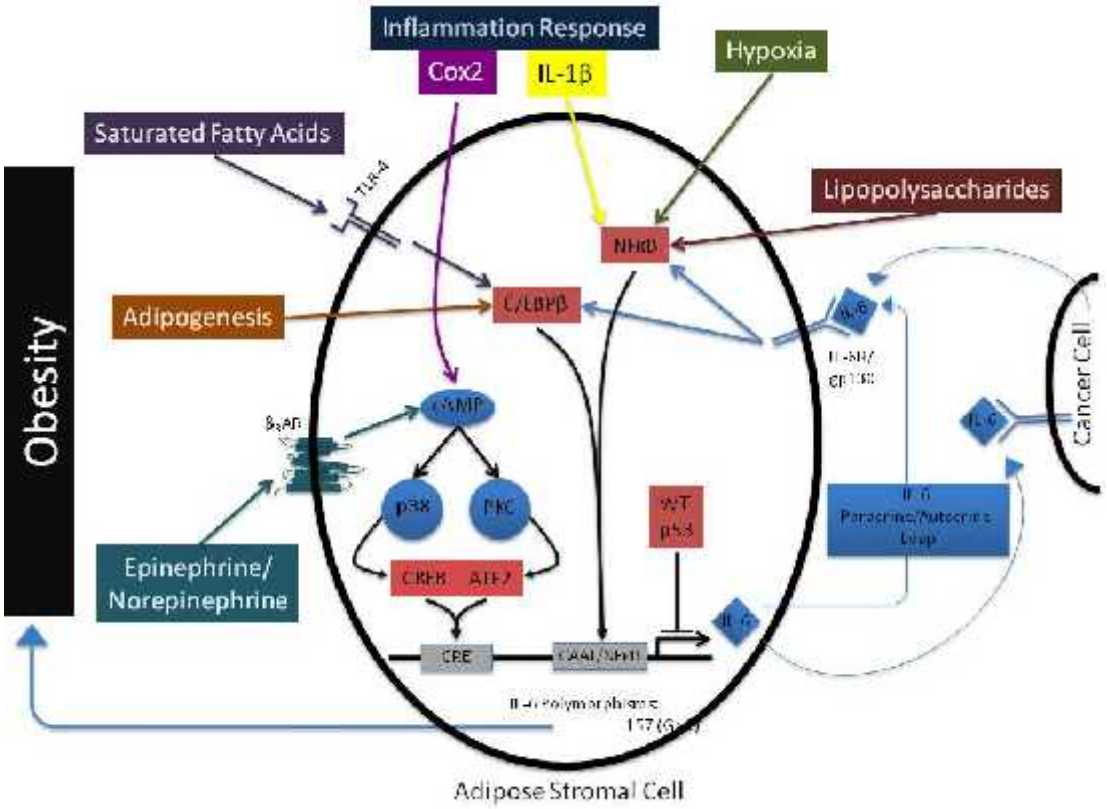

Figure 1. Obesity Induced Production of IL-6 in adipose tissue. Many pathways are activated in adipose stromal cells from various signals associated with obesity. These pathways in turn have been shown to activate IL-6 in adipose stromal cells. The main pathways that are activated due to obesity are NFkappaB and C/EBPbeta. IL-6 can then form a paracrine/autocrine loop with epithelial cells in tumor and other adipose stromal cells. This loop can increase the metastatic and proliferative effect of IL-6 on cancer. IL-6 polymorphisms may also contribute to this cycle, as certain polymorphisms have been associated with an increased risk of obesity.

prostate cancer cells, with the exception of the LNCaP cell line, in which IL-6 causes growth arrest and induces cell differentiation. However, a recent study showed that short term treatment of IL-6 inhibited LNCaP cell growth by a paracrine mechanism associated with neuroendocrine differentiation, whereas long-term IL-6 treatment promoted LNCaP cell growth by an autocrine mechanism accompanied by activation of AR signaling (119). The transition of IL-6 from a paracrine growth inhibitor to an autocrine growth stimulator, as well as its ability to activate AR in the absence of androgen, suggests a role for IL-6 during prostate cancer progression and possibly androgen-independent progression. IL-6 is also involved in regulation of VEGF expression as well as neuroendocrine differentiation in prostate tissue. Studies using an IL-6 antibody have reported induction of apoptosis, inhibition of tumour proliferation, and elimination of the progression to androgen-independent status in a prostate cancer xenograft model (120).

4.3.5. Obesity, IL-6 and esophageal cancer

Obesity is associated with a 3-fold increase in risk for adenocarcinoma of the esophagus (59,121). The link between obesity and risk of esophageal cancer has recently been confirmed by quantitative meta-analysis that included twelve case–control studies and two cohort studies (85). High BMI is associated with gastroesophageal reflux, and frequent reflux is very strongly associated with esophageal adenocarcinoma (122,123). Thus the increased occurrence in gastroesophageal reflux itself is considered to be a major risk factor for esophageal cancer. Elevated expression of IL-6 has also been detected in various epithelial tumors, including esophageal cancer (124,125,126). Recent study indicates that Regenerating gene 1 (Reg1) can stimulate IL-6 RNA and protein in esophageal cancer cells through mitogenic effects on gastric stem cells (127). Another study concludes that IL-6 -174 (G>C) gene polymorphism may confer high risk of predisposition to esophageal cancer its clinical characteristics (128).

4.3.6. Obesity, IL-6 and liver cancer

Primary liver cancer is one of the most common and deadly cancers worldwide. Incidence is increasing and hepatocellular carcinoma (HCC) has risen to become the fifth most common cancer and the third leading cause of cancer death (129,130). Obesity has been established as a significant risk factor for liver diseases. A large prospective

mortality study demonstrated that high BMI was significantly associated with higher rates of liver cancer-related death. Compared to patients with normal BMI, the relative risk of mortality from liver cancer was 1.68 times higher in women and 4.52 times higher in men with BMIN35 kg/m2 (4). Similarly, data obtained from the United Network of Organ Sharing (UNOS) database on all liver transplantation from 1991 to 2000 carried out in the United States showed that the overall incidence of HCC in patients undergoing liver transplantation was 3.4% with a slightly higher prevalence among obese patients at 4.0%. Moreover, in this study obesity was confirmed to be an independent risk factor for HCC in patients with alcoholic cirrhosis (odds ratio (OR), 3.2) and cryptogenic cirrhosis (OR, 11.1) (131). Obesity has definitively been established as a risk factor for the development of HCC. It is likely that this association represents the progression of underlying non alcohol fatty liver disease (NAFLD) to cirrhosis, but it remains unclear whether cirrhosis is a necessary prerequisite for the development of HCC (132). Animal models of NAFLD support the hypothesis that obesity-related metabolic abnormalities, rather than cirrhosis, initiate the hepatic neoplastic process during obesity (133).

Most HCC appears in cirrhotic livers after years of chronic liver inflammation caused by viral hepatitis and alcoholic and non-alcoholic steatohepatitis (129,134). Several cytokines (such as IL-6, IL-6 family cytokines, IL-22, etc) that activate STAT3 in hepatocytes have been shown to promote HCC growth *in vitro* and *in vivo* (135,136). Clinical studies reported that serum IL-6 concentrations were elevated in patients with chronic liver inflammation, including alcoholic hepatitis, viral hepatitis, and nonalcoholic steatohepatitis, and in patients with HCC (137). Notably, men are about three to five times more likely to develop HCC than women (138). A similar gender disparity was also seen in a murine model of HCC induced by diethylnitrosamine (DEN). It is believed that higher serum levels of IL-6 in male mice contributed to the higher susceptibility to DEN-induced liver cancer compared to female mice (136). A recent report from Park et. al. showed that obesity-promoted HCC development was dependent on enhanced production of the tumor promoting cytokines IL-6 and TNF, which cause hepatic inflammation and activation of the oncogenic transcription factor STAT3 (28). By using the DEN model they have emphatically shown that dietary or genetic obesity is a direct promoter of HCC development due to increased IL-6 production.

STAT3 is the major downstream signaling molecule of IL-6 (Figure 2), IL-22, and leptin in hepatocytes. Several lines of evidence suggest that STAT3 plays an important role in the development of liver cancer. First, constitutively activated STAT3 is detected in human hepatoma cells and human liver tumor tissues (139). In HCC tissues, strong STAT3 immunostaining was observed in the cytoplasm, and pY705STAT3 immunostaining was observed in the nucleus (139). In addition, blockage of STAT3 using chemical inhibitors or siRNA induced liver cancer cell apoptosis and cell cycle arrest *in vitro* and inhibited growth of transplanted liver cancer cells *in vivo* (139,140,141). Second, altered p-STAT3 expression was positively correlated with the histological grading and intra-tumor microvessel density in HCC (142). Third, deletion or methylation silencing of hepatic SOCS3, an inhibitor for STAT3, resulted in enhanced STAT3 activation in the liver and accelerated DEN-induced liver tumorigenesis (143,144), while overexpression of SOCS3 inhibited HCC cell growth (145). Finally, the conclusive evidence for an important role of STAT3 in liver cancer development is from the fact that conditional deletion of STAT3 in hepatocytes prevented DEN-induced liver cancer development in mice (146). Notably, recent studies suggest that STAT3 activation is also implicated in HCV- and obesity-mediated hepatocarcinogenesis (28,147). Another important line of evidence for the role of STAT3 in liver cancer development is that constitutively activated STAT3 is detected in cancer stem cells from HCC and likely contributes to liver cancer stem cell proliferation and survival (148). Collectively, activation of STAT3 plays an important role in liver tumorigenesis. Therefore, blockage of STAT3 may have a therapeutic potential in preventing and treating liver cancer.

5. REGULATION OF IL-6 EXPRESSION DURING INCREASING FAT MASS

IL-6 levels in the obese individuals can be enhanced several ways related to various pathways. Recently the toll-like receptor 4, which plays an important role in innate immunity through its ability to recognize bacterial lipopolysaccharides, has been postulated to play function in obesity-induced inflammatory response (149,150). It is also suggested that TLR-4 is majorly produced in the mature fat cells of adipose tissue, which in turn induces the production of inflammatory molecules, including IL-6, in the non-fat cells. Trayhurn and Wood (29) proposed a "hypoxia hypothesis", which suggests that hypoxia plays an important role in inflammatory response. The best evidence for this hypothesis is that adipose tissue is poorly oxygenated in obese individuals (151,152). Additionally, there is evidence that the adipose tissue from the ob/ob mouse is hypoxic in comparison to fat from obese mice, and that it induces production of adipokines including IL- 6 (151). Hypoxia may enhance the death of large fat cells leading to macrophages being drawn to the area increasing the inflammatory response. Another hypothesis is that as fat cells expand causing insufficient neovascularization to keep the cells from becoming hypoxic. This results in activation of a variety of responses including formation of inflammatory adipokines as well as activation of collagen synthesis and crosslinking enzymes like lysyl oxidase (153). This leads to "adipose fibrosis", a new hallmark in obesity. A likely scenario came up from our own study that indicates that changes in the matrix proteins due to the obese environment leads to a differential mechanical forces on the adipose stromal cells, which may trigger enhanced production of IL-6 in the obese tissue (unpublished data).

Almost every noxious stimulus induces IL-6 gene expression in many different cell types. The molecular dissection of the IL-6 promoter reveals it to be responsive to activation by all three signal transduction pathways: protein kinase C, cAMP/protein kinase A, and calcium ionophore. The multiple response elements MRE-1 and MRE-II in the IL-6 promoter represent overlapping DNA

targets for a variety of different activation pathways (154). Glucocorticoids and estrogens play important roles in modulating IL-6 transcription by engaging multiple transcription factors (155). Wild type p53 represses the IL-6 promoter, while tumor-derived mutations in p53 (Val-135 and Phe-132) up-regulated this promoter. The efficient induction of the IL-6 promoter depends upon the cooperative interactions of several transcription factors inducing C/EBP family members and NFkappaB (155). Mouse studies indicate that IKKbeta is up-regulated during obesity suggesting that NFkappaB is activated in this situation. C/EBPbeta plays a significant role in the adipocyte differentiation by determining the commitment stage of preadipocytes to become mature adipocytes (156). In a recent finding we have shown that while culturing in high density, a pre-requisite of adipogenesis, adipose stromal cells (ASC) can stimulate massive production of C/EBPbeta protein (157). Therefore, it can be predicted that as more and more cells are committed to adipogenesis in obese individuals, more C/EBPbeta is produced thereby stimulating IL-6 production in ASCs.

It is documented that the sympathetic nervous system is associated with IL-6 production. Epinepherine and norepinephrine regulate IL-6 release from adipocytes predominantly via activation of beta-adrenergic receptors (betaARs). Studies reveal that activation of $beta_3$ARs triggers protein kinase A (PKA), protein kinase C (PKC) and extracellular receptor kinase 1/2 (ERK1/2). In due course, PKA and PKC activate CREB protein, whereas, ERK1/2 stimulates p38 activation and phosphorylates ATF2. Activated CREB and ATF2 bind to the CRE sites of IL-6 promoters and stimulate transcription of IL-6 in a NFkappaB independent manner (Figure 1).

Polymorphisms of the *IL6* gene may significantly alter protein expression. The most common *IL6* SNPs are located at −174 (G>C, rs1800795), −572 (G>C, rs1800796), and −597 (G>A, rs1800797) base pairs from the transcription start site. The most studied and interesting polymorphism of *IL-6* gene is the *IL6*-174G/C mutation. The G allele of this SNP highly intensifies protein synthesis compared with the mutant C allele. The G allele is quite polymorphic among Caucasians, but almost monomorphic among Asians, Hispanics, and Africans (158). Although the *IL6*–174G/C polymorphism was identified long ago, the number of case–control studies on GC is relatively small. This polymorphism may not be useful in identifying associations with the development of disease in Asian populations because of a low frequency of the mutant C allele (<1%). Of note, the high-producing G allele of −174 was also associated with an elevated risk of Kaposi's sarcoma among HIV-infected patients (159), with poorer survival in patients with estrogen receptor–positive breast cancer (160) and increased neuroblastoma risk (161). The collected data allow us to suggest that the *IL6*–174G/C polymorphism is related to GC risk among Western populations because of increased cytokine production. De Michele *et al.* studied 124 node-positive breast cancer patients, and found -174G allele contributes to reduced survival of patients with node-positive breast cancer. This may be important in light of the fact that African-American and other non-Caucasian populations with high frequencies of this allele have poor breast cancer prognosis (162). The influence of the G allele on protein synthesis rate was not established to date, and the role of this SNP remains unclear. Further investigations are necessary to detect the impact of the *IL6*–572G/C polymorphism on cancer risk. A number of studies have found possible association between *IL-6*–174G/C gene polymorphisms and obesity, based on experimental evidence from mice knockouts of these genes, and suggested an influence on fat mass, fat metabolism, and body mass, and the development of obesity (163,164).

6. CANCER STEM CELL AND IL-6

Cancer development is a multistep process controlled by genetic perturbations such as activation of oncogenes or silencing of tumor suppressor genes; epigenetic events (DNA methylation) occurring within a cell; and environmental influences (inflammation). The cancer stem cell (CSC) theory implies that tumors are generated and maintained by a small population of cells with both self-renewal and differentiation properties that contribute to tumorigenesis and cancer cell heterogeneity. Similar to their normal counterparts, CSCs are regulated by intrinsic signals as well as extrinsic signals originating in the tumor microenvironment (165,166,167). Emerging evidence suggests that tumors and their microenvironment co-evolve during tumor progression (165). Bidirectional paracrine signals coordinately regulate tumorigenic cell populations including CSCs (83,168). Tumorigenic cells in turn produce factors that attract and regulate a diverse variety of cell types that constitute the tumor microenvironment (169,170). Inflammatory cytokines, such as IL-1, IL6 and IL-8 play important roles in mediating the interaction between CSCs and the microenvironment. In inflammatory cells, IL-6-mediated STAT3 signaling selectively induces a pro-carcinogenic, tumorigenic microenvironment (171). IL-6 has also been shown to be a direct regulator of breast CSC self-renewal by the IL-6/GP130 complex through the activation of STAT3 (83). STAT3 activation, in turn, leads to transcriptional activation of NFkappaB in inflammatory cells that secretes additional IL-6 and IL-8 acting on tumor cells. Thus, a positive feedback loop is generated between tumor cells and the surrounding cells in the microenvironment that further stimulates the cancer stem cell components accelerating metastasis and increasing therapeutic resistance. Max Wicha's group has demonstrated that bone marrow stem cells are recruited to sites of growing breast cancers by gradients of IL-6. Furthermore, IL-6 is a key component of a positive feedback loop involving these bone marrow mesenchymal stem cells and breast CSCs (169). Adipose-derived stem cells (ASCs) share similar properties with the mesenchymal stem cells and it has been documented that there is a constant renewal of the adipose-derived stem cells in obese individuals due to the constant death of mature adipocytes. It is also known that ASCs are rich source of IL-6, therefore, it can be assumed that during obesity ASCs may play an important role in interacting with and nurturing the CSCs by IL-6-mediated signaling. Blockade of these cytokine pathways reduced breast CSCs in preclinical models (172).

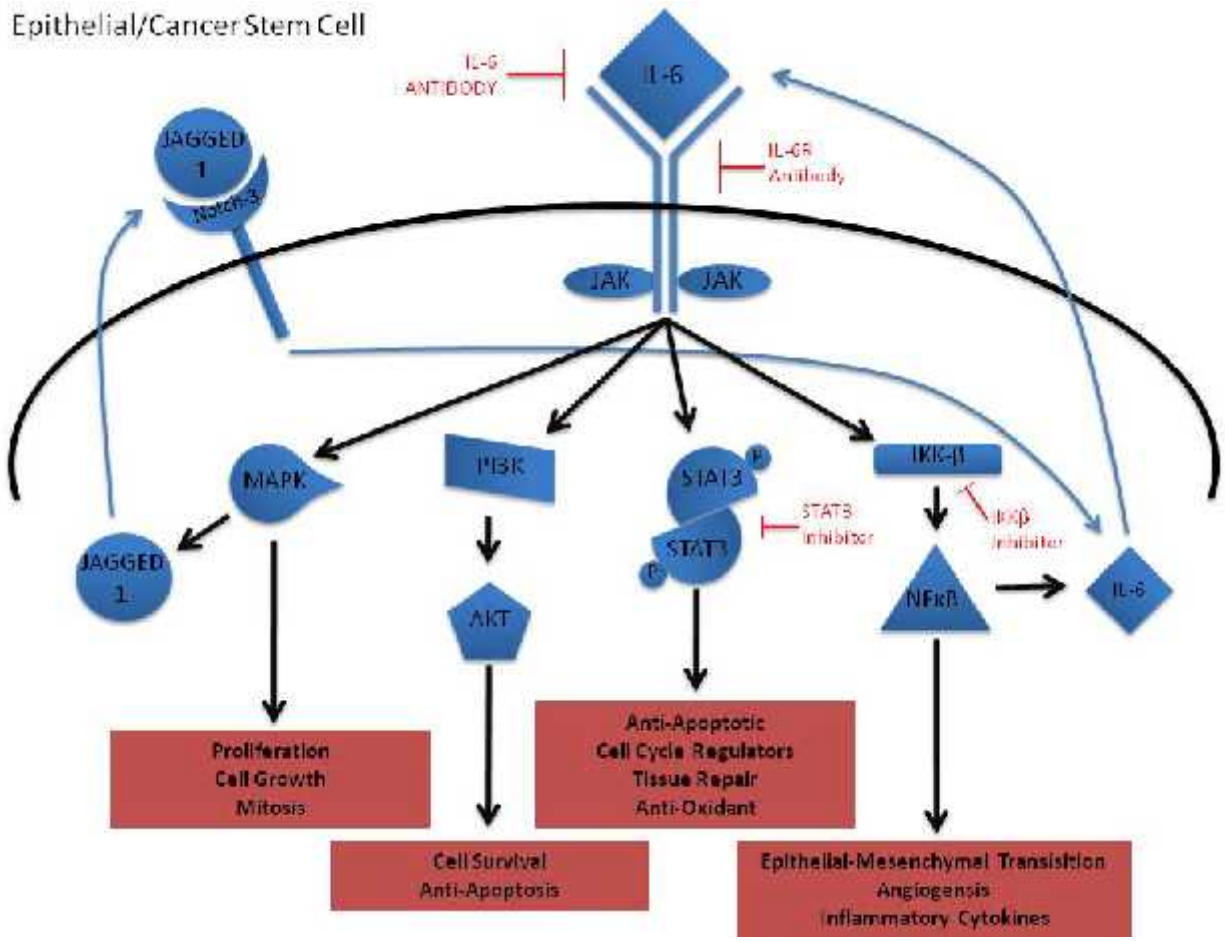

Figure 2. Activation of tumorigenic pathways by IL-6 in epithelial cancer cells. A number of kinases become activated by IL-6 and its receptor interaction. These pathways activate target genes that contribute to the proliferative and metastatic characteristics of cancer and cancer stem cells. IL-6 can also activate its own transcription through the NFkappaB pathway as well as the Notch/Jagged axis. This leads to an autocrine loop that may enhance the affect of IL-6 on cancer cells. There are a number of steps (marked in red), where IL-6 production can be modulated as a therapeutic intervention.

7. IL-6 TARGETED THERAPY TO CURB CANCER

Aberrantly hyperactivated IL-6-STAT3 signaling in cancer cells and the tumor microenvironment has been detected in a wide variety of human cancers and is considered to be an important factor for cancer initiation, development, and progression (173,174). The interplay of STAT3 in cancer cells and other cells around cancer cells likely plays an important role in modulating tumor growth via several steps. First, it is well known that IL-6/STAT3 signaling is crucial for tumor cell proliferation and survival via induction a variety of proto-oncogenes (109,175). In contrast to normal cells, in which STAT3 activation is rapid and transient, cancer cells routinely harbor persistently activated STAT3 proteins that promote a permanent alteration of some genes that control cellular processes. Constitutively activated STAT3 promotes tumorigenesis through the up-regulation of cell survival proteins (Bcl-xl and Bcl-2), cell cycle regulators (c-Myc and cyclin D) (174,176,177), anti-oxidant genes (Mn-SOD, ferritin, and catalse), and tissue repair genes (RegIIIβ, RegIIIγ, and Tff3) (176,178,179). IL-6 mediated activation of STAT pathway is governed by IL-6 receptor (IL-6R) and gp130.

Clinical trials using IL-6 blocking antibodies have been initiated for the treatment of multiple myeloma, and early results are encouraging (180). The humanized monoclonal antibody of IL-6R, Tocilizumab, has been approved by United States Food and Drug Administration (FDA) for the treatment of arthritis and has little toxicity (181). Recently it has been found to be effective as an antitumor agent against U87MG glioma cells. Tocilizumab exerts an inhibitory effect on the JAK/STAT pathway by preventing IL-6 from binding to its receptor, thereby inhibiting IL-6 signaling. Another anti-IL-6 drug being developed for the bone metastatic prostate and renal carcinomas and multiple myeloma is (Cetocor's) CNTO-328 (Siltuximab). The chimeric monoclonal antibody to IL-6 recently completed its clinical trials for prostate cancer, kidney cancer, and renal cell carcinoma with mixed results. Some preliminary results from the completed trials indicate minimal side effects with the inhibitor; however, there was

a general lack of correlation with IL-6 inhibition and reduction in tumor growth.

The use of antibodies for therapeutically inhibiting cytokines such as IL-6 may soon be replaced by utilizing small proteins, non-antibody based inhibitors called avimers. These small proteins are devoid of immunoglobulin domains and, therefore, are less immunoreactive. They have several advantages over conventional antibody therapy, in terms of high efficacy and potency, lower cost, and lower occurrences of side effects. Avida recently developed an avimer against IL-6 called C326 pr AMG-220. Although there is *in vitro*, *in vivo*, and preliminary clinical trials to suggest that specific anti-IL-6 therapies may improve cancer survival rates and reduce metastatic burden in some types of obesity-related cancers, additional studies and appropriate clinical trials are needed to be done fully ascertain the effectiveness of anti-IL-6 therapies in cancer patients. An alternate approach to diminish IL-6 production in adipose tissue related to obesity, and thereby reduce cancer risk, is to target the kinases that can regulate IL-6 production in adipose tissue.

8. PERSPECTIVE

IL-6 is an important cytokine engaged in various kinds of cellular function. Although we have discussed different derogatory roles of IL-6 in a range of cancers, its beneficial roles are often found in diverse physiological situations. Besides its pro-inflammatory properties, IL-6 also shows an anti-inflammatory activity, which reveals its beneficial role in various physiological conditions. For example, STAT3 exhibits tumor suppressor activity, particularly in brain malignancies (182). A targeted disruption of the IL-6 receptor complex gp130 resulted in hypoplastic ventricular myocardium, reduced numbers of pluripotent cells-mainly hematopoitic progenitors (183). This result shows that gp130 plays important roles in myocardial development and hematopoisis during embryogenesis. There are protective roles of IL-6 on a number of bacterial infections. In neonatal mouse models of Group B streptococcal disease IL-6 decreases TNF production, as well as the expression of TNF receptors in macrophages. Exogenous administration of IL-6 improved survival and complete inhibition of IL-6 resulted in a more rapid mortality.

With regards to the obesity related cancer and their intervention with the usage of inhibitors against IL-6 or its receptor, far more caution should be taken. Exercise is a critical activity to counter obesity and to restrict various obesity-related cancer risks. During exercise IL-6 is synthesized and released by skeletal muscle (184) and its plasma concentrations may be increased as much as 100-fold (185). It has been shown that IL-6 is rapidly released into the circulation following exercise. Therefore, it can be presumed that the abundant beneficial health effects of the exercise could be ultimately mediated by IL-6 and needs further elucidation.

In summary, IL-6 plays both "evil and good" roles in a tissue specific manner. IL-6 may play a derogatory role in the adipose tissue, but it has some beneficial role in the muscle tissue. Tocilizumab, a humanized anti IL-6-receptor monoclonal antibody, is a success story for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis, but has adverse effect on the anaphylactoid reaction and gastrointestinal hemorrhage (186). Therefore, to target IL-6 or its receptor with an antibody or blocking agent needs a careful look. A better comprehensive understanding of the regulation of the IL-6 production and activation of its downstream events in the various compartments of the adipose tissue is thoroughly necessary to separate its derogatory roles in obesity-induced cancer development. This will then allow us to generate a better and more specific therapeutic prevention to attenuate the IL-6-dependent risk in obesity-related cancer.

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Abbreviations: IL-6: Interleukin 6; IL-1b: Interleukin 1b; IL-8: Interleukin 8; TNFa: Tumor necrosis factor a; COX-2: Cyclooxygenase-2; TGFb: Tumor growth factor b; ASC: Adipose-derived stem/stromal cell; MSC: Mesenchymal stem cell; STAT: signal transducer activator of transcription; Akt: protein kinase B; BMI: body mass index; EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; ER: oestrogen receptor; ERK; extracellular signal-regulated kinase; HIF: hypoxia-induced factor; IGF: insulin-like growth factor; JAK: Janus kinase; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; NF-kappa B: nuclear factor kappa B; PI3K: phosphoinositide 3-kinase; PKA: VEGF: vascular endothelial growth factor.

Key Words: Obesity, Cancer, IL-6, Adipose Stromal Cells, Review

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