Diet-Induced Obesity, Inflammation, and Cancer

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ABSTRACT

Chronic inflammation plays critical roles in tumor initiation and progression. Inflammatory tumor microenvironment populating tumor cells, inflammatory cells, fibroblasts, and adipocytes and a web of signaling molecules are crucial in the promotion and progression of tumors. Numerous studies have identified transcription factors such as nuclear factor-kappa B, hypoxia-inducible factor-1α, and signal transducer and activator of transcription 3 as key modulators in driving inflammation to cancers. Inflammatory cells increase the levels of cytokines that activate these transcription factors to stimulate diverse protumorigenic processes. Additionally, these transcription factors induce production of chemokines that attract more inflammatory cells to maintain tumor-related inflammation. Although the mechanisms by which obesity enhances tumor growth and progression are not clearly defined, population-based studies show that obesity is associated with increased cancer risk. Obesity is associated with a state of chronic low-level inflammation due to the increase in adipocyte sizes as well as resident- and recruited-macrophage activities, which alter adipokine profiles. These alterations of adipokine profiles are responsible for paracrine and endocrine crosstalk with a variety of cell types, thus enhancing tumor growth and progression.

Key words: tumor metastasis, cytokines, chemokines, macrophages, angiogenesis

INTRODUCTION

Carcinogenesis is a long, multistep process which includes initiation, promotion, and progression; these processes are affected by genetic, epigenetic, and environmental factors. Over the past few decades, the proportion of people with excess body weight has been increasing in both developed and developing countries[1-3]. High levels of dietary fat intake induce obesity and insulin resistance in rodents and humans[4,5]. Epidemiological evidence indicates that overweight and obesity, classified by body mass index (BMI) greater than 25, are directly associated with cancer risk at several organs, including the breast (in postmenopausal women), esophagus, kidney, endometrium, and colon[1,6]. Fat cell number and size increase in the adipose depots and tumor tissues of obese animals. It may be that the crosstalk between adipocytes and other resident cells leads to alterations of intercellular and intracellular molecules which enhance tumor promotion and progression. The following is a brief review of potential molecular links between obesity, inflammation, and cancer. We subsequently discuss how our recent observation that a high fat diet (HFD) enhances solid tumor growth and metastasis of CT-26 colon cancer cells in BALB/c mice figure in these molecular mechanisms.

Ⅰ. *Inflammation and Cancer*

Inflammation is a complex set of interactions among cells, soluble factors, and extracellular matrix components that can take place in any tissue in reaction to diverse injuries. This process, by and large, leads to recovery from injury and to healing. However, if the resolution of inflammation is dysregulated, cellular responses change into patterns of chronic inflammation. Since the nineteenth century, it has been noted repeatedly that many cancers arise from sites of chronic infection, irritation, and inflammation[7], and chronic inflammatory diseases are strongly associated with increased cancer risk[8]. Additionally, the results of epidemiological studies and clinical trials indicate that the use of nonsteroidal anti-inflammatory drugs is associated with a reduced risk of certain cancers, including colorectal cancer[9]. Thus, it may be that chronic inflammation promotes cancer development and progression. The role of chronic inflammation in cancer initiation and promotion is not presented in detail here because of limited space and readers are referred to excellent reviews[10,11].

Ⅱ. *Roles of Macrophages in Tumor Promotion*

The chronic inflammatory microenvironment is predominated by macrophages[812]. Macrophages constitute a heterogeneous population, which can be divided into two main classes: M1 and M2 macrophages. M1 cells have

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important roles in inflammation and innate immunity, whereas M2 cells are associated with wound healing, angiogenesis, and immunosuppression[13]. Tumors are intricate bionetworks of multiple cell types and the full manifestation of the malignant potential of transformed epithelial cells requires interactions with the stroma. The stroma, which are composed of resident fibroblasts, adipocytes, infiltrated bone marrow-derived cells, and blood and lymph vessels, varies depending on the origin of the tumor. The presence of macrophages at the tumor site represents one of the hallmarks of cancer-associated inflammation[11, 14]. Tumor-associated macrophages (TAMs) resemble M2 cells and exhibit several pro-tumoral functions associated with increased angiogenesis, cancer cell invasion, and metastasis[15]. The crosstalk between cancer cells and TAMs, as well as other cell types in the tumor microenvironment, is a promising target for chemopreventive/therapeutic strategies[16].

Ⅲ. *Obesity and Inflammation*

Obesity is associated with a state of chronic low-level inflammation. A broad variety of inflammatory mediators and cytokines are overexpressed in adipose and other tissues in obese humans and mouse models of human obesity[17], and adipokines are key mediators linking adipose tissue, inflammation, and immune cells[18]. Cytokines/chemokines work in networks, and the combinational and additive actions of these molecules are crucial to inflammation. An essential feature of inflammation is the existence of immune cells such as macrophages, neutrophils and eosinophils in inflamed tissues. Infiltration of bone marrow-derived monocytes into obese adipose tissues in mice and humans has been previously described[19, 20].

Ⅳ. *Obesity and Cancer*

A significant correlation between cancer and adiposity suggests an important role of white adipose tissue in tumor growth and progression. Several mechanisms have been postulated to explain how obesity increases cancer risk. It is possible that adipose tissue may enhance tumor growth and progression via the alteration of adipokine secretion. For example, leptin may be a reasonable candidate to mediate the effects of obesity on carcinogenesis, as leptin levels are generally increased in obese humans and animals[21,22], and leptin has been shown to stimulate cellular proliferation in several tumor cell lines[23]. Insulin resistance is another candidate, because obesity is associated with a state of prolonged insulin resistance, which reduces the production of insulin-like growth factor binding protein (IGFBP)-1 and IGFBP-2. Increases in bioavailable IGF-I and prolonged hyperinsulinemia favor tumor development[24,25]. The high concentrations of circulating IGF-I and insulin activate Akt, which enhances cancer cell survival and proliferation in obese individuals[24]. However, obesity-associated insulin resistance can lead to decreased Akt activation[26]. mTOR activity may be elevated in obese tissues, and activation of mTOR and S6 kinase 1 reduces tyrosine phosphorylation and increases serine phosphorylation of insulin receptor substrate 1, thereby inhibiting Akt activation[26]. mTOR was identified as a critical regulator of normal and tumor cell growth[27]. A low-grade systemic inflammation state associated with obesity may be induced primarily as a result of increased adipocytes as well as fat resident- and recruited-macrophage activities. Peritumoral adipose tissue is involved in a variety of signaling mechanisms including secretion of extracellular matrix proteins and soluble factors from adipocytes and interaction with stromal and tumor cells[28]. Although it is likely that macrophage infiltration into adipose and tumor tissues contributes to the induction of inflammatory responses and enhancement of tumor growth and progression in obesity, the extent of the functional involvement of macrophages and adipocytes in these processes remains unclear.

Ⅴ. *Key Signaling Molecules: Cytokines/Chemokines and Transcription Factors Linking Obesity-Induced Inflammation to Cancer*

The promotion of inflammation appears to be an underlying mechanism by which obesity enhances cancer progression[24]. Proinflammatory cytokines [interleukin (IL)-4, IL-1β, and IL-6, tumor necrosis factor (TNF)], insulin, and IGF-1 activate several transcription factors such as NF-kappa B (NFκB), hypoxia-inducible factor (HIF)-1α, the activator protein-1 (AP-1), and signal transducer and activator of transcription (STAT)3[29-31]. NFκB is activated in obesity, and this transcription factor controls the expression of an array of anti-apoptotic proteins. Crosstalk exists between NFκB and other transcription factors such as STAT3, HIF-1α, AP-1, specificity protein, p53, peroxisome proliferator-activated receptor (PPAR)γ, β-catenin, androgen receptor, glucocorticoid receptor, and estrogen receptor[32]. In obesity, there is an unusual increase in c-Jun amino-terminal kinase (JNK) activity in liver and adipose tissues[33]. Hypoxic conditions exist[34] and HIF-Iα levels are markedly increased in the white adipose tissues of HFD-fed obese mice[35]. Hypoxia is a potential risk factor for chronic inflammation and metabolic syndrome. HIF-1α regulates the transcription of a broad variety of genes involved in cancer biology, including cell survival, glucose metabolism, angiogenesis, and metastasis[36]. Furthermore, it has been shown that, in obese mice, enhanced production of IL-6 and TNF leads to prolonged inflammation, which activates STAT3; STAT3, in turn, induces proliferation of aberrant liver cells and leads to hepatocarcinoma[37].

While some people appear to be genetically predisposed to staying lean no matter what or how much they eat, other people become obese. A frequently asked question is

"How much fat is dangerous for us"? We injected CT26 colon cancer cells into obesity-resistant syngeneic BALB/c mice, and observed prolonged consumption of an HFD-stimulated solid tumor growth with accompanying tumor angiogenesis and lung metastasis. Chronic consumption of an HFD led to an increase in the number of fat cells in tumor tissues and a minimal increase in epididymal fat pad mass without any discernible weight gain. Macrophage infiltration was increased in the tumor and adipose tissues of HFD-fed mice. HFD feeding increased tumor tissue levels of Ki67, cyclin A, cyclin D1, CDK2, Bcl-xL, and Bcl-2; reduced p53 levels and apoptotic cells; and increased the levels of CD31, vascular endothelial cell growth factor (VEGF), P-VEGF receptor-2, inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 as well as hemoglobin content. NFκB, STAT3, HIF-1α, and AP-1 were activated in the tumor tissues of mice fed on an HFD, as well as the activation of Akt, extracellular signal-regulated kinase-1/2, p38 mitogen-activated protein kinase, and JNK. HFD feeding increased the serum levels of EGF, insulin, IGF-I, interferon-γ, leptin, chemokine (C-C motif) ligand 5, monocyte chemoattractant protein–1, IL-1ra, and stromal cell-derived factor-1α. These results indicate that prolonged consumption of an HFD and/or even small increase in fat mass increases the secretion of growth factors and cytokines which activate a variety of transcription factors, thereby inducing the expression of many genes involved in the stimulation of inflammation, angiogenesis, and cell proliferation[38].

CONCLUSIONS

There is a well-established link between obesity and cancer. The classification of obesity for epidemiological purposes defines overweight as a BMI greater than 25 kg/m^2 and obesity as a BMI greater than 30 kg/m^2. However, we have recently determined that tumor growth and metastasis were stimulated in the presence of a small increase in fat mass in the tumor and adipose tissue of HFD-fed mice. These adipocytes induce macrophage infiltration and co-opt resident cells and extracellular matrix to increase the production of growth factors and proinflammatory and proangiogenic cytokines and chemokines which stimulates angiogenesis, cancer cell growth, and metastasis. In Figure 1, the mechanisms for the involvement of adipose tissues and inflammation in cancer development discussed in this review were summarized, although the story of their association has only begun to be unraveled. Tumor metastasis is responsible for most deaths of cancer patients, and can occur after a long period of tumor dormancy. As current medical therapies are not wholly effective in the treatment of metastatic cancer, it is important to find safe and effective lifestyle modifications--including dietary practices--to impede cancer development and metastasis. Evidence available to date indicates that avoiding a high-fat diet and body fat gain appears to be an important way to prevent cancer.

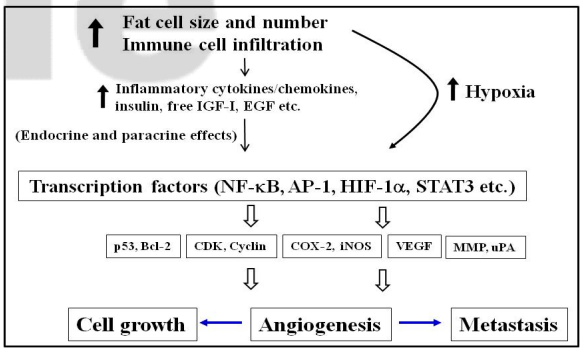

Figure 1. Summary of mechanisms underlying the enhancement of cancer development by an increase in adipocytes. Increased fat in tumor and adipose tissues recruit immune cells, and crosstalk between adipocytes, immune cells, cancer cells, and other resident cells increases local and circulating levels of growth factors and cytokines/chemokines. These growth factors, in turn, induce the activation of several transcription factors which subsequently stimulate the transcription of many genes involved in cell proliferation, metastasis, and angiogenesis. Additionally, hypoxia induced by increases in adipose mass performs an important role in the induction of chronic inflammation inherent to obesity, thereby enhancing tumor development and metastasis.

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