An Insight on Selective Signaling Pathways Linking Obesity and Cancer

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Date of
Submisssion: 22-03-2018
Acceptance: 06-05-2018

ABSTRACT

Obesity associated cancer is an important health issue. Major risk factors of obesity leading to cancer, through multiple signaling pathways, are insulin, insulin like growth factors, adipokines, and cytokines which are released from adipose tissue. The important signaling pathways are phosphoinositide 3-kinase (PI3K/Akt), mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 3 (STAT3). The PI3K/Akt and MAPK pathways have downstream effect on mammalian target of rapamycin (mTOR) leading to obesity associated cancer. Recent studies mostly focus on inhibition of mTOR for cancer therapy. It is essential to focus on PI3K/Akt, MAPK and STAT3 pathways which are under the impact of many cancer risk factors in obesity. Thus, signaling pathways may provide a novel approach for obesity associated cancer risk. In this review the signaling pathways linking obesity associated cancer are summarized.

INTRODUCTION

Obesity linked with adipose tissue inflammation is known to trigger associated metabolic disorders. It predisposes to several types of cancer.[1] Obesity is characterized by the accumulation of excess body fat and is considered to be a chronic low-grade disease by World Health Organization. It is classified based on the body mass index (BMI). Individuals having BMI in the range of 18.5–24.9 is considered as normal while overweight individuals have BMI in the range of 25–29.9. BMI >30 signifies obesity and can be further classified as Class I (BMI: 30–35), Class II (BMI:35–40) and Class III (BMI > 40)[2,3]

Obesity brings about abnormal metabolic changes that negatively impact human health leading to metabolic syndromes namely diabetes mellitus, cardiovascular diseases, and chronic kidney diseases among others.[4] Several studies have indicated that obesity is linked to many types of cancers (Figure 1). The most common cancers associated with obesity are breast cancer, colon cancer, endometrial cancer, esophageal adenocarcinoma, gall bladder, ovarian, liver and renal cancers.[5-8] The obesity-induced inflammation builds the fertile soil for the pathogenesis of the several disorders.[9] Therefore, understanding and resetting the immunological balance in obesity is a crucial approach for the management of obesity associated cancer.[10]

The inflammatory response triggered by obesity involves many components of the innate immune system and includes an increase in circulating inflammatory cytokines and acute phase proteins (e.g., C-reactive protein).[11] The nature of obesity-induced inflammation is unique compared with other inflammatory paradigms such as infections and autoimmune diseases.[12] Obesity produces a low-grade but chronic activation of the innate immune system involving recurrent episodes of nutrition-related immune response, which are also influenced by nutrient availability (fasting or high-fat meals).[13] Recent report in literature suggest that this fluctuation may be associated with the induction of tumors in later stages of obesity.[14]

Obesity-induced inflammation is mainly initiated and exacerbated in white adipose tissue (WAT).[15] Adipose tissue inflammation is further increased
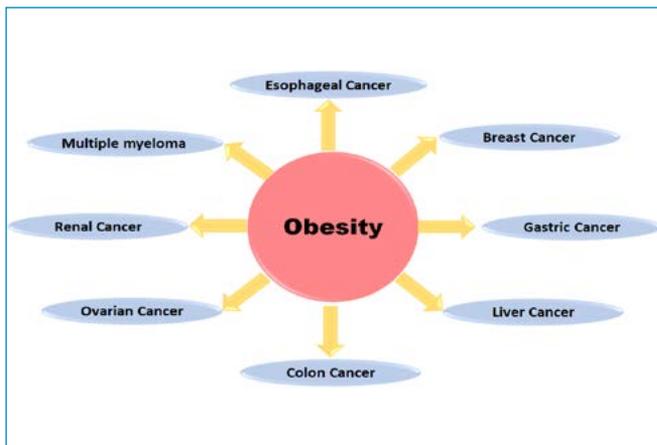
Figure 1 : Obesity and associated cancers

A MECHANISTIC ASPECT OF OBESITY-INDUCED TUMORIGENESIS

Insulin is the major regulator of metabolism and energy storage, secreted by pancreatic β cells in response to blood glucose level.[22,23] Glucose homeostasis and insulin induces fat regulation. In adipose tissue, insulin stimulates glucose uptake, however, suppresses the release of glucose from the liver which in turn stimulates the muscle to store excess glucose in the form of glycogen.[24] Adipose tissue dysfunction leads to hypertrophy and hyperplasia resulting in elevation of free fatty acids, leptin and reduction of adiponectin in circulation. An interplay among insulin, high circulating free fatty acids, adipose tissues and immune cells lead to development of insulin resistance (IR) and hyper-insulinemia associated with obesity. It provokes an inflammatory state in which low oxygen tension (Hypoxia) plays a vital role. As a result, the adipose tissue-derived inflammatory cytokines, angiogenic factor like extracellular matrix remodeling by adipocytes infiltration of macrophages leads to macrophage polarization that takes place with obesity-associated insulin resistance which stimulates microenvironment favorable for tumorigenesis. [25,26] (Figure 2)
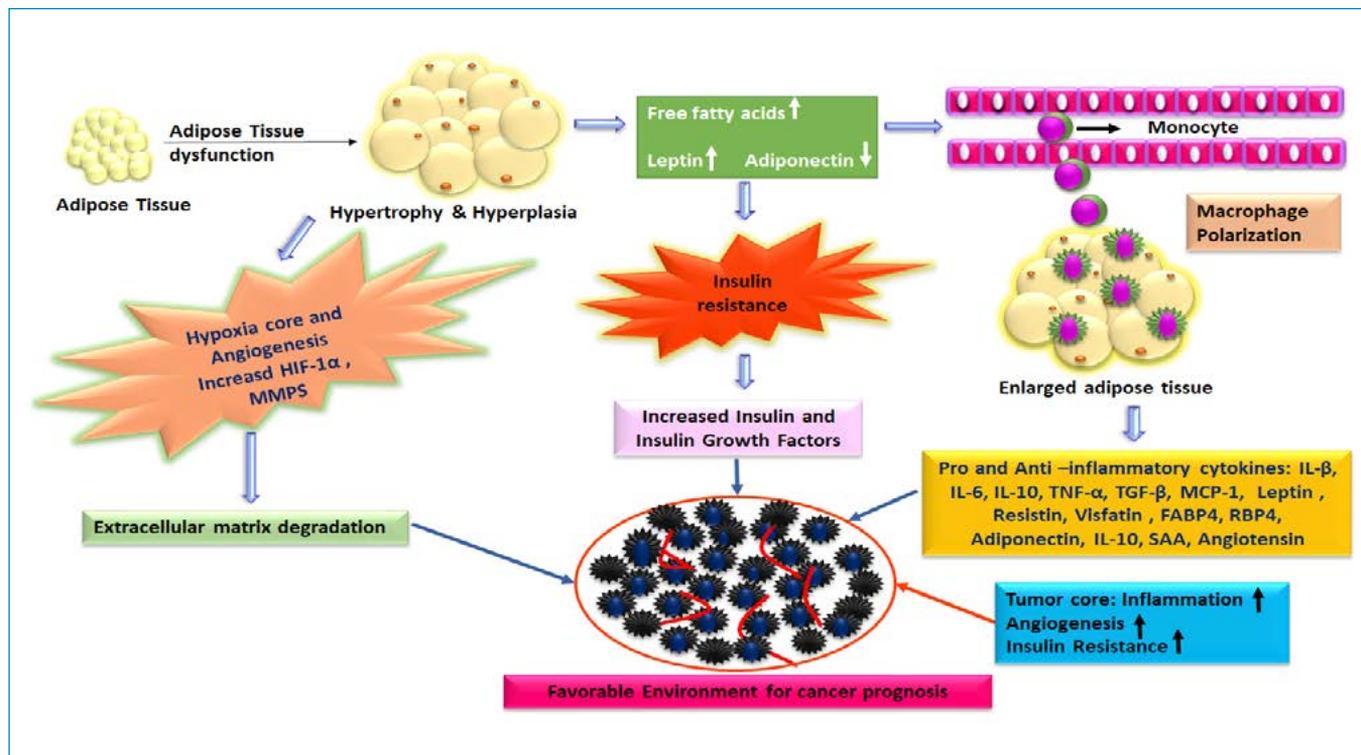
by the hypoxia in WAT (due to hypertrophy and hyperplasia of the adipocytes), endoplasmic reticulum stress and lipotoxicity triggered by inflammatory cytokines elevation during inflammation.[16-18] Obesity may lead to cancer development through dysfunctional adipose tissue and altered signaling pathways and possibly altered mRNA expression profile.[19-21]

Figure 2 : A mechanistic aspect of Obesity-induced tumorigenesis

HIF-1α, hypoxia-inducible factor-1α; IGF, insulin growth factor; IL-β, interleukin beta; IL-6, interleukin 6; IL-10, interleukin 10, TNF-α, Tumor necrosis factor –α; MCP-1, monocyte chemoattractant protein 1; MMP, matrix metalloproteinase; FABP4, fatty acid binding protein 4; RBP-4, Retinol-binding protein 4; TGF-β, transforming growth factor β; SAA, serum Amyloid A1.

ADIPOSE DERIVED FACTORS IMPACT ON TUMOR MICROENVIRONMENT

Obesity attributed cancer deaths are estimated to be 15-20%.[27] The pro-inflammatory cytokines released from inflamed adipocytes include tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein 1 (MCP-1), interleukins 1β and 6 (IL1β and IL-6) among others.[28-30] Activation of TNF-α in muscle primes to Jun N-terminal kinase 1 (JNK1) and mitogen-activated protein kinase 4 (MAPK4) pathway which in turn inhibits GLUT4 translocation and prompts serine phosphorylation of IRS.[31,32] TNF-α also inhibits expression and protein stability of peroxisome proliferator-activated receptor gamma (PPARγ) a nuclear hormone receptor. PPARγ gene expression regulates lipogenesis in adipocytes leads to the overproduction of FFAs.[33]

In adipose tissue, MCP-1 is overexpressed and serves as a chemoattractant for macrophages and immune cells, thereby exacerbating inflammation.[34] Adipose tissue from obese individuals consist of 50% of macrophages as compared to just 5-10% from the adipose tissue of lean subjects. Macrophages secrete TNF-α, which engages the (NF-kB and JNK-MAP4K4-AP1 pathways.[35]

Revealing the significance of TNF-α in adipose tissue biology, knockout of JNK1 in macrophages partly safeguards from high-fat diet-induced IR in mice. In human anti-inflammatory drugs like the salsalate, an NF-kB inhibitor, has shown some efficiency in improving IR in patients with obesity and type 2 diabetes mellitus.[36] Insulin resistance by cytokine-mediated inflammation paying to the tumor permissive microenvironment that facilitates tumorigenesis.[37]

ADIPOSE TISSUE HYPOXIA AND CANCER

Increased adipose mass and adipocyte size in obesity reduces oxygen availability in adipose tissue which causes hypoxic stress, with further reduced levels of insulin receptor and insulin receptor substrate 1 thereby disturbing their capability to sense insulin.[38] Hypoxia is found to affect the glucose transport machinery through decrease in AS160 (Akt substrate 160) phosphorylation and eventually lowered GLUT-4 expression.[39] Finally, reduced O_2 tension in adipocytes activates the O_2-sensitive transcription factor Hypoxia-Inducible Factor 1 alpha (HIF1-α), which is the master regulator of cellular response to hypoxia.[40] Existence of HIF-1 α in murine clonal adipocytes showed increased levels

Figure 3 : Signaling pathways in obesity-associated cancer
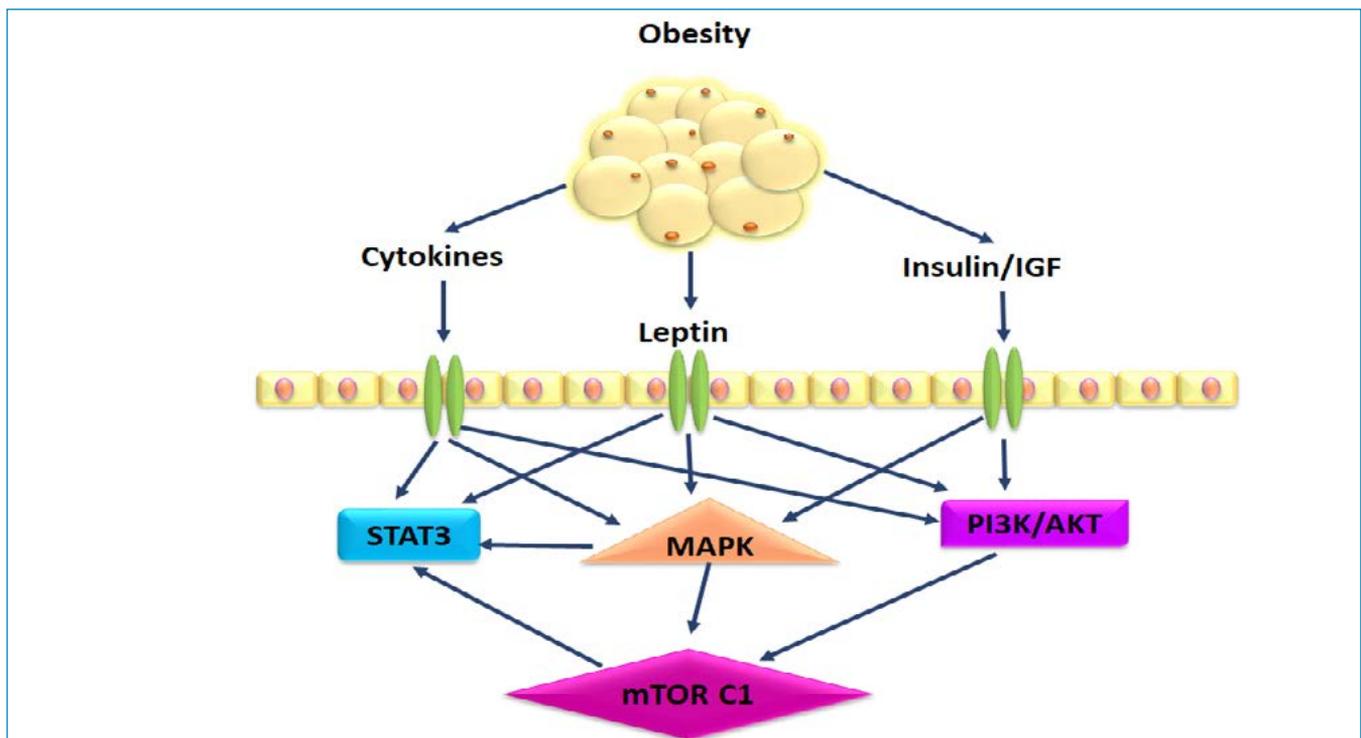
IGF, insulin-like growth factor; MAPK, mitogen-activated protein kinase; mTORC1, mammalian target of rapamycin complex 1; PI3K/Akt, phosphoinositide 3-kinase; STAT3, signal transducer and activator of transcription

of leptin and vascular endothelial growth factor in the cells under hypoxia.[41] Hypoxia increases the production of PAI-1 and thus inhibit the production of adiponectin in adipocytes of murine cells. HIF1- α is also found in human adipose tissue and reported to be increased in obesity. Interleukin 1(IL-1) up regulates HIF1- α protein by classically activated Nuclear factor - kappa B/Cyclooxygenase-2 (NF-kB/COX-2) inflammatory signaling pathway terminating the expression of the angiogenic factor VEGF needed for tumor growth, metastasis and increased vascularization.[42] HIF1- α is involved in the regulation of transcription of genes. It is involved in the mechanisms of carcinogenesis of factors includes angiogenesis, cell survival, invasion and metabolism of glucose.[43-45] To conclude, HIF1- α was linked with an increase incidence of metastases.

SIGNALING PATHWAYS IN OBESITY-ASSOCIATED CANCER

Various risk factors linking obesity and cancer are increased in obese cancer patients. It composed of insulin/IGF-1, cytokines, and leptin. The factors which are activated by signaling pathways like PI3K/Akt, MAPK, and STAT3 through their receptors. Both PI3K/Akt and MAPK activate mTOR. The activated mTOR can inhibit PI3K/Akt but activates STAT3. MAPK also triggers STAT3. (Figure 3)

PI3K/Akt, is an intracellular signaling pathway responsible for growth, proliferation, and metabolism of cells. It is one of the most significant pathways to study the pathophysiology of cells and downstream impact of obesity-associated cancer.[46] PI3K, a heterodimeric molecule consists of catalytic subunit which regulates the activation of PI3K/Akt pathway and responsible for carcinogenesis and metastasis of cancer. The PI3K/Akt, mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 3 (STAT3) have been verified to study the carcinogenic effects of human discretely in both cell cultures and animal models.[47] PI3K/AKT pathway activation promotes cell growth, proliferation and apoptosis which are decreased by tumor-inducing factors through various downstream targets.[48] In that one of the target is mammalian target of rapamycin complex 1 (mTORC1) which is associated with mTOR regulatory protein, mTOR-Raptor, some of the subunits of mammalian LST8/G –protein β –subunit-like mLST8/GbL- Deptor, mTORC1, and mTORC2 are different complexes of mTOR rapamycin-insensitive companion of mTOR – Rictor,

the stress-activated protein1- sin1 and GbL refers to mTORC1 complex.[49,50]

PI3K/Akt pathway shows elevated genomic stability, most potent factor for the gene mutation by the downstream effects of MAPK signaling pathway.[51] The extracellular signal-regulated kinase- ERK is activated by STAT3, through other kinases and mTOR transcriptional factors, lead to metastasis by cancer inducing factors.[52] STAT3 regulated genes promote vascular endothelial growth factors and other genes like Interleukin-17(IL-17), Interleukin-23(IL-23), B-cell lymphoma 2 (Bcl-2), B-cell lymphoma extra-large (Bcl-xL), cyclin D1 (CCND1) which support the invasion, angiogenesis, metastasis proliferation and survival.[53]

Several inhibitors like JSI-124, S31-201, S31-2001, STA-21, IS3295 decrease the activity of the PI3K/Akt and MAPK pathways to prevent carcinogenesis and metastasis by which STAT3 shows an elevated level of expression.[54] Cytokine IL-6 promote gene and protein stability in adipocytes and macrophages of adipose tissue which are known to promote cancer progression in circulation. IL-6 bind to the receptor IL-6R in the cell membrane which targets several signaling pathways of cancer.[55] STAT3 is widely studied pathway which plays a vital role in IL-6 mediated carcinogenesis. The effects of carcinogenesis can be reduced by knocking down IL-6 pathways. IL-6 is also activated by other signaling pathways inducing increased levels of carcinogenesis, thus leading the obesity-cancer association more complicated.[56,57] Hence, inhibiting these pathways may hold therapeutic potential in combating obesity associated carcinogenesis.

CONCLUSION

It is well established that adipose tissue inflammation is a key component in the development of obesity-induced insulin resistance and associated metabolic diseases. The accumulation of macrophages in adipose tissue is the initial event in obesity-induced inflammation. The later events leading to the complex interplay of immune cells, pro- inflammatory cytokines and hypoxia induced pathways creating a favorable milieu for tumorigenesis. Pathways involved in carcinogenesis like PI3K/Akt, MAPK, STAT3 and mTOR are also activated in obesity. Recent research has also shown that hypoxia, line in cancer, is an important driver of the signaling pathways induced in obesity as well. These findings strongly indicate the possibility of a link between chronic obesity and development of

tumors. Further research, especially in *in vivo* models is warranted to decipher the mechanisms linking obesity and associated carcinogenesis.

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Aspartate is a limiting metabolite for cancer cell proliferation under hypoxia in tumours

Researchers identify the amino acid aspartate as a metabolic limitation in certain cancers.

As oxygen is essential for many metabolic pathways, tumour hypoxia may impair cancer cell proliferation1,2,3,4. However, the limiting metabolites for proliferation under hypoxia and in tumours are unknown. Here, we assessed proliferation of a collection of cancer cells following inhibition of the mitochondrial electron transport chain (ETC), a major metabolic pathway requiring molecular oxygen5. Sensitivity to ETC inhibition varied across cell lines, and subsequent metabolomic analysis uncovered aspartate availability as a major determinant of sensitivity. Cell lines least sensitive to ETC inhibition maintain aspartate levels by importing it through an aspartate/glutamate transporter, SLC1A3. Genetic or pharmacologic modulation of SLC1A3 activity markedly altered cancer cell sensitivity to ETC inhibitors. Interestingly, aspartate levels also decrease under low oxygen, and increasing aspartate import by SLC1A3 provides a competitive advantage to cancer cells at low oxygen levels and in tumour xenografts. Finally, aspartate levels in primary human tumours negatively correlate with the expression of hypoxia markers, suggesting that tumour hypoxia is sufficient to inhibit ETC and, consequently, aspartate synthesis in vivo. Therefore, aspartate may be a limiting metabolite for tumour growth, and aspartate availability could be targeted for cancer therapy.

Source: Garcia-Bermudez J et al. Nature Cell Biology, 2018;