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Review

Signal Transducer and Activator of Transcription 3 in Obesity-induced Cancers

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ABSTRACT

According to accumulating epidemiological studies, obesity triggers various diseases, including cancer. Because cancer is a leading cause of death, revealing relationships between obesity and cancer is an urgent task. However, the exact mechanisms of cancer progression in an obese state are not fully understood. Signal transducer and activator of transcription 3 (STAT3) likely plays an important role in this mechanism. A variety of upstream molecules activate and regulate STAT3 and include obesity-related molecules, such as adipokines. STAT3 alters multiple cellular functions in cancer. In fact, STAT3 activation leads to inflammation, cell proliferation, invasion, stem cell-like properties, and drug resistance. STAT3 is increasingly reported to function as a bridge between obesity and cancer. Furthermore, recent studies indicate that STAT3 activation leads to obesity-related carcinogenesis.

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Key words : obesity, carcinogenesis, cancer stem cells, signal transduction, signal transducer and activator of transcription 3

INTRODUCTION

Both obesity and cancer are public health problems worldwide. In developed countries many people are obese and die of cancer. Obesity is a risk factor for lifestyle diseases, such as diabetes, hypertension, and dyslipidemia[1]. Moreover, epidemiological studies indicate that obesity is also a risk factor for many types of cancer and worsens the prognosis of patients who have cancer[2,3]. Obesity and cancer are considered to be causally related.

Although the direct mechanisms of this relationship are not fully understood, signaling pathways are important for the progression of obesity-induced cancer[4]. In signaling pathways, a key molecule is signal transducer and activator of transcription (STAT) 3, which regulates cancer progression[5-7]. Originally, STAT3 was identified as a downstream signaling molecule of interleukin 6 (IL-6) and Janus kinase (JAK)[8]. Activated via phosphorylation by JAK[9], STAT3 interacts with other proteins, is translocated to the nucleus, and regulates numerous genes. However, STAT3 is now known to be downstream of many signaling molecules, including cytokines and growth factors[7]. In this way, STAT3 signaling contributes to multiple biological functions, such as inflammation[10,11], cell proliferation[12], invasion[13,14], stemness[15,16], being an immune checkpoint[17,18], and resistance to anticancer drugs. In addition, STAT3 has widespread and profound effects on cellular function, especially in cancer. When diverse upstream molecules are activated, their effects converge and cause STAT3 to activate, resulting in carcinogenesis and cancer progression. To promote

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obesity-induced cancer is a newly revealed role of STAT3. A closer look at the function of STAT3 would lead us to better understand the process of carcinogenesis.

OBESITY AND CANCER

Obesity is a risk factor for several types of cancer, including those of the esophagus, gastric cardia, colon, rectum, liver, gall bladder, pancreas, breast, corpus uteri, ovary, kidney, meningioma, thyroid, and multiple myeloma[19]. Obesity increases the risks of cancers developing and of death from cancer[2]. The association between obesity and cancer has thereby been ensured.

However, mechanisms of this link are not fully understood, despite many questions having been addressed and several hypotheses having been made[4]. For example, chronic inflammation[20], insulin-like growth factor (IGF) 1[21,22], adipokines[23], hormones[24,25], microRNAs[26], and other growth factors[27] are believed to be the causes of obesity-induced cancers. Because the microenvironment of cancer growth is composed of a variety of stromal cells[28,29] and is influenced by many factors[20], a specific mechanism of carcinogenesis is difficult to identify. Any factors might interact with each other or work together to induce cancer. Among these factors, STAT3 has been found to play a central role in signal transduction[7].

STAT3 SIGNALING IN CANCER : RECENT FINDINGS

The STAT3 molecule is involved in multiple signaling pathways resulting in inflammation, cell proliferation, invasion, stemness, immune check points, and resistance to anticancer drugs. Known regulators of STAT3 activity in cancer cells include IL-6[8], G-protein-coupled receptors[30], Toll-like receptors[31], and microRNAs[32,33] (Fig. 1). Accumulating data suggest that STAT3 is oncogenic and is crucial for cancer progression. Several new upstream molecules and functions of STAT3, which suggest STAT3 signaling mediates carcinogenesis, have recently been reported and will be discussed below.

A newly reported upstream molecule of STAT3 is the melanoma differentiation-associated protein 9 (MDA-9), also known as syntenin (MDA-9/Syntenin)[34]. In many metastatic cancers, including melanoma, breast, gastric, and bladder cancers, MDA-9/Syntenin is expressed more strongly than in nonmetastatic cancers[35-37]. Therefore, MDA-9/Syntenin is believed to play a key role in cancer invasion and metastasis. Furthermore, MDA-9/Syntenin contributes to STAT3 activation, which is mediated by IGF binding protein 2 (IGFBP-2) secretion and IGF-1 receptor (IGF-1R) activation[8]. Therefore, STAT3 activation is essential for cancer invasion.

Another recently reported role of STAT3 is to contribute to antitumor immunity. Cancer and stromal cells, including antigen-presenting cells, effector T cells, regulatory T cells, and myeloid-derived suppressor cells (MDSCs), maintain an immunosuppressive state in the cancer microenvironment[38]. Among these cells, MDSCs are reportedly responsible for reducing the effect of immunotherapy against liver metastasis[39]. These cells secrete immunosuppressive cytokines in tumor microenvironments and inhibit the proliferation and activation of T cells and natural killer cells[38]. The activation of STAT3 in MDSCs helps cancer cells to evade T cell-induced apoptosis through transcriptional upregulation of MDSCs' immunosuppressive proteins, such as indoleamine 2,3-dioxygenase and programmed cell death (PD) ligand 1 (PD-L1)[40]. Such MDSCs are increased in number by obesity and contribute to cancer progression[41]. Moreover, MDSCs are obstacles for antitumor immunity and need to be eliminated to treat cancer.

Because MDSCs depend on STAT3 for survival, inhibitors of STAT3, such as Stattic and BBI608, induce Bax-dependent MDSC apoptosis[42]. The inhibition of STAT3 enhances the activity of chimeric antigen receptor T cells[42]. Moreover, STAT3 upregulates PD-L1 expression in mature T-cell lymphomas[43]. PD-L1 is a ligand of PD-1, and they compose the PD-L1-PD-1 pathway, an immune checkpoint. This pathway is a therapeutic target for treating cancer[44]. When PD-L1 is expressed on tumor cells and in the tumor microenvironment, T cells are inhibited[44]. These findings indicate that STAT3 promotes cancer cells to proliferate by regulating their transcription through signal transductions and by suppressing the anticancer immune system.

Another role of STAT3 is to regulate cancer stem cells (CSCs). These CSCs are regarded as a subset of cancer cells that are characterized by self-renewal, differentiation, and proliferation[45]. The CSC theory remains controversial, but because recent studies have demonstrated that CSCs exist in many cancer types, the theory is widely accepted[46,47]. The expression of CSC markers is upregulated by STAT3,

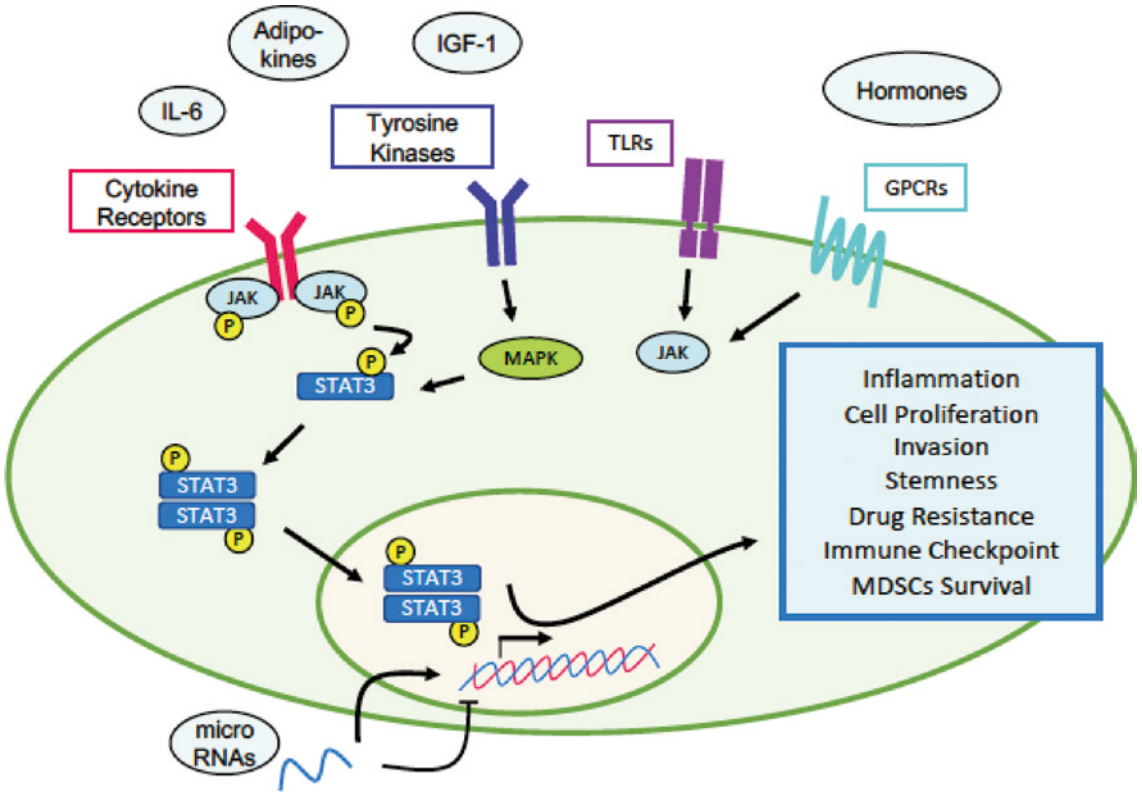

Fig. 1. Signal transducer and activator of transcription 3 (STAT3) is activated by various molecules and has multiple effects on cellular function.
Recent studies revealed the upstream molecules of STAT3. Basically, after ligands bind with their receptors, Janus kinase (JAK) phosphorylates and activates STAT3. The ligands include interleukin 6 (IL-6), adipokines, insulin-like growth factor (IGF) 1, and hormones. Cytokine receptors, tyrosine kinases, G-protein-coupled receptors (GPCRs), and Toll-like receptors (TLRs) are upstream receptors that transduce signals into the cells from the extracellular environment. STAT3 activation is regulated by interactions with other intracellular proteins, is translocated to the nucleus, and regulates various genes. Some microRNAs alter the gene regulation by STAT3. In cancer cells, STAT3 activation leads to inflammation, cell proliferation, invasion, stem cell-like properties, and drug resistance. On the other hand, in immune cells, STAT3 is essential for programmed death ligand 1 (PD-L1) expression and myeloid-derived suppressor cell (MDSC) survival.
Abbreviation : MAPK, mitogen-activated protein kinase

which is important for inducing stemness in cancer cells. Indeed, STAT3 is required for non-CSCs to convert into CSCs[48] and is activated in several types of cancers with stem-like characteristics[49-51]. For example, STAT3 increases CD133 expression by interacting with nuclear factor kappa B and regulating the transcription of hypoxia-inducible factor 1 alpha[52]. CD133 is a marker of CSCs in hepatocellular carcinoma (HCC), and increased CD133 expression is linked with tumorigenesis, shorter overall survival, and higher rates of proliferation and recurrence[53]. Downregulation of CD133 inhibits cell cycle progression and tumorigenicity. In this way, STAT3 is seen as an efficient therapeutic target for overcoming the stem-like characteristics of cancers.

Involvement of STAT3 in Obesity-induced Cancers

1. *Colorectal Cancer*

A role of STAT3 is to mediate obesity-induced colon carcinogenesis by the protein known as stimulated by retinoic acid 6 (STRA6). STRA6 is a transmembrane protein that functions as a vitamin A transporter and is activated by vitamin A-bound serum retinol binding protein 4 (RBP4)[54]. When STRA6 is activated, STAT3 is then activated and leads to carcinogenesis. Recently, STRA6 has been found to maintain colon CSCs. In addition, STRA6 upregulates CD44, a stem-cell marker, and regulates the capability for sphere formation. A high fat diet has been found to cause an STRA6-dependent increase of leucine-rich repeat-contain-

ing G-protein coupled receptor 5[55]. These findings indicate that the RBP4/STRA6/STAT3 axis might explain the start of obesity-induced colon cancer.

Another effect of obesity is to decrease adiponectin, an adipocyte-derived hormone[56] believed to dysregulate obesity. The adipokine IL-6 has recently been shown to induce colon cancer proliferation via STAT3 activation. Interestingly, this cancer progression is suppressed by adiponectin treatment[57]. Although IGF-1 also promotes colon cancer proliferation, adiponectin has no significant effect on this role of IGF-1[57], probably because insulin resistance is common in the obese state and because adiponectin does not suppress insulin-related cancers. With more research on the association between adiponectin and cancer, the biology of obesity-induced cancer might be better understood.

2. Breast Cancer

An adipokine that regulates obesity-induced breast cancer is leptin. This peptide hormone regulates energy balance and body weight control and plays significant roles in appetite regulation, bone formation, reproductive function, and angiogenesis[58-60]. Leptin is present at high levels in obese patients[61] and has recently be shown to be involved in obesity-induced cancers. A downstream signaling protein of leptin in breast cancer is STAT3 ; STAT3 interacts with histone methyltransferase G9a[62], which epigenetically upregulates leptin receptor (Ob-R) expression by silencing microRNA-200c[62]. The leptin/STAT3/G9a signaling pathway has been found to enhance CSC properties in breast cancer via Ob-R expression[62]. The CSCs in breast cancers are characterized by $CD24^{-}CD44^{+}$[63]. Interestingly, Ob-R expression is high in $CD24^{-}CD44^{+}$ cells[62]. In addition, leptin upregulates several CSC-related genes[62]. Because obesity is a lifestyle disease, mechanisms of carcinogenesis from obesity are expected to include an epigenetic alteration. How obesity initiates cancer might be explained by the leptin/STAT3/G9a/microRNA-200c axis.

The STAT3 signaling pathway in obesity-induced breast cancers might also be important for cancer development and progression. In a mouse model that expresses a dominant mutation of thyroid hormone receptor β, a high-fat diet induced obesity and elevated the serum leptin level[64]. Also caused by a high-fat diet is mammary gland hyperplasia[61]. However, when this mouse model was treated with a STAT3 inhibitor, mammary gland hyperplasia was suppressed[64]. Moreover, the STAT3 inhibitor upregulated E-cadherin expression so that epithelial-mesenchymal transition was suppressed[64]. In breast cancers, STAT3 activated by leptin is essential for proliferation and epithelial-mesenchymal transition and might be a therapeutic target.

For the association between obesity and breast cancer, another key to be demonstrated is adipocyte fatty acid binding protein (A-FABP). Fatty acid binding proteins (FABPs) are cytosolic proteins that regulate lipid transport and responses, and the FABP family consists of 9 members[65], including A-FABP in adipose tissue. These FABPs have been shown to differ in function. Recent studies suggest that serum A-FABP levels are elevated with obesity and that A-FABP levels are associated with the progression of breast and ovarian cancers[66,67]. A-FABP induces aldehyde dehydrogenase 1 activation, which enhances mammary tumor stemness, mediated by STAT3 signaling[68]. Furthermore, the development of obesity-induced breast cancer is suppressed if circulating levels of A-FABP are low, strongly suggesting that A-FABP is essential for the link between obesity and breast cancer[68]. In other words, obesity-induced breast cancer depends on STAT3 signaling.

3. HCC

Leptin has recently been found to link obesity and HCC. Because Ob-R is expressed at higher levels in tumorous liver tissue than in normal or peritumoral liver tissue, HCC is more sensitive to leptin signaling[69]. Leptin activates JAK/STAT3, extracellular signal-regulated kinase (ERK), and phosphatidylinositol 3-kinase (PI3K)/AKT[69]. With the PI3K/AKT-ERK kinase pathway, STAT3 contributes to invasion and proliferation of obesity-mediated HCC.

To promote obesity-induced HCC, both IL-6 and tumor necrosis factor are needed[70]. Both are involved in hepatitis and STAT3 activation. In mice fed a high-fat diet, levels of STAT3 and ERK activity and inflammation are increased via IL-6 and tumor necrosis factor signaling[70]. Taken together, these findings suggest that obesity gives rise to hepatitis and results in HCC.

Another molecule that mediates between obesity and HCC is T cell protein tyrosine phosphatase (TCPTP). As described above[70], HCC was once thought to develop after nonalcoholic steatohepatitis (NASH) leads to fibrosis. However, recent studies have shown that HCC can develop from nonalcoholic fatty liver disease alone. In hepatocytes,

TCPTP dephosphorylates STAT1 and STAT3[71,72]. In the obese state, TCPTP is oxidized and inactivated, resulting in STAT1 and STAT3 being activated[73]. If TCPTP is deleted, the same outcome occurs. Activation of STAT1 causes NASH and fibrosis, and activation of STAT3 causes HCC[73]. If TCPTP is deficient, the HCC that develops is highly proliferative[73]. When TCPTP is deleted, the expression of c-Myc and cyclin D1 is increased downstream of STAT3[73]. These findings show that STAT3 regulated by TCPTP is a significant factor for obesity-induced HCC.

Conclusion and Future Perspective

The molecule STAT3 plays a key role in multiple signaling pathways in several types of obesity-induced cancer, including colorectal cancer, breast cancer, and HCC (Fig. 2). Recent studies show that STAT3 leads to cell proliferation, stemness, and antitumor immunosuppression. These findings indicate that STAT3 has a carcinogenic function. Moreover, STAT3 has been found to contribute to HCC carcinogenesis independent of NASH, an inflammatory state of which carcinogenesis had traditionally been considered a consequence. However, this finding suggests that cancers might develop independently of chronic inflammation owing to STAT3 activation. Thus, STAT3 is a crucial signaling molecule for carcinogenesis in an obese state.

The activation of STAT3 is regulated by many molecules, such as IL-6, IGF-1, leptin, A-FABP, and TCPTP. Thus, obesity-induced cancers should result from the dysfunction of multiple signaling pathways. On the other hand, STAT3 might be an attractive therapeutic target which is involved in a wide range of causes of obesity-induced cancer. Unfortunately, a selective inhibitor of STAT3 is not yet clinically available because present inhibitors poorly penetrate cell walls, lack binding specificity for STAT3, and rapidly degrade[74]. A new selective inhibitor of STAT3 has not yet been developed. In addition, investigating which signaling pathway is most responsible for obesity-induced can-

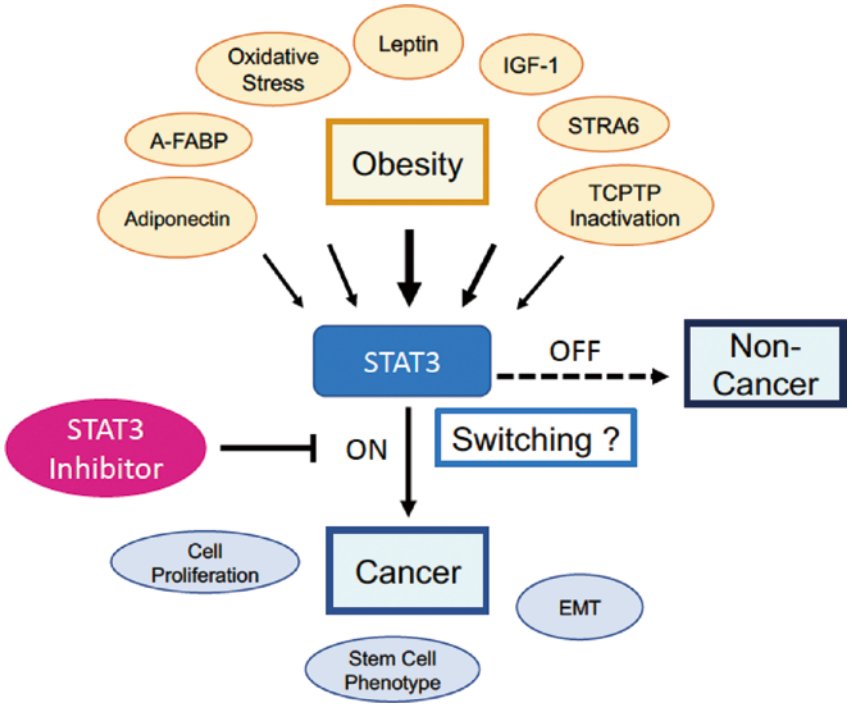

Fig. 2. Signal transducer and activator of transcription 3 (STAT3) contributes to the progression of obesity-induced cancers. Molecules related to obesity, namely stimulated by retinoic acid 6 (STRA6), adiponectin, leptin, adipocyte fatty acid binding protein (A-FABP), and T cell protein tyrosine phosphatase (TCPTP), regulate STAT3 activity. The STAT3 activation leads to cell proliferation, stem cell phenotype, and epithelial-mesenchymal transition and results in cancer progression. Consequently, STAT3 can be assumed to be a bridge between obesity and cancer. Furthermore, because cancers do not develop in all obese people, switching molecules might alter cellular properties from noncancer to cancer. STAT3 might be a switching molecule, and further exploration of switching molecules might lead us to a greater understanding of carcinogenesis. Abbreviations : STRA6, stimulated by retinoic acid 6 ; EMT, epithelial-mesenchymal transition ; IGF-1, insulin-like growth factor 1.

cers would be a key to understanding the mechanisms of cancer development related to obesity.

Although obesity-related factors, such as adipokines, including leptin, IL-6 and IGF-1, and A-FABP, and adipose cells, are always present, cancer does not always develop. A switching molecule or other mechanism might change cellular properties and functions from benign to malignant. To understand the mechanisms of obesity-induced carcinogenesis, crucial signaling pathways should be continuously searched for.

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