REVIEW ARTICLE

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The Role of Adiponectin in Breast Cancer: The mechanism and action

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ABSTRACT

Adiponectin is one of the most important members of adipokine family which is widely synthesized and secreted by adipose tissue. The action of adiponectin is via binding to main receptors. It has several actions including regulation of glucose level, lipid homeo¬stasis and reproductive system. Adiponectin can also influence vascular endothelium via preventing the migration of monocytes. The role of adiponectin has been detected in progression of certain cancers associated with obesity. Obesity is a risk factor for breast cancer and develops the progression of breast cancer, since adipocytokines are produced exclusively by adipose tissue and may influence the association between obesity and breast cancer risk. Therefore, it seems that obesity can play important role in the pathogenesis of breast cancer. The mechanism of adiponectin action in breast cancer is currently unknown. It seems that adiponectin motivates the sensitivity of peripheral tissue to insulin. Insulin can motivate the proliferation of breast cancer cells via signaling through insulin and insulin –like growth factor (IGF-1) receptors. Also insulin may upregulate a potent angiogenic agent including vascular endothelial growth factor (VEGF) expression that is secreted by breast cancer cells.

Keywords: Adiponectin, breast cancer, mechanism, action

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Introduction

Adiponectin as a 244 amino acid protein[1] is one of the most important members of adipokine family[2] which is widely synthesized and secreted by adipose tissue[3-8]. Adiponectin mRNA expression occurs exclusively in adipose tissue[9], although adiponectin may be expressed in limited quantities by bone, mammary glands, salivary glands and cardiac tissue[1]. The adiponectin gene is found on 3q27 in adipose tissue[1, 10] and composed of three exones and two introns[1]. It acts as GBP2 (gelatin-binding protein)[3] and be a relatively abundant plasma protein with approximately 30 kDa[11, 12]. Adiponctin, before secretion is synthesized as single subunit and then due to post-translational modifications 13 forms trimers, hexamers, and multimers[3]. The monomeric form is present exclusively in adipocyte, whereas it exists in circulatating as a disulfide-linked oligomer composed of trimers, hexamers and a high molecular mass multimers[1]. Single monomer form composed of four structurally distinct domains including amino terminal sequence, a variable region, a collagen-like domain and an amino terminal globular domain[1]. Moreover, it has five different configurations including[3] globular adiponectin, full-length adiponectin and low, median and high weight adiponectin (HMW) and various biological effects[3]. Also there is a similarity between adiponectin and globular fragments with complement C1q protein and TNF-α[1]. The action of adiponectin is via binding to main receptors, adiponectin receptor 1 and 2 (AdipoR1 and AdipoR2) placed on chromosomes 1p36.13-q41 and 12p13.3, respectively[3]. The property of these receptors is integral membrane proteins with seven transmembrane domains[3], but differ from G-protein coupled receptors structurally and functionally[2]. The property of these receptors is integral membrane proteins with seven transmembrane domains[3]. Also these receptors have 67% identity in their protein sequence and related structurally. The propensity of adiponectin receptors for binding to adiponectin isoforms as well as tissue propagation of these receptors are diverse[2]. AdiponectinR1 and R2 are abundantly expressed in skeletal muscle and liver, respectively. Although expression of these biomarkers is seen in almost every tissue, such as pancreatic β-cells[3]. Also there are adiponectin receptors in many cancer cell lines and human tumors such as breast, colorectal, gastric, endometrial, prostate and hepatocellular carcinoma cancer[14].

Adiponectin and disease

The role of adiponectin has been identified as an anti-inflammatory adipokine[14]. It decreases proinflammatory cytokines tumor necrosis factor a, and interleukin 6 secretion[14]. Adiponectin has various roles including regulation of glucose level, lipids homeo¬stasis and reproductive system[2]. Adiponectin can also influence vascular endothelium via preventing the migration of monocytes[14]. Also it acts as a potent inhibitor for angiogenesis in vivo[14] and via activation of caspases influences endothelial cells. The role of adiponectin in the regulation of body fat accumulation, adipose tissue development, energy metabolism and control of food intake has been documented[15-17]. Also the concentration of adiponectin is decreased in obese people[11]. The level of plasma adiponectin is inversely related to body fat, especially the amount of visceral fat[14]. Moreover, decreasing adiponectin level indicates obesity and diabetes[2]. Also decreasing of adiponectin level is associated with several type of cancer like breast cancer, colorectal, prostate, and digestive system[2]. Studies about the role of adiponectin in cancer are contradictory. For example increased level of adiponectin may cause poor survival in hepatocellular carcinoma (HCC) patients[18], whereas high level of adiponectin is associated with decreased risk of

breast cancer[19].

Adiponectin and carcinogenesis mechanisms

Evidence showed that adiponectin has anti-neoplastic effect[3] or anti inflammatory effect[13]through two mechanisms. First, adiponectin via enhancing receptor-mediated signaling ways influences tumor cells. Secondary, adiponectin via regulating inflammatory responses, influences cancer angiogenesis and regulates insulin sensitivity at the target tissue[3]. The signaling pathways which is related to adiponectin to prevent tumorigenesis include multiple intracellular signaling pathways, 5' AMP activated protein kinase (AMPK), phosphatidylinositol 3-kinase (PI3K)/v-Akt murine thymoma viral oncogene homolog (Akt), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 3 (STAT 3), c-Jun NH2-terminal kinase (JNK), nuclear factor-κB (NFκB) and the sphingolipid metabolic pathway[3], but it is noteworthy that most of the effects of adiponectin on cancer cell line is mediated via AMPK and the anti-neoplastic effect of adiponectin is associated with decreased cellular growth and mutagenesis, enhanced cell Cycle arrest and apoptosis[3](**Figure 1**).

Carcinogenesis mechanisms independent of AMPK linking to adiponectin

Superoxide production (ROS) can be inhibited by adiponectin via inhibition of cellular NADPH ox-

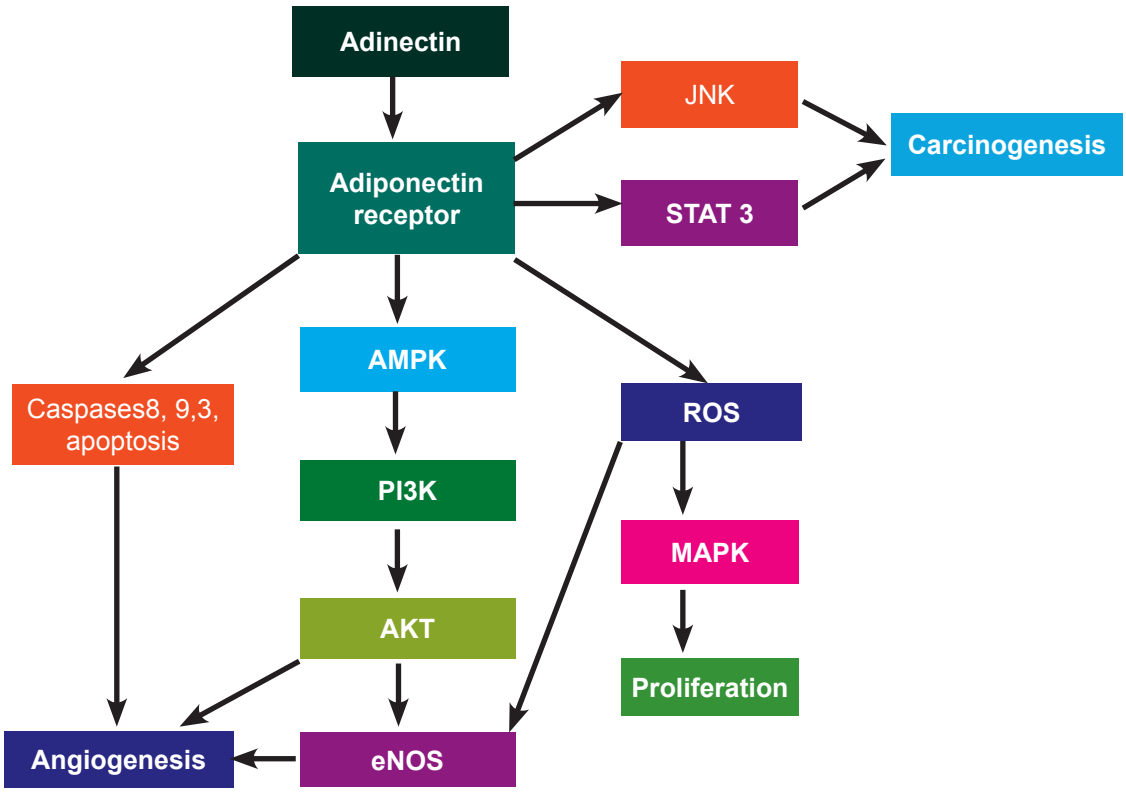

Figure1: Multiple potential signaling pathways for adiponectin[20].

idase activity. Reduced ROS via improvement of the suppression of eNOS activity by ROS may be related with increased NO production. Also reduced cell proliferation via blocking oxLDL induced mitogen-activated protein kinase pathway (MAPK) activation via blocking oxLDL(**Figure 2**)[20]. Also, recent studies showed that adiponectin through the classical adiponectin receptors can motivate ceramidase activity independently of AMPK, contributing amount prosurvival sphingosin 1 phosphatase(S1P). Elevated S1P causes enhanced cell survival and higher local pro-angiogenicactiity seen in mammary tumor mouse models[3].

The enzymes downstream of AMPK contain mammalian homologue of target of rapamycin (mTOR) fatty acid synthase (FAS). AMPK also inhibit FAS (a key lipogenic enzyme), which has been associated with colon, breast, prostate and ovarian cancer. Also AMPK acts via phosphorylating actinates TSC2, a tumor suppressor that negatively regulates protein synthesis by inhibiting mTOR,[20]. **Figure 2** shows this mechanism.

(The regulation of TSC2 and mTOR by AMPK might have special implications because the PI3K-Akt signalling pathway is constitutively active in many cancers)[20].

Adiponectin and carcinogenesis mechanisms

The role of adiponectin has been detected in progression of certain cancers associated with obesity[14], because it is a link between obesity[21,22] and cancer[18]. Obesity is a risk factor for breast cancer[23] and develops the progression of breast cancer, since adipocytokines which are produced exclusively by adipose tissue, may influence the association between obesity and breast cancer risk[1]. On the other hand, obesity may influence breast cancer due to the fact that adipose tissue secretes several factors such as adiponectin[24], therefore, obesity and estrogens can play important role in the pathogenesis of breast cancer[1]. The mechanism of adiponectin action in breast cancer is currently unknown. It seems that adiponectin motivates the sensitivity of peripheral tissue to in-

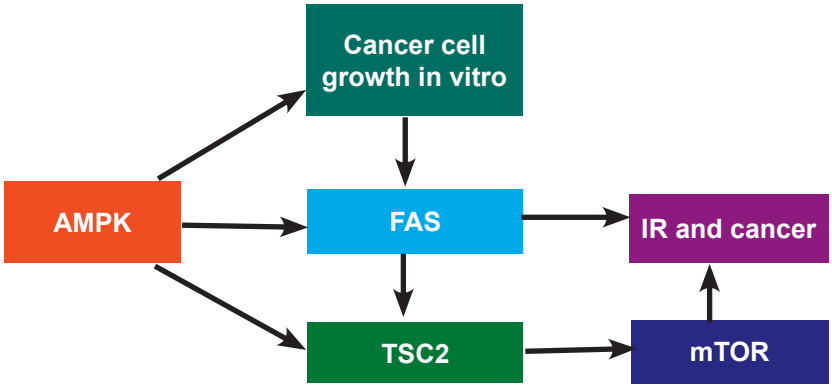

Figure 2: Possible molecular mechanisms of regulation of tumor cell growth by AMPK[20]

sulin. Decreased level of adiponectin is associated with increased level of insulin caused insulin resistance[1]. Insulin can motivate the proliferation of breast cancer cells via signaling through insulin and insulin –like growth factor (IGF-1) receptors[1]. Also insulin may upregulate vascular endothelial growth factor (VEGF) expression. It acts as a potent angiogenic agent that is secreted by breast cancer cells[1]. Moreover, crosstalk between adiponectin/ AdipoR1 and IGF-IR in breast cancer has been detected[25]. Adiponectin acts via increasing of IGF-IR-β subunit tyrosine phosphorylation and the downstreaming of MAPK activation in granulosa cells. Also low concentration of adiponectin is associated with increased IGF-IR phosphorylation in ERα-positive breast cancer cells, concomitantly with ligand-independent activation of ERα[25]. Also, since there is inverse relation between adiponectin and estrogen, it seems that adiponectin may affect breast cancer risk via altering circulating estrogen levels[1]. Moreover, there is inverse relation between circulating adiponectin levels and risk of breast cancer, independent of age, menopause and hormone receptor status and lymph nodes metastases[20]. Additionally, some studies showed that arising of breast tumors in women with low-serum adiponectin levels may be due to more aggressive phenotype (large size of tumor and high histological grade)[20].

Gulcelik MA et al. in 2012 reported that both breast and colon cancer have low level of serum adiponectin[1]. Sonmez B et al. in 2011 showed that there is inverse relation between serum adiponectin levels and tumor tissue adiponectin levels. Kang JH et al in 2007 reported that there is association between low serum adiponectin levels and increased breast cancer risk in Korean women[1]. Karaduman M et al. in 2007 reported that high tissue adiponectin level has been detected in breast cancer patients and be as an increased risk for breast cancer [1]. Mantzoros C et al 2004 showed that significant association between adiponectin and breast cancer has been seen in premenopausal women[1]. Ahmad et al, in 2015 reported that elevated serum adiponectin caused decreased risk of breast cancer[19]. Protective role of adiponectin is explained through an intricate mechanism of masking mitogenic growth factors in breast carcinogenesis[19].

Conclusion

Obesity is a risk factor for breast cancer and develops its progression. Obesity may influence breast cancer due to the fact that adipose tissue secretes several factors such as adiponectin. Therefore, it seems that obesity can play important role in the pathogenesis of breast cancer.

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