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Molecular Pathways: Adiponectin and Leptin Signaling in Cancer

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Abstract

The increasing percentage of obese individuals in the population and its independent association of increased risk for the development of cancer have heightened the necessity to understand the molecular mechanisms that underlie this connection. The deregulation of adipokines in the setting of obesity and their impact on cancer progression and metastasis is one such area of research. Adipokines are bioactive proteins that mediate metabolism, inflammation, angiogenesis, and proliferation. Altered levels of adipokines or their cognate receptors in cancers can ultimately lead to an imbalance in downstream molecular pathways. Discovery of adipokine receptors in various cancers has highlighted the potential for novel therapeutic targets. Leptin and adiponectin represent two adipokines that elicit generally opposing molecular effects. Epidemiological studies have highlighted associations between increased serum leptin levels and increased tumor growth, while adiponectin exhibits an inverse correlation with cancer development. This review addresses the current level of understanding of molecular pathways activated by adiponectin and leptin to identify areas of intervention and facilitate advancement in the field.

Background

A strong correlation between obesity and cancer, coupled with the rising obesity epidemic, has led to a prediction of an increase in forthcoming new cancer cases. Obesity commonly leads to deregulation of adipokines, bioactive proteins primarily secreted from adipocytes, which elicit their biological effects upon binding to cognate receptors. The primary role of adipokines is to help maintain metabolic homeostasis, yet expanded roles for adipokines have demonstrated their ability to modulate inflammation, angiogenesis, proliferation and apoptosis. With these processes in mind, a role for adipokines in cancer progression and metastasis has become apparent. The majority of cancer related studies have focused *in vitro* on the ability of adipokines to affect the typical hallmarks of cancer including proliferation, evasion of apoptosis, tumor cell migration and invasion, angiogenesis and vascular stimulation, and evasion of immune detection. More pertinent are preclinical studies that have validated the impact of adipokines on cancer progression *in vivo*, yet the signaling mechanisms through which these adipokines are mediating oncogenic phenotypes still require further elucidation. This review will address the molecular pathways of two prominent adipokines, leptin and adiponectin, and the potential to develop novel cancer therapeutics.

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Disclosure of Potential Conflicts of Interest

The author: Michael Nathan VanSaun has disclosed no potential conflicts of interest.

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Adipokines: Leptin and Adiponectin

Leptin is a 16kD bioactive protein encoded by the Ob gene, secreted from adipocytes as well as other tissues, which acts as a regulator of energy to control satiety through stimulation in the central nervous system as well as to modulate glucose and insulin homeostasis through activation in peripheral tissues [1]. Leptin typically circulates in the blood at a concentration of 5–10ng/mL in healthy patients, yet its level increases in obese and diabetic patients upwards of 50ng/mL [2]. Leptin stimulates a specific set of receptors from the extended class I cytokine-receptor family, comprising six isoforms that dimerize with each other, but lack intrinsic kinase activity [3]. Leptin receptor isoforms vary with respect to tissue and cell type as well as with respect to ligand stimulation. Auto-regulation of receptor levels as well as ligand-dependent activity may additionally lead to leptin resistance [4, 5].

Adiponectin is part of the complement 1q family of proteins that is primarily secreted by adipocytes as a monomeric protein, which can further oligomerize to form low molecular weight, high molecular weight and multimeric complexes [6]. Additionally, adiponectin can be cleaved by leukocyte elastase to generate a globular oligomeric complex [7]. Adiponectin is generally maintained between 7–15ug/mL in the plasma of healthy humans and exhibits a negative correlation with body mass index as well as percent body fat [8, 9]. Adiponectin activates two main seven transmembrane receptors, adiponectin receptor 1 (adipoR1) and adiponectin receptor 2 (adipoR2) [10]. AdipoR1 has a greater affinity for globular adiponectin while adipoR2 binds full length and multimeric adiponectin more avidly [10]. Stimulation of either receptor leads to regulation of metabolic effects through the activation and phosphorylation of AMPK, ACC as well as p38 MAPK [10]. Knockout of each receptor resulted in an opposition of effects on locomotor activity and metabolism where adipoR1 was shown be associated with increased adiposity and decreased glucose tolerance while adipoR2 is resistant to diet induced obesity [11, 12].

Antagonistic Signaling Between Leptin and Adiponectin

Leptin and adiponectin generally affect cellular behavior in an opposing manner. Highlights of these studies suggest that adiponectin administration in vivo has been shown to decrease growth and proliferation, increase apoptosis, decrease invasion, and decrease vessel density in murine cancer models [13–17]. Leptin has been shown to increase proliferation, migration and invasion of cancer cells [18–25] as well as contribute to release of VEGF[26]. The ratio of leptin to adiponectin was recently described to be a potential key for outcome when assessing plasma levels [27]. An important aspect of this consideration is that adiponectin can antagonize the actions of leptin. The molecular mechanisms through which adiponectin and leptin affect cancer cell behavior still require further elucidation. Figure 1 illustrates the dynamic signaling pathways for leptin and adiponectin, which we have combined to ascertain common mediators as potential key components for therapeutic intervention.

Leptin binding to all four forms of the short leptin receptor (Ob-Ra, Ob-Rc, Ob-Rd and Ob-Rf), elicits activation of Janus Kinase (JAK)2 and subsequent phosphorylation of insulin receptor substrates (IRS), initiating activation of the PI3-K/Akt pathway [3]. The long form of the receptor (Ob-Rb) contains an intracellular carboxy terminal extension that provides an additional three tyrosine residues (Tyr985, Tyr1077, and Tyr1138), necessary to confer binding and activation of signal transducer and activator of transcription (STAT)3 and STAT5 [3, 28, 29]. Additionally, a secreted isoform lacking the intracellular signaling domains (Ob-Re) [30], functions to sequester and block leptin induced STAT3 activation [31].

Leptin dependent activation of JAK2 additionally confers phosphorylation of both Tyr985 and Tyr1138 as well as activation of IRS1/2. Phosphorylation of Tyr985 is essential for phosphorylation of Tyr1138 which promotes Src mediated activation of STAT3 [28].

Additionally, phosphorylation of Tyr985 promotes recruitment of SHP2, a protein phosphatase, and SOCS3, an inhibitor of STAT3 [32]. Leptin mediated SHP2 binding leads to activation of ERK[33, 34] as well as attenuation of p62Dok[35], a RasGTPase, leading to activation of Ras and subsequent proliferation. SOCS3 and PPARgamma are upregulated via activation of STAT5 at Tyr1077 subsequent to leptin stimulation [32]. Leptin mediated upregulation of SOCS3 is thought to be involved during chronic leptin stimulation, which then acts as a negative regulator to directly bind and block Ob-Rb signaling and well as JAK2 activity [36, 37]. Additionally, adiponectin can increase PTP1B, protein tyrosine phosphatase 1B, which then dephosphorylates STAT3 as well as JAK2, further antagonizing leptin signaling [38].

Adiponectin binding can occur through either receptor 1 (AdipoR1) or receptor 2 (AdipoR2), which homodimerize or heterodimerize [6]. While gAdN preferentially binds to adipoR1, HMW adiponectin preferentially stimulates adipoR2 [10]. Knockout studies suggest that adipoR1 is necessary for AMPK activity while adipoR2 is necessary for PPARalpha activity, yet both receptors have been shown to be able to increase phosphorylation of AMPK [11, 12]. APPL1, a pleckstrin homology adaptor protein, binds to the intracellular portion of the adiponectin receptors and participates in AMPK activation leading to GLUT4 membrane translocation, p38 MAPK activation and phosphorylation of acetyl-CoA carboxylase, ACC [39]. AMPK activation inhibits the mTOR complex via Raptor in the mTorc1 complex as well as activating TSC2, an inhibitor of mTOR [40]. Phosphorylation of AMPK further activates TP53[41] and pro-apoptotic pathways as well as the activation of PP2A, protein phosphatase 2A, which can negatively regulate Akt in response to adiponectin stimulation[42] and therefore antagonize leptin induced Akt. Adiponectin stimulation of APPL1 alternately activates Akt to enhance mTOR in the absence of PTEN[43], phosphatase and tensin homolog deleted on chromosome ten, which normally inhibits PI3K activation of Akt. Therefore, crosstalk between leptin and adiponectin as well as the activation of multiple pathways keep proliferative signaling in balance.

Leptin and Leptin Receptors in Cancer

Tumor associated leptin receptor levels are thought to contribute to tumor growth and progression. Increased detection of ObR in ovarian cancers was correlated with decreased survival [44]. Leptin receptor expression is enhanced in 83% of human breast cancers, and 34% of patients with high leptin receptor level and high ligand level had detectable distant metastases [45]. In the murine MMTV-TGF-alpha model, deficiency in the long form of the leptin receptor (Db/Db) resulted in failure of mammary tumor formation [46]. Knockdown of the ObR through siRNA in MCF-7 breast cancer cells resulted in suppression of tumor volume in a mouse xenograft model [47]. Knockdown of the long form of the leptin receptor can abolish integrin dependent migration of chondrosarcoma cells through involvement of IRS-1/PI3K-dependent activation of Akt [48]. In addition, pancreatic tumors grown in leptin receptor mutant mice (Lep^{DB}) had larger tumors and more metastases when compared to wildtype mice [49]. Additionally, mutational status may affect receptor function. Three single nucleotide polymorphisms in the leptin receptor gene (K109R, K656N, and Q223R) showed an association with increased basal-like breast cancer risk [50]. These results suggest that tumor leptin receptor levels directly influence growth and progression.

Circulating levels of leptin have been investigated to determine the correlation with cancer and progressive disease. Elevated leptin levels in cancer patients compared to normal or preoperative levels have been reported in hepatocellular carcinoma and prostate cancer, while levels are relatively equivocal in breast cancer patients [51–55]. Yet, in pancreatic cancer and colon cancer patients, leptin levels were generally found to be decreased [56–59]. Complications such as pancreatic dysfunction, advanced progression of disease, weight loss and/or cachexia might be underlying factors for decreased leptin levels. Leptin produced by

adjacent adipose might provide a local increased level of stimulation to tumors [60–62], suggesting the presence of tumor associated adipose represents an important microenvironmental influence. Although normally secreted from adipose, self-sufficiency for leptin has recently been shown to be secreted from glioblastoma and breast cancer cells [63, 64]. Further, intra-tumoral mRNA leptin levels in patients with high leptin receptor levels correlated with decreased relapse-free survival [55].

Adiponectin and Adiponectin Receptors in Cancer

Epidemiologic studies show low levels of adiponectin have an inverse association with risk for the development of multiple cancers as well as advanced progression of disease [65]. Two adiponectin single nucleotide polymorphisms have been shown to increase prostate, colon and breast cancer risk [66–68]. Adiponectin deficiency through the use of knockout mice has shown accelerated hepatic tumor formation [69] and increased colon polyp formation [70], yet it delayed tumor growth in a mammary MMTV-PyV-mT model due to decreased vascularization and increased apoptosis in early stages of disease [71, 72]. Tumor promoting effects are likely secondary to initiation, but no clear studies have implicated adiponectin as an initiator of cancer development.

The adiponectin receptors have been detected in gastric, colon, prostate, breast, pancreatic and many other cancers [16, 56, 73–75]. Adiponectin receptors detection in gastric cancers was associated with longer overall survival [76]. Two single nucleotide polymorphisms of adiponectin receptor 1 associate with prostate cancer risk and one with breast cancer risk [67, 68]. Six genetic associations in the adipoR1 and adipoR2 genes have been detected in diabetic patients [77]. Deletion of the adipoR1, but not adipoR2, resulted in a promotion of epithelial cell proliferation and increased number of aberrant crypt foci in a murine model [70]. Future studies addressing the functional role of each adiponectin receptor in cancer initiation and progression will add a substantial contribution to our understanding and the importance of adiponectin signaling in these diseases.

Clinical-Translational Advances

Preclinical Advances

Currently, preclinical advances modulating adipokines have been limited for cancer therapeutics. Recombinant leptin treatment increased MDA-MB-231 breast tumor xenograft growth[22] as well as melanoma [78]. In an animal study, female mice in the MMTV-TGF-alpha breast cancer model fail to develop tumors when crossed with leptin deficient mice [46]. Conversely; leptin antagonist treatment was shown to decrease the growth of triple negative breast tumors in mice[79] as well as decrease 4T1 mouse mammary tumor growth *in vivo* through reduced VEGF, pSTAT3 and Cyclin D1 [80]. Recent evidence suggests that C reactive protein as well as soluble leptin receptor can act to bind circulating leptin and attenuate its activity [81, 82]. This provides insight into novel mediators of leptin action that may mediate its activity in cancer patients. Anti-leptin therapy could potentially be used to decrease circulating levels of leptin or to alter the adiponectin:leptin ratio in cancer patients, although additional preclinical studies will be needed to test the impact of altered leptin and adiponectin signaling *in vivo*.

Adiponectin treatment decreases the number of polyps especially those larger in size, in the ApcMin intestinal tumor model [83]. Adiponectin treatment induced apoptosis of gastric cancer cells *in vitro* while *in vivo* its infusion into mice led to decreased metastasis [16]. Additionally, liver tumor growth and lung metastases were lowered by adiponectin overexpression [14]. Interestingly, rosiglitazone treatment increased adiponectin serum concentrations[84] as well as adiponectin receptor expression [85]. Additionally, hypocaloric

diet and exercise led to an altered oligomeric distribution of adiponectin as well as it increased adipoR1 and adipoR2 expression [86].

Clinical Advances

The administration of leptin, adiponectin, or direct antagonists of either of these adipokines has not been reported in the literature for the treatment of human cancers. Leptin therapy was shown ineffective for patients with Type II diabetes, yet it did improve insulin sensitivity in leptin deficient patients [87]. Currently, clinical applications of adiponectin and leptin therapeutics are more likely to address metabolic disorders, obesity, and diabetes than cancer therapeutics. Yet, the application of anti-leptin therapy or administration of adiponectin could both provide straightforward treatment options in cancer therapeutics through direct interactions in cancer cells or indirectly by reducing obesity and metabolic disorders which have been associated with increased risk for cancer.

Alternately, targeting downstream adipokine signaling mediators are likely to be an advantageous choice. Downstream targeting of the adiponectin with Metformin can lead to activation of AMPK. Metformin is gaining wide attention for its role as an anti-diabetic as well as its anti-tumor effects for breast, prostate, lung, colon, ovarian cancers [88]. Metformin therapy preceding cancer diagnosis was associated with better survival in diabetic as well as non-diabetics [89]. Use of metformin and thiazolidinediones among a defined patient population of diabetics with either stage 2 to advanced HER2+ breast cancer or those with prostate cancer associated with decreased mortality [90, 91]. Thiazolidinediones, which are PPAR gamma agonists and include pioglitazone and rosiglitazone, increase the secretion of HMW adiponectin from adipocytes [92]. Recent data from randomized controlled trials indicated that thiazolidinedione use provides a modest decrease in the risk for lung, colorectal and breast cancers [93]. Additionally, administration of a cholesterol reducing drug, fenofibrate, increased plasma adiponectin concentration [94]. Mechanisms to target the leptin pathway include the use of common pathway inhibitors such as STAT3 inhibitors[95], Akt inhibitors [96], and RAF inhibitors [97]. Novel mechanisms of adipokine modulation through PTP1B and PP2A may additionally be used to inhibit the leptin receptor. Dual targeted therapies directed toward decreasing response from leptin stimulation and increasing the response from adiponectin pathways have the potential for more efficacious cancer therapy.

Conclusions

Obesity is a growing clinical problem and is independently associated with multiple cancers [98]. This review illustrates that adipokines contribute to multiple aspects of cancer progression and elicit a broad range of effects in normal as well as transformed cells. Adipokine stimulation appears not to follow a straightforward direct pathway, but instead contributes to a highly integrated cellular response. Determining circulating levels of adipokines as well as their receptors is equally important in determining which pathways are active and dominant. Additionally, cancers acquire genetic mutations and epigenetic modifications that can result in activation of oncogenes such as Ras, RAF, ERK and Akt or that can result in inactivation of tumor suppressors such as p53 and PTEN. In the future, we will likely have to consider individualized mutational status for cancer as well as in cancer cell lines in order to understand the impact these alterations have on adipokine signaling pathways. Integration of these aspects will then allow for targeted therapeutics and manipulation of adipokine pathways in cancer.

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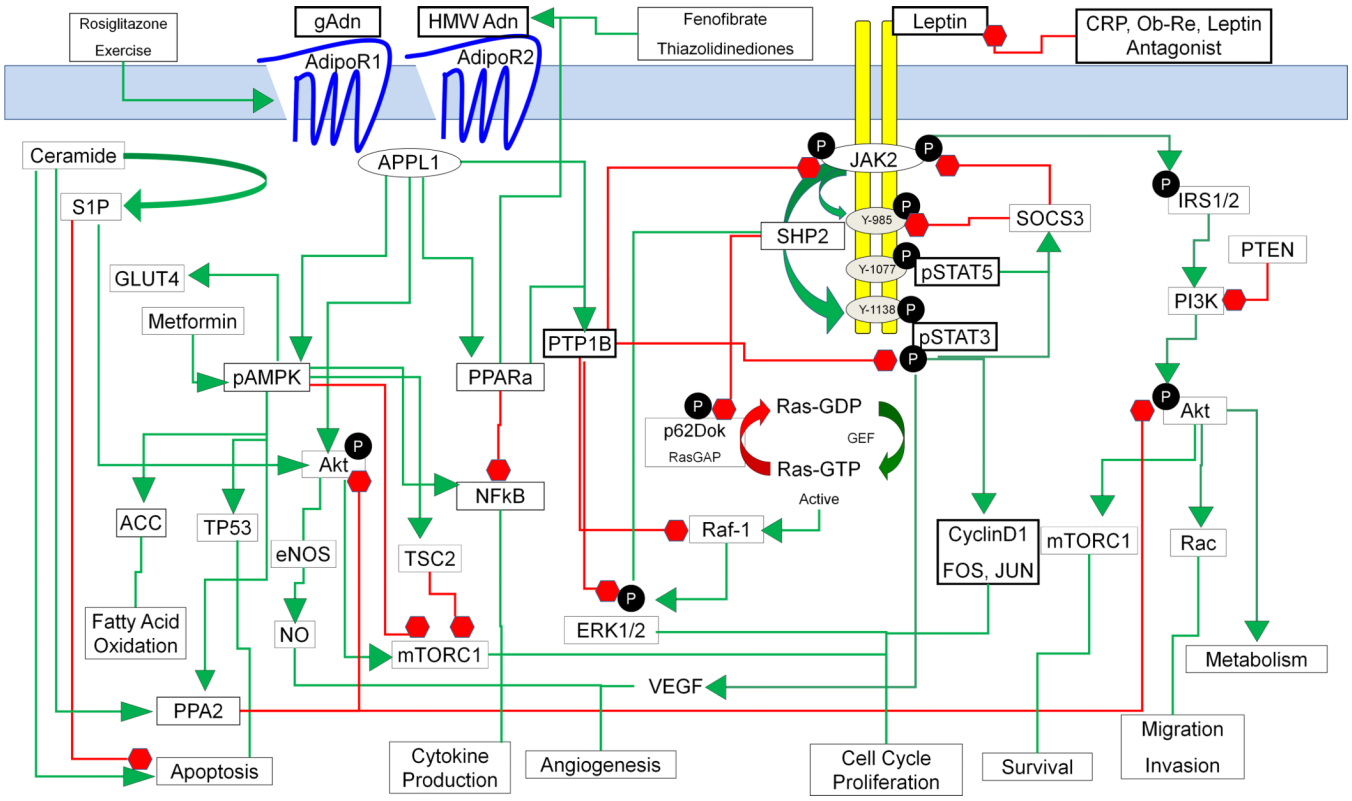

Figure 1.

Leptin and adiponectin activate signaling components that integrate PI3K/Akt, RAS/MAPK, and pAMPK/mTor pathways. Green arrows indicate activation of target protein, while red lines indicate inhibitory effects. Leptin stimulation of the long receptor isoform leads to JAK2 phosphorylation and subsequent phosphorylation of tyrosine residues 985 and 1138, which confer PI3K/Akt and STAT3 pathway activation. Leptin stimulation can be prevented with c-reactive peptide, soluble leptin receptor (Ob-Re) or leptin antagonists. Chronic stimulation leads to an increase in SOCS3 which negatively regulates leptin signaling by inhibiting JAK2 activities. Additionally, leptin receptor stimulation activates SHP2 leading to increased Ras/RAF/ERK signaling. Adiponectin receptor 1 (AdipoR1) and receptor 2 (AdipoR2) are preferentially stimulated by the globular (gAdn) and high molecular weight (HMW Adn) oligomers of adiponectin respectively, although both receptors respond with lower affinity to other adiponectin oligomers. Serum levels of adiponectin can be increased through thiazolidinediones or fenofibrates, while the receptor levels can be increased with rosiglitazone or exercise. Adiponectin receptors associate with adaptor protein APPL1 to activate AMPK and PPAR alpha. Adiponectin can antagonize leptin mediated proliferation through activation of phosphatase PTP1B, leading to inhibition of JAK2, dephosphorylation of STAT3, and dephosphorylation of ERK1/2; as well as phosphatase PP2A to decrease phosphor-Akt. Adiponectin also inhibits leptin action through increased AMPK inhibition on mTORC1 directly as well as indirectly through TSC2. Metformin additionally antagonizes leptin action through activation of AMPK. Adiponectin activation also leads to modulation of NFkB, TP53, eNOS, ACC, and ceramidase activity; yet direct antagonism of leptin through these mediators is unclear. Ultimate outcome for a particular pathway in cancer is highly dependent upon genetic integrity and deficiencies in key regulatory mediators will dictate which pathway will dominate.