The effect of adiponectin and adiponectin receptor regulation and expression in several cancers and limits cell proliferation and induces apoptosis as potential therapeutics on cancer, and metabolic disorders (Part four)

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Abstract

Adiponectin is a white and brown adipose tissue hormone, also known as gelatin-binding protein-28 (GBP28), AdipoQ, adipocyte complement-related protein (ACRP30), or apM1.

Many cancer cell lines express adiponectin receptors, and adiponectin in vitro limits cell proliferation and induces apoptosis. Recent in vitro studies demonstrate the antiangiogenic and tumor growth-limiting properties of adiponectin.

Studies in both animals and humans have investigated adiponectin and adiponectin receptor regulation and expression in several cancers.

Current evidence supports a role of adiponectin as a novel risk factor and potential diagnostic and prognostic biomarker in cancer. In addition, either adiponectin per se or medications that increase adiponectin levels or up-regulate signaling pathways downstream of adiponectin may prove to be useful anticancer agents.

In this article, I discuss direct mechanisms of action, In vitro studies, Animal studies, and indirect mechanisms of action, Insulin-sensitizing effects and Anti-inflammatory effects

Key Word: Adiponectin, In vitro studies, Animal studies, direct mechanisms of action, and indirect mechanisms of action

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1. Introduction

Adiponectin is a protein produced and secreted almost exclusively by adipocytes (1). First described over a decade ago, the interest in the biology of adiponectin was spurred by the discovery of measurable concentrations in plasma, its structural resemblance to complement factor C1q and the consistent fi nding of decreased levels in obesity (2). Adiponectin circulates in high concentrations in healthy adults and mice, accounting for 0.01% of total plasma protein and its plasma levels are a thousand times that of leptin (3). Circulating levels of adiponectin range between 2 and 30 µg/ml in humans (2),(4), and are generally higher in females than males (5). Th is sexual dimorphism has been attributed to the eff ect of testosterone on adiponectin secretion (6). Th e gene encoding human adiponectin has been mapped to chromosome 3q27 (7). In serum, adiponectin exists as three main forms: trimers, hexamers and highmolecular weight (HMW) multimers. To create these forms, a number of post-translational modifications are required. Th e source of adipokines is either the adipocytes themselves or the stromal vascular fraction within adipose tissue, comprising preadipocytes, endothelial cells, fi broblasts, leukocytes and macrophages (8). Resident stromal macrophages are a source of IL-10 and arginase. However, 'classically activated' macrophages recruited from the circulation to obese adipose tissue secrete the pro-infl ammatory cytokines TNF-α, inducible nitric oxide synthase, and IL-6. Adipocytes are responsible for the production of adiponectin, leptin, angiotensinogen and retinol-binding protein. Some adipokines, including monocyte chemoattractant protein-1 and apelin, are produced by both fractions (8),(9). In rats with induced polymicrobial sepsis, plasma adiponectin levels negatively correlated with plasma endotoxin and TNF-α levels (10). Adiponectin was found to directly bind LPS and suppress limulus amoebocyte lysate in vitro. Th is animal model also provided the fi rst evidence that the two adipokines, adiponectin and TNF-α, inversely regulate each other's circulating concentration. A recent study of patients with acute respiratory failure showed that increased plasma adiponectin levels measured within 48 hours of respiratory failure are associated with mortality (11). In a study of paediatric patients with sepsis, increased levels of HMW adiponectin were found in the septic shock cohort on day 1 and the plasma levels correlated with risk of mortality scores. Th is was associated with an increase in PPAR-γ activity in peripheral blood mono nuclear cells (12).

2. Adiponectin and Carcinogenesis Mechanisms

Accumulating evidence suggests that adiponectin exerts antineoplastic effects via two mechanisms. First, it can act directly on cancer cells by stimulating receptor-mediated signaling pathways. Secondly, it may act indirectly by modulating insulin sensitivity at the target tissue site, regulating inflammatory responses and influencing tumor angiogenesis.

2.1. Direct mechanisms of action

2.1.1. In vitro studies

Expression of adiponectin's two main receptors, AdipoR1 and AdipoR2, has been reported in numerous cancer cell types *in vitro* and *in vivo*, as mentioned in *Section IV*. Thus, adiponectin can exert direct receptor-mediated action on cancer cells and tissues. Adiponectin negatively influences growth of most obesity- related cancer types, although conflicting results have been published for some. Treatment of CC cell lines with adiponectin generally led to growth inhibition (13),(14),(15),(16), or had no effect on proliferation (17). An exception was noted in one study, wherein adiponectin promoted growth of colonic HT-29 cells and stimulated secretion of various proinflammatory cytokines (18). Interestingly, glucose availability was recently suggested to play an important role in the response of colon cancer cells to adiponectin. Under glucose deprivation, adiponectin positively influenced HT-29 and DLD-1 colorectal cell survival through enhancement of autophagic response in colon cancer cells, whereas it inhibited growth in glucosecontaining medium (19). In the case of liver (20), and gastric carcinoma (21), EA (22), and endometrial (23), and prostate carcinoma (24),(25),(26), adiponectin exhibited clear anticarcinogenic effects, whereas it had no influence on melanoma cell proliferation (27). For clearcell renal carcinoma, only indirect evidence, indicative of a negative effect of adiponectin on carcinogenesis, has been published so far (28). Studies on breast cancer have been conflicting and point toward cell line-dependent effects. A complete overview of the effect of adiponectin on breast cancer has recently been reviewed elsewhere (29). In general, adiponectin has been shown to inhibit with a varying degree of efficiency the growth of normal MCF- 10A (30), human mammary epithelial cells as well as cancerous MCF7 (30),(31),(30),(32),(33), T-47D (32, 34),(35), MDAMB-231 (35),(36),(37),(38),(39), and SK-BR-3 (254) cells, whereas it had no effect on MDA-MB-361 (254), and Hs 578T (39), cells. Differential expression of ER might be one explanation because proliferation of ER cells was reduced at lower adiponectin concentrations than proliferation of ER cells (254) Indeed, the establishment of an ER MDA-MB-231 cell line exhibiting markedly increased sensitivity to adiponectin treatment supports this notion (254) On the other hand, ER expression cannot be the only explanation, because variability also exists for the same cell line between different studies, as seen for example in the case of MCF7 (33), (39),(40), and T-47D (106),(38). Possible reasons may be biological variations between the several lines of the respective cells used in various laboratories, as well as differences in culture conditions (41),(42). The latter can be exemplified in the usage of serum because serum-free media alone might favor an inhibition of cell growth (43). Indeed, the previously mentioned positive effect on HT29 colon cancer cell proliferation was seen with1%fetal bovine serum (44), whereas another study reported no effect under serum-free conditions (17). Moreover, similar studies onHT29cells proving inhibition of proliferation made use of gAd (15),(16). Thus,

cellular responses might also be dependent on the specific adiponectin isoform used. This was also seen in the case of prostate carcinoma cells, where only HMW adiponectin was capable of inhibiting cell proliferation (45). Finally, incubation time or dosage might modulate the effect of adiponectin on cell growth (46). MCF7 breast cancer cells, for example, exhibited a reduction in proliferation when incubated for 48 h with 5g/ml adiponectin (47). whereas no effect was visible upon treatment with 10 g/ml for up to 6 d (30). Adiponectin can induce apoptosis in liver (48),(20), Gastric (21), and endometrial (23), carcinoma as well as EA (267). This effect was shown to be mediated via upregulation of the proapoptotic Bax and down-regulation of the antiapoptotic Bcl-2 protein in EA cells (267) as well as increased caspase 3 activity in HCC cells (285). Interestingly, the exact mechanism herein seems to depend on the cancer cell line used, as seen in the case of endometrial cancer (23). Additionally, adiponectin can enhance apoptosis in colon cancer cells (13),(14), although exceptions were noted (17),(44). In the case of breast cancer, the effect of adiponectin on apoptosis remains inconclusive. Whereas adiponectin does not affect the viability of T47-D (34),(35),(39),(49),(50), SK-BR-3 (49),(50), or Hs 578T (345) breast cancer cells, it was shown to stimulate apoptosis in MCF7 (31),(30),(32),(33),(50), and MDA-MB-231 (37),(38),(39). Other studies, however, have suggested an opposite or no effect of adiponectin on both MCF7 (30),(49),(51), and MDA-MB-231 (35), (50), breast cancer cells. Invasiveness, a common trait of many malignancies, is also influenced by adiponectin, and the outcome seems to depend on cancer cell type. Studies on breast (52),(53), and liver cancer (54) proved a negative effect of adiponectin on migration. Particularly in the latter, adiponectin was able to block signaling pathways related to invasion and down-regulated formation of lamellipodia, important for cell migration (54). On the other hand, apromigratory effect was seen in the case of prostate cancer (55), and chondrosarcoma (56), whereas adiponectin treated cells exhibited increased expression of the integrins 5,1 and ,2,1, respectively. In addition to cell line dependency, differences in the used adiponectin dosage might explain the divergent results. Studies noting a negative effect on migration used more than 10 g/ml adiponectin (52),(53),(54). whereas studies indicating a positive influence used less than 1 g/ml (55),(56). In addition to the above receptor-dependent actions, adiponectin can exert receptor-independent, antiproliferative effects through controlling the bioavailability of certain growth and inflammatory factors, both of which have been associated with carcinogenesis (57). By selectively binding and sequestrating platelet-derived growth factor BB, heparin-binding epidermal growth factor, and basic fibroblast growth factor, adiponectin was able to attenuate DNA synthesis, proliferation, and migration of cultured smooth muscle cells (58),(59). These interactions were shown to depend on different oligomeric forms of adiponectin as well as distinct binding sites in the protein (59). Moreover, adiponectin was shown to decrease IL-1-induced secretion of pro-inflammatory factors from stromal endometrial cells, thus exerting protective actions on the endometrium (60). Finally, *in vitro* evidence points toward interactions between adiponectin and other hormonal signaling pathways, highlighting the complex mechanisms that regulate carcinogenesis *in vivo*. Generally, adiponectin was able to inhibit leptin-induced proliferation and cell growth, as shown for breast (30),(36), colon (61), liver (48), and prostate cancer (26), as well as EA (62). Furthermore, a cross talk exists between adiponectin and sex steroids. Pfeiler *et al.* (40), showed that whereas adiponectin alone had no effect on growth of breast cancer cells, a slight reduction was induced in hormone-independent MDAMB- 231 and SK-BR-3 cell lines, with an additional apoptosis stimulation in the former. On the other hand, hormone- dependent MCF7 cells exhibited an increased proliferation rate (40). Moreover, in LNCaP androgendependent prostate cancer cells,HMWadiponectin inhibited dihydrotestosterone-induced cell growth (26). IGF-I (31), and IL-6 (63), signaling can also be

influenced by adiponectin. An example for the complex interactions can be seen in the case of colon cancer, where the outcome was shown to also depend on tumor stage. Fenton *et al* (61). demonstrated that adiponectin reduced cell proliferation and blocked leptin-induced autocrine IL-6 production as well as trans-IL-6 signaling in a model of preneoplastic [adenomatous polyposis coli (Apc)] colon epithelial cells. Normal colon epithelial cells (Apc) on the other hand, were leptin insensitive and also less responsive to adiponectin alone (61). Moreover, in MC38 late-stage colon carcinoma cells, adiponectin treatment was not able to reduce insulin-induced proliferation (63),(64), whereas it could inhibit IL-6-dependent signaling. Leptin treatment alone had no effect on MC38 cell proliferation (63). Thus, along the continuum to carcinoma, adiponectin may influence cell homeostasis and proliferation via distinct mechanisms and interactions.

2.1.2. Summary of signaling pathways activated by adiponectin in malignancies

Physiological responses to adiponectin involve several intracellular signaling pathways including AMPK, mTOR, PI3K/Akt, MAPK, STAT3, NF-_B, and the sphingolipid metabolic pathway (*Section II.E*). Evidence suggests an involvement of these pathways in adiponectin mediated inhibition of carcinogenesis. Activation of cAMP/protein kinase A (PKA) (31), inhibition of-catenin (37),(39), as well as reduction of reactive oxygen species (ROS) (65), have also been implicated in the response of cancer cells to adiponectin. The signaling pathways described herein are depicted in Fig. 1. Conversely, new compelling molecular data suggest that adiponectin and its receptors show potent proangiogenic effects that could promote tumor growth particularly in murine mammary cancer models (66),(67),(68). Interestingly, a new array of observations provides insight in the ceramidase activity contained by the classical adiponectin receptors. Upon activation, AdipoR1/R2 catabolize ceramides to downstream degradation products such as sphingosines and the S1P. Elevated S1P is associated with increased cell survival and higher local proangiogenic activity seen in mammary tumor mouse models in which adiponectin levels have been manipulated (66),(68),(69). Based on these data, the sphingolipid metabolic pathway that is a critical mediator of inflammation, cell survival, and growth could represent an important component of adiponectin signaling in malignancies. Most of the effects of adiponectin on cancer are mediated through AMPK. AMPK can be stimulated by adiponectin through an increase of AMP levels, the adaptor protein APPL-1, calcium-dependent kinases (*Section II.E*), as well as the Ser/Thr kinase LKB1 (70). Importantly, in the case of breast cancer cells, LKB1 has recently been proven necessary for adiponectin-induced AMPK activation and subsequent inhibition of adhesion, migration, and invasion. *LKB1* expression was also shown to be directly stimulated by adiponectin (52). AMPK negatively influences carcinogenesis through affecting cell growth mechanisms. It down-regulates the TSC2/mTOR/S6 axis, thus reducing protein expression, and inhibits *de novo* fatty acid synthesis via blocking sterol regulatory elementbinding protein-1c-mediated induction of ACC and fatty acid synthase (71). Additionally, it induces p53 and p21 expression, important regulators of growth arrest and apoptosis (71). Short-term adiponectin treatment was shown to activate AMPK in colon (13),(15),(16), breast (34),(31),(33),(52),(53), liver (20), prostate (24),(72), and endometrial (23), cancer as well as EA(62), mediating growth inhibition. Down-regulation of mTOR/S6 signaling was implicated in many of these studies(15),(15),(20),(16). Activation of protein phosphatase 2A (PP2A), a tumor suppressor involved in the inhibition of Akt and small GTP hydrolase Ras-like A (73), was also shown to depend on adiponectin/AMPK signaling in MDA-MB-231 breast cancer cells (53). Moreover, in colon cancer cells, adiponectin-induced

AMPK activation was directly involved in increased expression of cyclindependent kinase inhibitors p21 and p27, leading to cell cycle arrest as well as reduced levels of sterol regulatory element binding protein-1c (13). Additionally, studies point toward a direct negative effect of adiponectin on the PI3K/Akt pathway. In response to various growth factors, PI3K becomes activated, initiates phosphorylation of Akt, and stimulates a plethora of effector molecules positively regulating cell survival, growth, and proliferation. Interestingly, Akt can also phosphorylate and inhibit TSC2, thus counteracting the effects of activated AMPK. Phosphatase and tensin homolog (PTEN) acts as an inhibitor of PI3K signaling (74), and cell line-specific PTEN deficiency may determine whether AMPK or Akt prevails in regulating mTOR activation (72). Treatment of colon (19), and breast cancer Cells (31), with adiponectin was shown to significantly reduce the phosphorylation and activation of PI3K and Akt. Moreover, adiponectin alleviated thioredoxin- and thioredoxin reductase-mediated inhibition of PTEN, thus indirectly influencing PI3K/Akt signaling (75). Further mediators of adiponectin signaling can be found in the MAPK cascade, comprising among others JNK, p38, and ERK1/2, or p42/p44. The effects of stress activated kinases JNK and p38 on proliferation and apoptosis depend on the cellular context, whereas ERK1/2 largely have mitogenic influences (76). In prostate (77), and hepatocellular (77),(20), carcinoma cells, adiponectin treatment led to increased JNK activity resulting in caspase 3-mediated apoptosis (20). Interestingly, AMPK activity seems to be pivotal for the phosphorylation of JNK, as shown in the case of liver cancer cells (20). Adiponectin- induced inhibition of ERK1/2 signaling has been noted in endometrial (23), and breast (34),(33), cancer cell lines contributing to a reduction in viability. Importantly, in MCF7 breast cancer cells, prolonged adiponectin treatment resulted in decreased levels of *c-myc*, *cyclin D* (over a period of 2 to 6 h), and Bcl-2 (8 h) while increasing expression of p53 and Bax (24 h), thus leading to cell cycle arrest and apoptosis (33). In contrast, adiponectin has been associated with increased p38 activity in several studies positively influencing carcinogenesis, as mentioned previously Adiponectin also modulates STAT3 sig (44),(55),(56). naling. STAT3 is activated by adipokine-induced (*e.g.*, leptin) or cytokine- induced JAK phosphorylation and regulates many cancer-related processes such as cell survival and differentiation. Consequently, dysregulation of the JAK/STAT3 pathway favors carcinogenesis (78). Adiponectin treatment of liver cancer cells down-regulated leptin-induced STAT3 phosphorylation and subsequently reduced cell growth and migration. Importantly, suppressor of cytokine signaling 3, a JAK2/STAT3 inhibitor, was found elevated and may explain the adiponectin-leptin cross talk (48). Adiponectin was also able to suppress constitutively active STAT3-signaling in prostate (DU145) and hepatocellular (HepG2) carcinoma cell lines (77). Overactivation of wingless-type protein (Wnt)-signaling along with increased -catenin-induced expression of positive cell cycle regulators has been observed in many human cancer types (79). Wnt signals through frizzled to inactivate glycogen synthase kinase-3 (GSK-3), which forms part of the -catenin degradation complex, allowing accumulation of -catenin in the nucleus (79). In MDA-MB-231 breast cancer cells, prolonged adiponectin treatment (24 h) inhibited phosphorylation of GSK-3, destabilizing -catenin and thus significantly reducing *cyclin D1* expression. This effect was probably mediated by decreased Akt phosphorylation (39), as well as direct induction of Wnt inhibitory factor 1 expression, a molecule involved in down-regulating_-catenin signaling (37). Interestingly, cross talk between the canonical Wnt/_- catenin and PI3K/Akt pathways has been reported previously (80),(371), supporting the former assumption. In addition, adiponectin was shown to mediate cell cycle arrest and apoptosis in MCF7 breast cancer cells through modulating the cAMP/PKA pathway. Particularly, adiponectin treatment increased intracellular cAMP levels (at 15 min or 6 h), thus activating PKA (at 30 min or 6 h) and inhibiting expression of *cyclin D1*

(24 h) and *E2* (48 h) (31). Phosphorylation ofAMPK(30 min) was also found increased, but it depended on PKA activity (31). Inhibition of NF-_B, a transcriptional regulator involved in inflammation and cancer (81), has also been implicated in adiponectin signaling (61). Finally, adiponectin is able to decrease ROS production (65), which can promote growth factor signaling and induce DNA mutations (82). The reduction in intracellular ROS levels was shown to be mediated via down-regulation of nicotinamide adenine dinucleotide phosphate-oxidase activity and ultimately led to inactivation of MAPK, thus counteracting cell proliferation (65). Of note, adiponectin's influence in cancer cells may not only be of a direct nature but may also depend on endocrine (tumor micro-environment) and paracrine (distal) interactions of adipocytes with tumor tissues (83). An example can be seen in the case of breast cancer, where tumor cells and adipocytes reside in close proximity to each other (83). In adipocytes, adiponectin induces LKB1/AMPK-dependent inhibition of aromatase activity, subsequently lowering estrogen production (84). Reduced ER-stimulation in hormone-dependent cancer cells negatively impacts prosurvival pathways. This can be seen for epidermal growth factor receptor (EGFR) signaling (85), which induces proliferation through activating kinases such as ERK, PI3K and the STAT family of transcription factors (85),(86). In fact, EGFR signaling seems to be a point of convergence for direct and indirect effects of adipokines on cancer cells because adiponectin may also influence EGFR pathways directly through AdipoR1/R2-stimulation (83). However, the interaction between adipocytes and cancer cells is far more complex because it also involves other adipocyte-secreted molecules like, for example, leptin, in-flammatory cytokines (TNF, IL-6), extracellular matrix constituents, and proangiogenic factors (VEGF), as well as metabolic regulators like insulin (83).

3. Animal studies

The physiological relevance of the *in vitro* findings has recently been evaluated in animal experiments. Various models of carcinogenesis, combined with adiponectin deficiency and/or administration, have been able to confirm an antitumorigenic role for adiponectin. Examination of influences mediated by diet further contributed toward elucidating the complex mechanisms that underlie the action of adiponectin *in vivo*. Inhibition of tumor growth has been demonstrated for colon(87),(88),(89), gastric (21), liver (20),(90), breast (37),(39), (53),(75), and lung cancer as well as melanoma (27). Adiponectin deficiency promoted azoxymethane (AOM)-induced colorectal and liver tumor formation and correlated with higher colon tumor stage (89). Also, cell proliferation was increased and associated with a concomitant increase of cyclooxygenase-2 (COX-2) expression, predominantly in tumor myofibroblasts (89). Thus, adiponectin might negatively regulate tumor growth by influencing COX-2 expression in stromal myofibroblasts (89), which have been shown to secrete prostaglandin E2 upon COX-2 expression and consequently stimulate cell proliferation (91). Along the same lines, Mutoh *et al.* (87), detected a gradual increase in polyp formation in Apc (multiple intestinal neoplasia) mice with adiponectin haplodeficiency and complete deficiency. Diminished AMPK phosphorylation resulting in elevated serum levels of plasminogen activator inhibitor-1, an adipocytokine positively involved in colon carcinogenesis, was associated with loss of adiponectin (87). Growth of intestinal adenomas in Apc (multiple intestinal neoplasia) mice was further shown to be suppressed by ip administration of adiponectin. This effect was probably mediated by binding to AdipoR1 and AdipoR2 because both receptors were present in cancerous tissues and their expression levels remained unaltered after treatment (88). Similar results were obtained in a nude mice-xenograft model of gastric cancer. Local and systemic adiponectin administration

markedly inhibited growth and metastasis, and *in vitro* studies pointed toward an involvement of both receptors in the antitumorigenic response to adiponectin (21). To date, a relative paucity of studies exists regarding the beneficial effect of adiponectin on colon and gastric carcinogenesis. The main focus has been adiponectin- deficiency models or models utilizing adiponectin as a treatment of already established malignancies. Chemoprevention studies, on the other hand, have not been performed. These would be useful for fully elucidating the action of adiponectin on colon and gastric carcinogenesis from the beginning and for evaluating whether adiponectin could be used as a preventative agent. In the case of liver cancer, mouse xenograft experiments provided evidence that adiponectin can reduce tumor growth and lung metastasis via increasing JNK phosphorylation (20), and inhibiting angiogenesis (90). Moreover, adiponectin has been shown to counteract leptininduced stimulation of tumor growth (48). Finally, adiponectin deficiency in the context of a mouse model of nonalcoholic steatohepatitis accelerated liver cirrhosis and tumor formation through elevated oxidative stress (92). Thus, hypoadiponectinemia, as seen in the context of obesity, may be a risk factor for nonalcoholic steatohepatitis- related liver tumorigenesis (92). Studies on breast cancer have so far published conflicting results. First of all, adiponectin haploinsufficiency was shown to promote tumor onset and aggressiveness through increased PI3K/Akt/_-catenin signaling (75). Furthermore, in a MDA-MB-231 xenograft model, pretreatment of cells with adiponectin as well as intratumoral or systemic administration of adiponectin negatively influenced mammary tumorigenesis. Inhibition of PI3K/Akt and GSK 3-catenin signaling (39), possibly through elevated expression of Wnt inhibitory factor 1 (37), were found to be implicated. Additionally, direct adiponectin administration resulted in an AMPK-mediated increase of PP2A activity (53). On the other hand, complete adiponectin deficiency was shown to suppress mammary carcinogenesis in a mouse mammary tumor virus-polyoma middle T antigen (MMTV-PyVmT) tumor model, accompanied by decreased tumor angiogenesis (68),(69). Possible reasons for the observed contradictions are discussed in *Section V.B.3*. Adiponectin has also been implicated in negatively regulating the growth of lung cancer and melanoma xenografts. The underlying mechanism may involve macrophage infiltration into tumor tissue because tumors from adiponectin knockout mice exhibited reduced macrophage numbers (27). A number of studies have examined the importance of dietary fat intake and obesity on tumorigenesis. Ahigh-fat diet, corresponding to thecommonWestern-style diet, has been shown to positively and directly influence pancreas (93), colon (94), and Lewis lung (95), cancer as well as ALL (96). Furthermore, genetically induced obesity, as seen in *ob/ob* and *db/db* mice, has been associated with PaCpromotion and dissemination, particularly in the context of insulin resistance and decreased levels of circulating adiponectin (97). Onthe other hand, intermittent caloric restriction was shown to reduce tumorigenesis in a mouse mammary tumor model. This effect was associated with an elevated adiponectin/leptin ratio, increased expression of AdipoR1 in mammary tissue, and higher levels of adiponectin in mammary fat pads (98). A direct role of adiponectin in the context of a high-fat diet has been studied in the case of AOM-induced colon cancer formation. By generating adiponectin-, AdipoR1-, and AdipoR2-deficient mice, Fujisawa *et al.*(99), provided evidence that adiponectin suppresses colonic epithelial proliferation exclusively under the high-fat diet condition. The observed effect involved AdipoR1-mediated activation of AMPK and subsequent inhibition of Mtor (99). Interestingly, supraphysiological serum levels of adiponectin do not seem to protect against cancer development on the basis of adiponectin transgenic mouse models. A recent study utilizing adiponectin transgenic animals showed that growth of AOM-induced colon cancer was not attenuated by adiponectin overexpression (13). Insulin resistance, on the other hand, induced by high-fat diet treatment 1

wk after the final AOM injection, was efficiently prevented (13). These results seem to contradict previously mentioned studies on the beneficial effect of adiponectin on obesity-related colon tumorigenesis. However, a high-fat diet may not play a key role in the development of colon cancer in the model of Ealey *et al.* (13), because it was used during the final stages of the disease. It is known that obesity takes time to develop after feeding mice a high-fat diet (100). In fact, adiponectin levels decrease only after 10wkof high-fat diet treatment or later (100). In addition, other factors may change during later stages of high-fat feeding, as shown for insulin and leptin (101). During these stages, AOM-induced colon cancer is already well established. Thus, the study by Ealey *et al.(13),* can only provide evidence for chemically induced and not obesity-induced colon carcinogenesis. Further chemoprevention studies administering different levels of adiponectin in combination with a high-fat diet are needed to examine the potential preventative effect of adiponectin on obesity-related colon cancer. In summary, accumulating evidence provides support for an antitumorigenic effect of adiponectin on various cancer types, most of which are associated with obesity. Importantly, adiponectin seems to exert the strongest effect under the high-fat diet condition (99), *i.e.*, a condition directly related with insulin resistance and proinflammatory state, a fact with important implications for its potential use in anticancer therapy.

3.1. Indirect mechanisms of action

Adiponectin exerts indirect antineoplastic action through an insulin-sensitizing and antiinflammatory effect. Additionally, it has been proposed to play a role in angiogenesis regulation, although conflicting evidence has been published.

3.2.. Insulin-sensitizing effects

Insulin resistance and hyperinsulinemia have been proposed to play an important role in cancer development, particularly in the context of obesity (102). High insulin levels increase the bioavailability of IGF-I by stimulating its expression and simultaneously downregulating IGFBP-1 and IGFBP-2. Insulin and IGF-I then signal through the IR and IGF-I receptor to inhibit apoptosis and enhance cellular proliferation. The resulting mitogenic and antiapoptotic environment favors the accumulation of genetic mutations and thus carcinogenesis(103). Many clinical studies have found an association between high levels of IGF-I and/or insulin with an increased risk for several malignancies, including colorectal and postmenopausal breast cancer (103),(104),(105),(106),(107),(108),(109),(110),(111). An indirect link between the insulin pathway, adiponectin, and thus carcinogenesis has been established in many studies. Serum adiponectin levels are inversely associated with fasting insulin concentrations (2), and reduced in the context of obesity and insulin resistance (112),(113). Moreover, adiponectin exhibits potent insulin- sensitizing actions. Intraperitoneal injection of adiponectin lowers glucose levels in wild-type mice and transiently reverses hyperglycemia in *ob/ob*, nonobese diabetic, or streptozotocin-treated mice (114). These effects were shown to be mediated via increased ability of insulin to suppress glucose production in adiponectintreated primary rat hepatocytes (114). Adiponectin deficiency, on the other hand, results in severe dietinduced insulin resistance (115). The mechanism underlying the observed adiponectin- mediated reversal of insulin resistance is slowly being unraveled. In *Section III.A*, direct AMPK-mediated effects on glucose and fatty acid metabolism are described more detail. In addition to these direct effects,may exert indirect influence on the insulinsignaling pathway. Administration of adiponectin increased insulin-

induced phosphorylation of the IR and whole-body insulin sensitivity in rodents. Additionally, plasma adiponectin levels were found positively associated with skeletal muscle IR phosphorylation in humans (116). Moreover, adiponectin enhanced the ability of insulin to stimulate phosphorylation of the adaptor protein IRS-1 and Akt by reversing the S6 kinase-mediated negative regulation of IRS-1. Particularly, treatment of muscle cells with adiponectin activated the LKB1 /AMPK/TSC1/2 pathway, ultimately leading to a reduction of S6 kinase phosphorylation (117). Recently, new additions have been made to the established pathways linking adiponectin with insulin sensitivity. Ceramides, a class of sphingolipids, have been associated with impaired insulin sensitivity in muscle (66). Adiponectin was shown to stimulate ceramidase activity through AdipoR1 and AdipoR2 independently of AMPK. Thus, ceramide catabolism was induced and subsequently led to increased levels of the antiapoptotic S1P (66). This could present important implications for cells expressing adiponectin receptors, whereas in cells lacking adiponectin receptors ceramidase activity is impaired, resulting in an enhanced susceptibility to cell death. Moreover, adiponectin has been implicated in the inhibition of autophagy, which fuels gluconeogenesis (118). Cowerd *et al.* (118), provided evidence that activation of the PI3K pathway through APPL-1 in adiponectin-treated hepatoma cells increased expression of suppressor of glucose by autophagy, a novel negative regulator of autophagy (118). Finally, adiponectin was able to reduce cholesteryl ester formation in cultured macrophages via inhibition of acyl coenzyme A:cholesterol acyltransferase 1 (119), which has been implicated in positive regulation of tumor cell growth and invasion (120).

3.3.. Antiinflammatory effects

Inflammation is a well-established pathway leading to cancer promotion and progression. In response to tissue injury or infection, a cascade of events is initiated. These lead to increased cell proliferation and production of reactive oxygen and nitrogen species from infiltrating immune cells. Thus, an environment is created that favors mutagenesis in rapidly dividing cells, a prerequisite for cancer development (121). Epidemiological studies have associated chronic inflammation with increased risk of several types of cancer. Persistent infections can lead to chronic inflammation, and thus cancer, as seen for example in the case of gastric cancer due to *Helicobacter pylori* infection (121). Additionally, there are strong associations between inflammatory bowel diseases, characterized by chronic inflammation, and CC (121).
Obesity reflects a low-grade systemic inflammatory state and is associated with increased pro-inflammatory markers such as IL-6,TNF-α_, andCRP (122). CRPconfers increased cancer risk, and both systemic IL-6 and TNF-α_ have been correlated with higher cancer rates, as examined in the case of colorectal neoplasia (122). Potential mechanisms might involve prosurvival effects of TNF-α_ on cancer cells and overstimulation of the JAK/STAT3 pathway by IL-6 (102). Matrix metalloproteinases (MMP) involved in cancer-cell invasion and metastasis and inflammation induced oxidative stress are additional factors that have been implicated in the link between obesity, inflammation, and cancer development (102). Adiponectin has been shown to exert anti-inflammatory actions and may thus counteract the increased cancer risk seen in obesity-induced inflammation. Particularly, adiponectin influences the function of myelomonocytic cells, important mediators of innate immunity. Adiponectin inhibited proliferation of myelomonocytic precursor cells (123), and reduced secretion of proinflammatory cytokines TNF-α_ and IL-6 from activated macrophages (123),(124), while increasing the production of antiinflammatory cytokine IL-10 (124), and tissue inhibitor of metalloproteinase-1, an inhibitor of MMP and tissue remodeling (125). Moreover, adiponectin negatively influenced macrophage

phagocytic activity (123), promoted the antiinflammatory M2 phenotype *in vitro* and *in vivo* (126), attenuated leukocyteendothelium interactions *in vivo* (127), and prevented systemic inflammation by enhancing calreticulin-dependent opsonization of apoptotic bodies and their subsequent macrophage-mediated clearance (128). Adiponectin was also found to suppress IL-2-stimulated natural killer cell cytotoxicity by reducing the expression of interferon-_ and apoptotic effector molecules (129). Recently, adiponectin was implicated in the modulation of dendritic cell activity. Tsang *et al.*(130), showed that adiponectin- treated dendritic cells decreased T-cell proliferation and increased the percentage of CD4 CD25 FOXP3 regulatory T cells via up-regulation of the inhibitory molecule programmed cell death-1. Finally, adiponectin can influence T- and B-cell function. Through down-regulating T-cell chemoattractants from activated macrophages, adiponectin was able to reduce Tcell recruitment in atherogenesis (131). Adiponectin was also found to suppress B-cell lymphopoiesis, but only when stromal cells were present and when cultures were initiated with the earliest category of lymphocyte precursors (132). Inhibition of NF-_B and ERK1/2 signaling has been implicated in some of the observed effects(124), as well as increased activation of PPAR-_ and PPAR-_(126). Additionally, adiponectin was shown to induce the expression of multiple genes with antiinflammatory properties, *e.g.*, suppressor of cytokine signaling 3, in cultured macrophages (133).

3.4. Angiogenesis

Angiogenesis is very important for the growth of most primary tumors and their metastases. Up to a size of 1–2 mm, tumors can absorb sufficient nutrients and oxygen by diffusion. After that point, their further growth requires attachment to the vasculature (134). Inhibition of angiogenesis has been shown to suppress tumor growth (135),(136), and may represent a promising therapeutic target. On the other hand, antiangiogenic therapy should be used with caution because the resulting hypoxic environment and selective pressure can favor evasive mechanisms that reinitiate tumorigenesis in certain cancer types (136). The effect of adiponectin on neovascularization based on published results remains contradictory in that both pro- and antiangiogenic effects have been reported. Regarding the proangiogenic action of adiponectin, Ouchi *et al.* (137), showed that it can induce capillary-like structure formation, enhance the migration of human umbilical endothelial cells, and stimulate blood vessel growth *in vivo* (137). Activation of AMPK, Akt, and endothelial nitric oxide synthase was found to be implicated (137). Also, in a separate study, adiponectin was able to rescue endothelial cells from serum starvation-induced apoptosis by suppressing caspase 3 activity (138). These findings seem to be particularly relevant in the case of obesity and metabolic syndrome, where patients exhibit, among other factors, impaired collateral artery formation (139). Hypoadiponectinemia has been suggested to causally link obesity with the observed cardiovascular dysfunction (139). Indeed, in a hind limb ischemia model, adiponectin mediated AMPK signaling enhanced angiogenesis and improved limb reperfusion (139). Furthermore, in the context of atherosclerotic cardiovascular disease, adiponectin was shown to reverse the effects of IL-18. IL-18, a potent proinflammatory cytokine, is increasingly expressed in atherosclerotic lesions (140). In the study of Chandrasekar *et al.* (140), pretreatment of endothelial cells with adiponectin blocked IL-18-mediated apoptosis via APPL-1- dependentAMPKphosphorylation and subsequent PI3K/ Akt signaling. Adiponectin also has positive effects on endothelial progenitor cells, which may contribute toward the formation of new blood vessels. Shibata *et al.* (141), and Yang *et al.* (142), showed that adiponectin can stimulate endothelial cell differentiation from human peripheral blood mononuclear cells (141), and human peripheral blood CD14 monocytes (142),

respectively. In addition, adiponectin was able to increase endothelial cell migratory activity through Akt-dependent cell division control protein 42 homolog/Ras-related C3 botulinum toxin substrate 1 stimulation (143), and enhance the formation of network structures *(141)* The clinical relevance of the above findings has been validated recently in the case of diabetes. Leicht *et al. (144),* proved that adiponectin-pretreated endothelial progenitors isolated from diabetic patients exhibited markedly improved neovascularization capabilities in nude mice xenografts. Thus, the proangiogenic role of adiponectin may contribute to its potent antidiabetic effects. In the context of carcinogenesis, *in vivo* studies employing the MMTV-PyMT mouse mammary tumor model have found a positive influence of adiponectin on tumor vasculature. Denzel *et al.* showed that tumors from adiponectin null mice exhibited reduced growth and angiogenesis along with increased hypoxia and apoptosis. These results were confirmed by Landskroner-Eiger *et al.* (68), for early stages of mouse mammary tumorigenesis (9wk). Surprisingly, at 12 to 14 wk of age, when tumors characteristically progress to late carcinomas, adiponectin deficiency led to opposite effects, enhancing tumor growth and metabolic activity (68). Increased mobilization of circulating endothelial progenitors, along with up-regulated VEGF-A expression in tumor tissues, possibly fueled tumor growth (68). Additionally, the tumors exhibited greater aggressiveness, as seen by transcriptional profiling (68), and increased pulmonary metastases (69) Landskroner-Eiger *et al.* (68), hypothesized that the observed antiangiogenic stress and reduced nutrient/oxygen flow triggered an adaptive mechanism enabling the tumor cells at later stages to circumvent impairments caused by adiponectin deficiency. Accumulating evidence suggests that T-cadherin may mediate the effects of adiponectin on tumor neovascularization. T-Cadherin was found to be selectively expressed in intratumoral capillaries of human HCC, whereas no expression was detected in nonneoplastic hepatocytes (145). Furthermore, adiponectin and T-cadherin were shown to colocalize in tumor vasculature (67) ,(69), and the association was lost upon T-cadherin deficiency, accompanied by increased serum adiponectin levels (67). Moreover, adiponectin (69), and T-cadherin (67), null mice exhibited striking parallels in mammary tumor growth and phenotype. Thus, T-cadherin seems to be necessary for adiponectin-mediated signaling at the level of endothelial cells, possibly by regulating the bioavailability of circulating adiponectin or by interacting with other receptors. The coincident reduction of T-cadherin and AdipoR2 in mouse mammary tumors supports the latter notion (69). On the other hand, there are studies arguing for an antiangiogenic role of adiponectin. Adiponectin directly binds to proangiogenic growth factors(59), and inhibits both the production of TNF-α from macrophages and its action on endothelial cells (146). Considering the fact that TNF-α can stimulate angiogenesis (147), these results provide evidence for an indirect effect of adiponectin on the vasculature. Importantly, mouse xenograft experiments directly contradict the above-mentioned *in vivo* proangiogenic findings. Bråkenhielm *et al.(135),* demonstrated that adi-ponectin treatment inhibits growth of murine fibrosarcoma cells sc injected into mice. The underlying mechanism involved loss of growth-enhancing angiogenesis (135). *In vitro* experiments revealed that adiponectin specifically reduced endothelial cell proliferation and migration and induced caspase 8-mediated apoptosis (135). Similar results were obtained in a mouse model of liver carcinogenesis. Adiponectin treatment reduced tumor growth and invasiveness and decreased microvessel density while inhibiting endothelial tube formation *in vitro*. Down-regulation of Rho-associated kinase, interferon-_ inducible protein 10, MMP9, angiopoietin 1, and VEGF was found to be implicated (54). Furthermore, adiponectin inhibited neovascularization in peritoneal metastases of gastric cancer cells injected into nude mice (21). One possible explanation for the observed controversies lies in the mouse models used. Evidence for the

antiangiogenic role of adiponectin was obtained from xenografts, whereas support for a proangiogenic effect of adiponectin came from MMTV-PyMT mouse mammary tumor models. Autochthonous tumors may replicate human disease more accurately than transplants (148). Importantly, contradictions between the two models have been noted, especially in the case of angiogenesis, suggesting that variability in the respective microenvironments might exert different influences on vascularization (149). Usage of bacterially produced adiponectin as seen in the antiangiogenic studies, and variations in the preparation of the recombinant protein could also be problematic in recapitulating the human condition (68). In summary, the role of adiponectin in tumor angiogenesis remains to be defined. One possibility is that adiponectin differentially affects physiological and pathological angiogenesis, as has been reported for statins (150). Additionally, the influence of adiponectin might depend on cancer cell type, as can be seen in the previously discussed effects of adiponectin on proliferation. In the case of mammary tumors, however, direct comparison between the used models argues for a general proangiogenic contribution of adiponectin. The MMTV-PyMT model has been suggested to closely recapitulate human disease (68),(69). Moreover, the decline in adiponectin levels during tumor progression, along with the accelerated tumor growth under adiponectin deficiency in later stages of the disease (68), is consistent with epidemiological findings associating low adiponectin levels in women with increased breast cancer risk (151), higher histological grade (27), and metastases (33). Thus, not angiogenesis but hypoxia induced by hypoadiponectinemia along with increased selective pressure may be more detrimental for human cancer progression, allowing tumors to assume a highly aggressive phenotype (69). The general antitumorigenic role of adiponectin therefore remains consistent with a possible proangiogenic function.

4. Conclusion

Adiponectin, the most abundant adipokine produced by the human adipose tissue, is linked to obesity, metabolic syndrome, insulin resistance, type 2 diabetes, coronary heart disease, inflammation, and several types of cancer. adiponectin exerts an insulin-sensitizing action via an enhancement of AMPK and PPARα, this having profound effects on fatty acid oxidation and inflammation. Drugs affecting the levels of adiponectin may have a role in the treatment of NAFLD, cardiovascular disease, type II diabetes, and possibly in preventing metabolic syndrome-related cancers.

Several in-vitro and in-vivo studies have marked progress in exploring the physiological mechanism via which adiponectin exerts its action. Clinical studies aimed at reducing the deleterious effects of a number of ailments have been undertaken and this, in conjunction with a better understanding of the adiponectin genetic bases for these processes and the cellular events that underlie them should enhance our ability to devise new and better approaches aimed at minimizing the adverse effects of these diseases.

A new adiponectin-based short peptide, ADP 355, mimicking adiponectin action, restricted proliferation in a dose-dependent manner in several adiponectin receptor-positive cancer cell lines, modulated several key adiponectin signaling pathways (AMPK, Akt, STAT3, ERK1/2), and suppressed the growth of orthotopic human breast cancer xenografts

5. Reference

1. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. Journal of Biological chemistry. 1995;270(45):26746-9.
2. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arteriosclerosis, thrombosis, and vascular biology. 2000;20(6):1595-9.
3. Whitehead J, Richards A, Hickman I, Macdonald G, Prins J. Adiponectin–a key adipokine in the metabolic syndrome. Diabetes, Obesity and Metabolism. 2006;8(3):264-80.
4. Takahashi M, Arita Y, Yamagata K, Matsukawa Y, Okutomi K, Horie M, et al. Genomic structure and mutations in adipose-specific gene, adiponectin. International journal of obesity. 2000;24(7):861.
5. Combs TP, Berg AH, Rajala MW, Klebanov S, Iyengar P, Jimenez-Chillaron JC, et al. Sexual differentiation, pregnancy, calorie restriction, and aging affect the adipocyte-specific secretory protein adiponectin. Diabetes. 2003;52(2):268-76.
6. Nishizawa H, Shimomura I, Kishida K, Maeda N, Kuriyama H, Nagaretani H, et al. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. Diabetes. 2002;51(9):2734-41.
7. Saito K, Tobe T, Minoshima S, Asakawa S, Sumiya J, Yoda M, et al. Organization of the gene for gelatin-binding protein (GBP28). Gene. 1999;229(1):67-73.
8. Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Molecular and cellular endocrinology. 2010;316(2):129-39.
9. Maury E, Brichard S. Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Molecular and cellular endocrinology. 2010;314(1):1-16.
10. Tsuchihashi H, Yamamoto H, Maeda K, Ugi S, Mori T, Shimizu T, et al. Circulating concentrations of adiponectin, an endogenous lipopolysaccharide neutralizing protein, decrease in rats with polymicrobial sepsis. Journal of Surgical Research. 2006;134(2):348-53.
11. Walkey AJ, Rice TW, Konter J, Ouchi N, Shibata R, Walsh K. Plasma adiponectin and mortality in critically ill subjects with acute respiratory failure. Critical care medicine. 2010;38(12):2329.
12. Kaplan JM, Denenberg A, Monaco M, Nowell M, Wong H, Zingarelli B. Changes in peroxisome proliferator-activated receptor-gamma activity in children with septic shock. Intensive care medicine. 2010;36(1):123-30.
13. Kim AY, Lee YS, Kim KH, Lee JH, Lee HK, Jang S-H, et al. Adiponectin represses colon cancer cell proliferation via AdipoR1-and-R2-mediated AMPK activation. Molecular endocrinology. 2010;24(7):1441-52.
14. Byeon JS, Jeong JY, Kim MJ, Lee SM, Nam WH, Myung SJ, et al. Adiponectin and adiponectin receptor in relation to colorectal cancer progression. International journal of cancer. 2010;127(12):2758-67.
15. Sugiyama M, Takahashi H, Hosono K, Endo H, Kato S, Yoneda K, et al. Adiponectin inhibits colorectal cancer cell growth through the AMPK/mTOR pathway. International journal of oncology. 2009;34(2):339.

16. Carvajal-Carmona LG, Spain S, Kerr D, Houlston R, Cazier J-B, Tomlinson I. Common variation at the adiponectin locus is not associated with colorectal cancer risk in the UK. Human molecular genetics. 2009;18(10):1889-92.
17. Williams CJ, Mitsiades N, Sozopoulos E, Hsi A, Wolk A, Nifli A-P, et al. Adiponectin receptor expression is elevated in colorectal carcinomas but not in gastrointestinal stromal tumors. Endocrine-related cancer. 2008;15(1):289-99.
18. Partida-Pérez M, de la Luz Ayala-Madrigal M, Peregrina-Sandoval J, Macías-Gómez N, Moreno-Ortiz J, Leal-Ugarte E, et al. Association of LEP and ADIPOQ common variants with colorectal cancer in Mexican patients. Cancer Biomarkers. 2010;7(3):117-21.
19. Habeeb BS, Kitayama J, Nagawa H. Adiponectin supports cell survival in glucose deprivation through enhancement of autophagic response in colorectal cancer cells. Cancer science. 2011;102(5):999-1006.
20. Saxena NK, Fu PP, Nagalingam A, Wang J, Handy J, Cohen C, et al. Adiponectin modulates C-jun N-terminal kinase and mammalian target of rapamycin and inhibits hepatocellular carcinoma. Gastroenterology. 2010;139(5):1762-73. e5.
21. Ishikawa M, Kitayama J, Yamauchi T, Kadowaki T, Maki T, Miyato H, et al. Adiponectin inhibits the growth and peritoneal metastasis of gastric cancer through its specific membrane receptors AdipoR1 and AdipoR2. Cancer science. 2007;98(7):1120-7.
22. Konturek PC, Burnat G, Rau T, Hahn EG, Konturek S. Effect of adiponectin and ghrelin on apoptosis of Barrett adenocarcinoma cell line. Digestive diseases and sciences. 2008;53(3):597-605.
23. Cong L, Gasser J, Zhao J, Yang B, Li F, Zhao AZ. Human adiponectin inhibits cell growth and induces apoptosis in human endometrial carcinoma cells, HEC-1-A and RL95–2. Endocrine-related cancer. 2007;14(3):713-20.
24. Zakikhani M, Dowling RJ, Sonenberg N, Pollak MN. The effects of adiponectin and metformin on prostate and colon neoplasia involve activation of AMP-activated protein kinase. Cancer prevention research. 2008;1(5):369-75.
25. Grossmann ME, Mizuno NK, Bonorden MJ, Ray A, Sokolchik I, Narasimhan ML, et al. Role of the adiponectin leptin ratio in prostate cancer. Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics. 2009;18(5-1):269-77.
26. Bub JD, Miyazaki T, Iwamoto Y. Adiponectin as a growth inhibitor in prostate cancer cells. Biochemical and biophysical research communications. 2006;340(4):1158-66.
27. Sun Y, Lodish HF. Adiponectin deficiency promotes tumor growth in mice by reducing macrophage infiltration. PLoS One. 2010;5(8):e11987.
28. Drabkin HA, Gemmill RM. Obesity, cholesterol, and clear-cell renal cell carcinoma (RCC). Advances in cancer research. 2010;107:39-56.
29. Jardé T, Perrier S, Vasson M-P, Caldefie-Chézet F. Molecular mechanisms of leptin and adiponectin in breast cancer. European journal of cancer. 2011;47(1):33-43.
30. Jardé T, Caldefie-Chézet F, Goncalves-Mendes N, Mishellany F, Buechler C, Penault-Llorca F, et al. Involvement of adiponectin and leptin in breast cancer: clinical and in vitro studies. Endocrine-related cancer. 2009;16(4):1197-210.
31. Li G, Cong L, Gasser J, Zhao J, Chen K, Li F. Mechanisms Underlying the Anti-Proliferative Actions of Adiponectin in Human Breast Cancer Cells, MCF7–Dependency on the cAMP/Protein Kinase-A Pathway. Nutrition and cancer. 2011;63(1):80-8.
32. Cleary MP, Grossmann ME. Obesity and breast cancer: the estrogen connection. Endocrinology. 2009;150(6):2537-42.

33. Dieudonne M-N, Bussiere M, Dos Santos E, Leneveu M-C, Giudicelli Y, Pecquery R. Adiponectin mediates antiproliferative and apoptotic responses in human MCF7 breast cancer cells. Biochemical and biophysical research communications. 2006;345(1):271-9.
34. Körner A, Pazaitou-Panayiotou K, Kelesidis T, Kelesidis I, Williams CJ, Kaprara A, et al. Total and high-molecular-weight adiponectin in breast cancer: in vitro and in vivo studies. The Journal of Clinical Endocrinology & Metabolism. 2007;92(3):1041-8.
35. Nakayama S, Miyoshi Y, Ishihara H, Noguchi S. Growth-inhibitory effect of adiponectin via adiponectin receptor 1 on human breast cancer cells through inhibition of S-phase entry without inducing apoptosis. Breast cancer research and treatment. 2008;112(3):405-10.
36. Grossmann ME, Ray A, Dogan S, Mizuno NK, Cleary MP. Balance of adiponectin and leptin modulates breast cancer cell growth. Cell research. 2008;18(11):1154.
37. Liu J, Lam JB, Chow KH, Xu A, Lam KS, Moon RT, et al. Adiponectin stimulates Wnt inhibitory factor-1 expression through epigenetic regulations involving the transcription factor specificity protein 1. Carcinogenesis. 2008;29(11):2195-202.
38. Dos Santos E, Benaitreau D, Dieudonne M-N, Leneveu M-C, Serazin V, Giudicelli Y, et al. Adiponectin mediates an antiproliferative response in human MDA-MB 231 breast cancer cells. Oncol Rep. 2008;20(4):971-7.
39. Wang Y, Lam JB, Lam KS, Liu J, Lam MC, Hoo RL, et al. Adiponectin modulates the glycogen synthase kinase-3β/β-catenin signaling pathway and attenuates mammary tumorigenesis of MDA-MB-231 cells in nude mice. Cancer research. 2006;66(23):11462-70.
40. Pfeiler GH, Buechler C, Neumeier M, Schäffler A, Schmitz G, Ortmann O, et al. Adiponectin effects on human breast cancer cells are dependent on 17-ss estradiol. Oncology reports. 2008;19(3):787-93.
41. Nakajima TE, Yamada Y, Hamano T, Furuta K, Gotoda T, Katai H, et al. Adipocytokine levels in gastric cancer patients: resistin and visfatin as biomarkers of gastric cancer. Journal of gastroenterology. 2009;44(7):685-90.
42. Vona-Davis L, Rose DP. Adipokines as endocrine, paracrine, and autocrine factors in breast cancer risk and progression. Endocrine-related cancer. 2007;14(2):189-206.
43. Lang K, Ratke J. Leptin and Adiponectin: new players in the field of tumor cell and leukocyte migration. Cell Communication and Signaling. 2009;7(1):27.
44. Ogunwobi OO, Beales IL. Adiponectin stimulates proliferation and cytokine secretion in colonic epithelial cells. Regulatory peptides. 2006;134(2):105-13.
45. Vrieling A, Buck K, Kaaks R, Chang-Claude J. Adult weight gain in relation to breast cancer risk by estrogen and progesterone receptor status: a meta-analysis. Breast cancer research and treatment. 2010;123(3):641-9.
46. Chen D-C, Chung Y-F, Yeh Y-T, Chaung H-C, Kuo F-C, Fu O-Y, et al. Serum adiponectin and leptin levels in Taiwanese breast cancer patients. Cancer letters. 2006;237(1):109-14.
47. Jeong Y-J, Bong J-G, Park S-H, Choi J-H, Oh H-K. Expression of leptin, leptin receptor, adiponectin, and adiponectin receptor in ductal carcinoma in situ and invasive breast cancer. Journal of breast cancer. 2011;14(2):96-103.
48. Sharma D, Wang J, Fu PP, Sharma S, Nagalingam A, Mells J, et al. Adiponectin antagonizes the oncogenic actions of leptin in hepatocellular carcinogenesis. Hepatology. 2010;52(5):1713-22.
49. Kang JH, Lee YY, Yu BY, Yang B-S, Cho K-H, Yoon DK, et al. Adiponectin induces growth arrest and apoptosis of MDA-MB-231 breast cancer cell. Archives of pharmacal research. 2005;28(11):1263-9.

50. Nkhata KJ, Ray A, Schuster TF, Grossmann ME, Cleary MP. Effects of adiponectin and leptin co-treatment on human breast cancer cell growth. Oncology reports. 2009;21(6):1611.
51. Arditi J, Venihaki M, Karalis K, Chrousos G. Antiproliferative effect of adiponectin on MCF7 breast cancer cells: a potential hormonal link between obesity and cancer. Hormone and Metabolic Research. 2007;39(01):9-13.
52. Taliaferro-Smith L, Nagalingam A, Zhong D, Zhou W, Knight B, Oberlick E, et al. Abstract# 5332: Adiponectin-mediated inhibition of metastatic properties of breast cancer cells involves upregulation of tumor suppressor gene, LKB1 and modulation of AMPK-S6K axis. AACR; 2009.
53. Kim K-y, Baek A, Hwang J-E, Choi YA, Jeong J, Lee M-S, et al. Adiponectin-activated AMPK stimulates dephosphorylation of AKT through protein phosphatase 2A activation. Cancer research. 2009;69(9):4018-26.
54. Man K, Ng KT, Xu A, Cheng Q, Lo CM, Xiao JW, et al. Suppression of liver tumor growth and metastasis by adiponectin in nude mice through inhibition of tumor angiogenesis and downregulation of Rho kinase/IFN-inducible protein 10/matrix metalloproteinase 9 signaling. Clinical Cancer Research. 2010;16(3):967-77.
55. Tang CH, Lu ME. Adiponectin increases motility of human prostate cancer cells via adipoR, p38, AMPK, and NF-κB pathways. The Prostate. 2009;69(16):1781-9.
56. Chiu Y-C, Shieh D-C, Tong K-M, Chen C-P, Huang K-C, Chen P-C, et al. Involvement of AdipoR receptor in adiponectin-induced motility and α2β1 integrin upregulation in human chondrosarcoma cells. Carcinogenesis. 2009;30(10):1651-9.
57. Aaronson SA. Growth factors and cancer. Science. 1991;254(5035):1146.
58. Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, et al. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB–binding protein and regulates growth factor–induced common postreceptor signal in vascular smooth muscle cell. Circulation. 2002;105(24):2893-8.
59. Wang Y, Lam KS, Xu JY, Lu G, Xu LY, Cooper GJ, et al. Adiponectin inhibits cell proliferation by interacting with several growth factors in an oligomerization-dependent manner. Journal of Biological Chemistry. 2005;280(18):18341-7.
60. Takemura Y, Osuga Y, Yamauchi T, Kobayashi M, Harada M, Hirata T, et al. Expression of adiponectin receptors and its possible implication in the human endometrium. Endocrinology. 2006;147(7):3203-10.
61. Fenton JI, Birmingham JM, Hursting SD, Hord NG. Adiponectin blocks multiple signaling cascades associated with leptin-induced cell proliferation in ApcMin/+ colon epithelial cells. International journal of cancer. 2008;122(11):2437-45.
62. Zhang R, Wu J, Liu D, Shan H, Zhang J. Anti-inflammatory effect of full-length adiponectin and proinflammatory effect of globular adiponectin in esophageal adenocarcinoma cells. Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics. 2013;21(1):15-21.
63. Fenton JI, Birmingham JM. Adipokine regulation of colon cancer: Adiponectin attenuates interleukin-6-induced colon carcinoma cell proliferation via STAT-3. Molecular carcinogenesis. 2010;49(7):700-9.
64. Rondini EA, Harvey AE, Steibel JP, Hursting SD, Fenton JI. Energy balance modulates colon tumor growth: interactive roles of insulin and estrogen. Molecular carcinogenesis. 2011;50(5):370-82.
65. Goldstein BJ, Scalia R. Adiponectin: a novel adipokine linking adipocytes and vascular function. The Journal of Clinical Endocrinology & Metabolism. 2004;89(6):2563-8.

66. Holland WL, Miller RA, Wang ZV, Sun K, Barth BM, Bui HH, et al. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. Nature medicine. 2011;17(1):55-63.
67. Hebbard LW, Garlatti M, Young LJ, Cardiff RD, Oshima RG, Ranscht B. T-cadherin supports angiogenesis and adiponectin association with the vasculature in a mouse mammary tumor model. Cancer research. 2008;68(5):1407-16.
68. Landskroner-Eiger S, Qian B, Muise ES, Nawrocki AR, Berger JP, Fine EJ, et al. Proangiogenic contribution of adiponectin toward mammary tumor growth in vivo. Clinical Cancer Research. 2009;15(10):3265-76.
69. Denzel MS, Hebbard LW, Shostak G, Shapiro L, Cardiff RD, Ranscht B. Adiponectin deficiency limits tumor vascularization in the MMTV-PyV-mT mouse model of mammary cancer. Clinical Cancer Research. 2009;15(10):3256-64.
70. Mihaylova MM, Shaw RJ. The AMP-activated protein kinase (AMPK) signaling pathway coordinates cell growth, autophagy, & metabolism. Nature cell biology. 2012;13(9):1016.
71. Motoshima H, Goldstein BJ, Igata M, Araki E. AMPK and cell proliferation–AMPK as a therapeutic target for atherosclerosis and cancer. The Journal of physiology. 2006;574(1):63-71.
72. Barb D, Neuwirth A, Mantzoros C, Balk S. Adiponectin signals in prostate cancer cells through Akt to activate the mammalian target of rapamycin pathway. Endocrine-related cancer. 2007;14(4):995-1005.
73. Sablina AA, Hahn WC. The role of PP2A A subunits in tumor suppression. Cell adhesion & migration. 2007;1(3):140-1.
74. Vara JÁF, Casado E, de Castro J, Cejas P, Belda-Iniesta C, González-Barón M. PI3K/Akt signalling pathway and cancer. Cancer treatment reviews. 2004;30(2):193-204.
75. Lam JB, Chow KH, Xu A, Lam KS, Liu J, Wong N-S, et al. Adiponectin haploinsufficiency promotes mammary tumor development in MMTV-PyVT mice by modulation of phosphatase and tensin homolog activities. PloS one. 2009;4(3):e4968.
76. Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. Oncogene. 2007;26(22):3279.
77. Miyazaki T, Bub JD, Uzuki M, Iwamoto Y. Adiponectin activates c-Jun NH 2-terminal kinase and inhibits signal transducer and activator of transcription 3. Biochemical and biophysical research communications. 2005;333(1):79-87.
78. Bowman T, Garcia R, Turkson J, Jove R. STATs in oncogenesis. Oncogene. 2000;19(21):2474.
79. Karim RZ, Scolyer RA, Tse GM, Tan P-H, Putti TC, Lee CS. Pathogenic mechanisms in the initiation and progression of mammary phyllodes tumours. Pathology. 2009;41(2):105-17.
80. Turecková J, Kucerová D, Vojtechová M, Sloncová E, Tuhácková Z. Expression of b-catenin is regulated by PI-3 kinase and sodium butyrate in colorectal cancer cells. International journal of molecular medicine. 2006;17(1):69-76.
81. Karin M, Cao Y, Greten FR, Zhi-Wei L. NF-[kappa] B in cancer: from innocent bystander to major culprit. Nature reviews Cancer. 2002;2(4):301.
82. Fruehauf JP, Meyskens FL. Reactive oxygen species: a breath of life or death? Clinical Cancer Research. 2007;13(3):789-94.
83. Park J, Euhus DM, Scherer PE. Paracrine and endocrine effects of adipose tissue on cancer development and progression. Endocrine reviews. 2011;32(4):550-70.
84. Brown KA, Simpson ER. Obesity and breast cancer: progress to understanding the relationship. Cancer research. 2010;70(1):4-7.

85. Fox EM, Andrade J, Shupnik MA. Novel actions of estrogen to promote proliferation: integration of cytoplasmic and nuclear pathways. Steroids. 2009;74(7):622-7.
86. Silva CM. Role of STATs as downstream signal transducers in Src family kinase-mediated tumorigenesis. Oncogene. 2004;23(48):8017.
87. Mutoh M, Teraoka N, Takasu S, Takahashi M, Onuma K, Yamamoto M, et al. Loss of adiponectin promotes intestinal carcinogenesis in Min and wild-type mice. Gastroenterology. 2011;140(7):2000-8. e2.
88. Otani K, Kitayama J, Yasuda K, Nio Y, Iwabu M, Okudaira S, et al. Adiponectin suppresses tumorigenesis in ApcMin/+ mice. Cancer letters. 2010;288(2):177-82.
89. Nishihara T, Baba M, Matsuda M, Inoue M, Nishizawa Y, Fukuhara A, et al. Adiponectin deficiency enhances colorectal carcinogenesis and liver tumor formation induced by azoxymethane in mice. World J Gastroenterol. 2008;14(42):6473-80.
90. Moon H-S, Chamberland JP, Aronis K, Tseleni-Balafouta S, Mantzoros CS. Direct role of adiponectin and adiponectin receptors in endometrial cancer: in vitro and ex vivo studies in humans. Molecular cancer therapeutics. 2011;10(12):2234-43.
91. Sonoshita M, Takaku K, Sasaki N, Sugimoto Y, Ushikubi F, Narumiya S, et al. Acceleration of intestinal polyposis through prostaglandin receptor EP2 in Apc [Delta] 716 knockout mice. Nature medicine. 2001;7(9):1048.
92. Kamada Y, Matsumoto H, Tamura S, Fukushima J, Kiso S, Fukui K, et al. Hypoadiponectinemia accelerates hepatic tumor formation in a nonalcoholic steatohepatitis mouse model. Journal of hepatology. 2007;47(4):556-64.
93. White PB, True EM, Ziegler KM, Wang SS, Swartz-Basile DA, Pitt HA, et al. Insulin, leptin, and tumoral adipocytes promote murine pancreatic cancer growth. Journal of Gastrointestinal Surgery. 2010;14(12):1888-94.
94. Endo H, Hosono K, Fujisawa T, Takahashi H, Sugiyama M, Yoneda K, et al. Involvement of JNK pathway in the promotion of the early stage of colorectal carcinogenesis under high-fat dietary conditions. Gut. 2009;58(12):1637-43.
95. Yan L, DeMars LC. Effects of dietary fat on spontaneous metastasis of Lewis lung carcinoma in mice. Clinical & experimental metastasis. 2010;27(8):581-90.
96. Yun JP, Behan JW, Heisterkamp N, Butturini A, Klemm L, Ji L, et al. Diet-induced obesity accelerates acute lymphoblastic leukemia progression in two murine models. Cancer Prevention Research. 2010;3(10):1259-64.
97. Zyromski NJ, Mathur A, Pitt HA, Wade TE, Wang S, Nakshatri P, et al. Obesity potentiates the growth and dissemination of pancreatic cancer. Surgery. 2009;146(2):258-63.
98. Rogozina OP, Bonorden MJ, Seppanen CN, Grande JP, Cleary MP. Effect of chronic and intermittent calorie restriction on serum adiponectin and leptin and mammary tumorigenesis. Cancer Prevention Research. 2011;4(4):568-81.
99. Fujisawa T, Endo H, Tomimoto A, Sugiyama M, Takahashi H, Saito S, et al. Adiponectin suppresses colorectal carcinogenesis under the high-fat diet condition. Gut. 2008;57(11):1531-8.
100. Bullen JW, Bluher S, Kelesidis T, Mantzoros CS. Regulation of adiponectin and its receptors in response to development of diet-induced obesity in mice. American Journal of Physiology-Endocrinology and Metabolism. 2007;292(4):E1079-E86.
101. Lin S, Thomas T, Storlien L, Huang X. Development of high fat diet-induced obesity and leptin resistance in C57Bl/6J mice. International journal of obesity. 2000;24(5):639.
102. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. Cancer Epidemiology and Prevention Biomarkers. 2009;18(10):2569-78.

103. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. Nature Reviews Cancer. 2004;4(7):505-18.
104. Manousos O, Souglakos J, Bosetti C, Tzonou A, Chatzidakis V, Trichopoulos D, et al. IGF-I and IGF-II in relation to colorectal cancer. International journal of cancer. 1999;83(1):15-7.
105. Moschos SJ, Mantzoros CS. The role of the IGF system in cancer: from basic to clinical studies and clinical applications. Oncology. 2002;63(4):317-32.
106. Petridou E, Dessypris N, Spanos E, Mantzoros C, Skalkidou A, Kalmanti M, et al. Insulin-like growth factor-I and binding protein-3 in relation to childhood leukaemia. International journal of cancer. 1999;80(4):494-6.
107. Bohlke K, Cramer DW, Trichopoulos D, Mantzoros CS. Insulin-like growth factor-I in relation to premenopausal ductal carcinoma in situ of the breast. Epidemiology. 1998;9(5):570-3.
108. Wolk A, Mantzoros CS, Andersson S-O, Bergström R, Signorello LB, Lagiou P, et al. Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study. Journal of the National Cancer Institute. 1998;90(12):911-5.
109. Spentzos D, Cannistra SA, Grall F, Levine DA, Pillay K, Libermann TA, et al. IGF axis gene expression patterns are prognostic of survival in epithelial ovarian cancer. Endocrine-related cancer. 2007;14(3):781-90.
110. Petridou E, Skalkidou A, Dessypris N, Moustaki M, Mantzoros C, Spanos E, et al. Insulin-like growth factor binding protein-3 predicts survival from acute childhood leukemia. Oncology. 2001;60(3):252-7.
111. Petridou E, Skalkidou A, Dessypris N, Moustaki M, Mantzoros C, Spanos E, et al. Endogenous risk factors for childhood leukemia in relation to the IGF system (Greece). Cancer Causes and Control. 2000;11(8):765-71.
112. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. The Journal of Clinical Endocrinology & Metabolism. 2001;86(5):1930-5.
113. Arita Y. Reprint of "paradoxical decrease of an adipose-specific protein, adiponectin, in obesity". Biochemical and biophysical research communications. 2012;425(3):560-4.
114. Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, et al. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin implications for metabolic regulation and bioactivity. Journal of Biological Chemistry. 2003;278(11):9073-85.
115. Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nature medicine. 2002;8(7):731.
116. Stefan N, Vozarova B, Funahashi T, Matsuzawa Y, Weyer C, Lindsay RS, et al. Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. Diabetes. 2002;51(6):1884-8.
117. Wang C, Mao X, Wang L, Liu M, Wetzel MD, Guan K-L, et al. Adiponectin sensitizes insulin signaling by reducing p70 S6 kinase-mediated serine phosphorylation of IRS-1. Journal of Biological Chemistry. 2007;282(11):7991-6.
118. Cowerd RB, Asmar MM, Alderman JM, Alderman EA, Garland AL, Busby WH, et al. Adiponectin lowers glucose production by increasing SOGA. The American journal of pathology. 2010;177(4):1936-45.
119. Furukawa K, Hori M, Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, et al. Adiponectin down-regulates acyl-coenzyme A: cholesterol acyltransferase-1 in cultured human monocyte-derived macrophages. Biochemical and biophysical research communications. 2004;317(3):831-6.

120. Paillasse MR, De Medina P, Amouroux G, Mhamdi L, Poirot M, Silvente-Poirot S. Signaling through cholesterol esterification: a new pathway for the cholecystokinin 2 receptor involved in cell growth and invasion. Journal of lipid research. 2009;50(11):2203-11.
121. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 2009;30(7):1073-81.
122. Kim S, Keku TO, Martin C, Galanko J, Woosley JT, Schroeder JC, et al. Circulating levels of inflammatory cytokines and risk of colorectal adenomas. Cancer research. 2008;68(1):323-8.
123. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, et al. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood. 2000;96(5):1723-32.
124. Wulster-Radcliffe MC, Ajuwon KM, Wang J, Christian JA, Spurlock ME. Adiponectin differentially regulates cytokines in porcine macrophages. Biochemical and biophysical research communications. 2004;316(3):924-9.
125. Kumada M, Kihara S, Ouchi N, Kobayashi H, Okamoto Y, Ohashi K, et al. Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. Circulation. 2004;109(17):2046-9.
126. Lovren F, Pan Y, Quan A, Szmitko PE, Singh KK, Shukla PC, et al. Adiponectin primes human monocytes into alternative anti-inflammatory M2 macrophages. American Journal of Physiology-Heart and Circulatory Physiology. 2010;299(3):H656-H63.
127. Ouedraogo R, Gong Y, Berzins B, Wu X, Mahadev K, Hough K, et al. Adiponectin deficiency increases leukocyte-endothelium interactions via upregulation of endothelial cell adhesion molecules in vivo. The Journal of clinical investigation. 2007;117(6):1718-26.
128. Takemura Y, Ouchi N, Shibata R, Aprahamian T, Kirber MT, Summer RS, et al. Adiponectin modulates inflammatory reactions via calreticulin receptor–dependent clearance of early apoptotic bodies. The Journal of clinical investigation. 2007;117(2):375-86.
129. Kim K-y, Kim JK, Han SH, Lim J-S, Kim KI, Cho DH, et al. Adiponectin is a negative regulator of NK cell cytotoxicity. The Journal of Immunology. 2006;176(10):5958-64.
130. Tsang JYS, Li D, Ho D, Peng J, Xu A, Lamb J, et al. Novel immunomodulatory effects of adiponectin on dendritic cell functions. International immunopharmacology. 2011;11(5):604-9.
131. Okamoto Y, Folco EJ, Minami M, Wara A, Feinberg MW, Sukhova GK, et al. Adiponectin inhibits the production of CXC receptor 3 chemokine ligands in macrophages and reduces T-lymphocyte recruitment in atherogenesis. Circulation research. 2008;102(2):218-25.
132. Yokota T, Meka CR, Kouro T, Medina KL, Igarashi H, Takahashi M, et al. Adiponectin, a fat cell product, influences the earliest lymphocyte precursors in bone marrow cultures by activation of the cyclooxygenase-prostaglandin pathway in stromal cells. The Journal of Immunology. 2003;171(10):5091-9.
133. Folco EJ, Rocha VZ, López-Ilasaca M, Libby P. Adiponectin inhibits pro-inflammatory signaling in human macrophages independent of interleukin-10. Journal of Biological chemistry. 2009;284(38):25569-75.
134. Kerbel RS. Tumor angiogenesis: past, present and the near future. Carcinogenesis. 2000;21(3):505-15.
135. Bråkenhielm E, Veitonmäki N, Cao R, Kihara S, Matsuzawa Y, Zhivotovsky B, et al. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(8):2476-81.
136. Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. Nature reviews Cancer. 2008;8(8):592.

137. Ouchi N, Kobayashi H, Kihara S, Kumada M, Sato K, Inoue T, et al. Adiponectin stimulates angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling in endothelial cells. Journal of Biological Chemistry. 2004;279(2):1304-9.
138. Kobayashi H, Ouchi N, Kihara S, Walsh K, Kumada M, Abe Y, et al. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. Circulation research. 2004;94(4):e27-e31.
139. Shibata R, Ouchi N, Kihara S, Sato K, Funahashi T, Walsh K. Adiponectin stimulates angiogenesis in response to tissue ischemia through stimulation of amp-activated protein kinase signaling. Journal of Biological Chemistry. 2004;279(27):28670-4.
140. Chandrasekar B, Boylston WH, Venkatachalam K, Webster NJ, Prabhu SD, Valente AJ. Adiponectin blocks interleukin-18-mediated endothelial cell death via APPL1-dependent AMP-activated protein kinase (AMPK) activation and IKK/NF-κB/PTEN suppression. Journal of Biological Chemistry. 2008;283(36):24889-98.
141. Shibata R, Skurk C, Ouchi N, Galasso G, Kondo K, Ohashi T, et al. Adiponectin promotes endothelial progenitor cell number and function. FEBS letters. 2008;582(11):1607-12.
142. Yang H, Zhang R, Mu H, Li M, Yao Q, Chen C. Adiponectin promotes endothelial cell differentiation from human peripheral CD14 positive monocytes in vitro. Journal of Surgical Research. 2006;130(2):203.
143. Nakamura N, Naruse K, Matsuki T, Hamada Y, Nakashima E, Kamiya H, et al. Adiponectin promotes migration activities of endothelial progenitor cells via Cdc42/Rac1. FEBS letters. 2009;583(15):2457-63.
144. Leicht SF, Schwarz TM, Hermann PC, Seissler J, Aicher A, Heeschen C. Adiponectin pretreatment counteracts the detrimental effect of a diabetic environment on endothelial progenitors. Diabetes. 2011;60(2):652-61.
145. Adachi Y, Takeuchi T, Sonobe H, Ohtsuki Y. An adiponectin receptor, T-cadherin, was selectively expressed in intratumoral capillary endothelial cells in hepatocellular carcinoma: possible cross talk between T-cadherin and FGF-2 pathways. Virchows Archiv. 2006;448(3):311-8.
146. Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-κB signaling through a cAMP-dependent pathway. Circulation. 2000;102(11):1296-301.
147. Rose D, Komninou D, Stephenson G. Obesity, adipocytokines, and insulin resistance in breast cancer. Obesity reviews. 2004;5(3):153-65.
148. Talmadge JE, Singh RK, Fidler IJ, Raz A. Murine models to evaluate novel and conventional therapeutic strategies for cancer. The American journal of pathology. 2007;170(3):793-804.
149. Sikder H, Huso DL, Zhang H, Wang B, Ryu B, Hwang ST, et al. Disruption of Id1 reveals major differences in angiogenesis between transplanted and autochthonous tumors. Cancer cell. 2003;4(4):291-9.
150. Sata M, Nishimatsu H, Osuga J-i, Tanaka K, Ishizaka N, Ishibashi S, et al. Statins augment collateral growth in response to ischemia but they do not promote cancer and atherosclerosis. Hypertension. 2004;43(6):1214-20.
151. Mantzoros C, Petridou E, Dessypris N, Chavelas C, Dalamaga M, Alexe DM, et al. Adiponectin and breast cancer risk. The Journal of Clinical Endocrinology & Metabolism. 2004;89(3):1102-7.