Cancer Biol Med 2016. doi: 10.28092/j.issn.2095-3941.2015.0092

REVIEW

Evolving role of adiponectin in cancer-controversies and update

Arnav Katira[1], Peng H. Tan[1, 2]

[1]UCL Medical School, UCL Faculty of Medical Science, University College London, London WC1E 6BT, UK; [2]Breast Unit, Whittington Health, London N19 5NF, UK

ABSTRACT Adiponectin (APN), an adipokine produced by adipocytes, has been shown to have a critical role in the pathogenesis of obesity-associated malignancies. Through its receptor interactions, APN may exert its anti-carcinogenic effects including regulating cell survival, apoptosis and metastasis via a plethora of signalling pathways. Despite the strong evidence supporting this notion, some work may indicate otherwise. Our review addresses all controversies critically. On the whole, hypoadiponectinaemia is associated with increased risk of several malignancies and poor prognosis. In addition, various genetic polymorphisms may predispose individuals to increased risk of obesity-associated malignancies. We also provide an updated summary on therapeutic interventions to increase APN levels that are of key interest in this field. To date efforts to manipulate APN levels have been promising, but much work remains to be done.

KEYWORDS Adiponectin; cancer; therapeutic target

Introduction

Obesity is defined as a chronic and excessive growth of adipose tissue. It is a growing health problem worldwide and has been described as a "global pandemic". Thus, obesity-associated diseases provide a substantial public health challenge, as they are a major cause of avoidable mortality and morbidity. In particular, excess adiposity is thought to be associated with about 20% of all cancers[1].

Adipose tissue, originally thought as a passive depot for fat metabolism, is being increasingly recognized as an active endocrine organ. It secretes a wide array of bioactive molecules called adipocytokines, which act as key mediators in several obesity-associated diseases. Amongst these adipocytokines, adiponectin (APN), also known as the "guardian angel cytokine", has been proposed as having a key role in the pathogenesis of obesity-associated cancers along with other diseases such as cardiovascular disease[2] and type 2 diabetes[3,4]. It is important to stress that adipocytes also produce many pro-inflammatory adipocytokines that have been implicated in the pathogenesis of cancer. The production harmony of these countering adipocytokines may represent the beauty of nature regulating oneself. Dysregulation of this harmony may signify the early development of diseases such as carcinogenesis.

Tempering this axis of disharmony may represent an opportunity to correct disease process. Hence, the possibility of targeting APN and its signalling pathways therapeutically has led to a surge in interest in this field and several recent developments, which we are reviewing here.

APN structure

APN is produced mainly from white adipose tissue, but also in lower quantities from brown adipose tissue[5]. Reports are also found suggesting that APN is expressed, but at much lower concentrations, in several other tissues such as skeletal muscle[6], cardiomyocytes[7], liver[8], bone marrow[9] and cerebrospinal fluid[10].

Monomeric APN is a 30kDa gylcoprotein composed of 244 amino acids[11]. APN is encoded on human chromosome 3q27 by the ADIPOQ gene[12]. Structurally, APN consists of a signal peptide domain at the N-terminus, a short variable region, a collagenous domain and a C-terminal globular domain, which is homologous to C1q[13]. Thus, with its C-terminal domain, APN structurally belongs to the C1q/tumor necrosis factor (TNF) superfamily[14].

Correspondence to: Peng H. Tan
E-mail: peng.tan@nhs.net
Received October 23, 2015; accepted January 5, 2016.
Available at www.cancerbiomed.org

A globular version of APN (gAcrp) also exists at small concentrations in plasma. It comprises of the C-terminal globular domain formed from proteolytic cleavage. Full-length APN (flAcrp) can exist in a variety of different isoforms (**Figure 1**), with monomeric APN able to trimerize to form low molecular weight (LMW) APN. Two trimers can then self-associate to form a middle molecular weight (MMW) hexamers. The trimers are also able to form 12- or 18-mers [high molecular weight (HMW) APN] via disulphide bonds. Post-translational modifications are thought to be critical to oligomer formation, particularly HMW APN. These post-translational modifications are also important for APN's receptor binding and biological activity. Monomeric APN is thought to be found only in adipocytes, whereas oligomeric APN is present in the circulation at concentrations of around 5-30 μg/mL. Active HMW or flAcrp appears to be present at higher concentrations, but LMW and gAcrp are also present in the circulation at low levels, possibly because of a shorter half-life. The HMW isoform is the most biologically active. The different isoforms of APN may also mediate different effects in different tissues. For example, the HMW isoform has been suggested to mediate the pro-inflammatory actions of APN, whereas the LMW isoform may be responsible for its anti-inflammatory activity[15].

However, APN concentration levels are thought to be altered in various disease states, with them being reduced in type 2 diabetes[16], coronary heart disease and atherosclerosis[17], as well as obesity and insulin resistance[18]. In addition, APN levels have been seen to be reduced in several cancers.

APN receptors

To date, three APN receptors have been discovered. These are AdipoR1[16], AdipoR2[16] and the more recently found T-Cadherin[19].

The two classical APN receptors, AdipoR1 and AdipoR2, are seven transmembrane domain receptors with an internal N-terminal region and an external C-terminal region. This structure is the opposite of that seen in other G-protein coupled receptors[16]. These two receptors have highly comparable structures with their protein sequences sharing 67% homology[20]. AdipoR1 is a 42.4kDa protein, whereas AdipoR2 is a 35.4kDa protein. Recent study of the crystal structures of these two receptors shows that they have a large cavity, where three histidine residues co-ordinate a zinc ion[21]. This is seen to be crucial to APN receptor interactions such as 5' adenosine monophosphate-actiavted protein kinase (AMPK) phosphorylation and uncoupling protein 2(UCP2) upregulation[21].

Studies utilizing small-interfering RNA (siRNA) show that AdpoR1 has a high affinity for gAcrp and a low affinity for flAcrp, whereas AdipoR2 has moderate affinity for both gAcrp and flAcrp[16]. AdipoR1 is ubiquitously expressed and is particularly abundant in skeletal muscle and endothelial cells, whereas AdipoR2 is highly present in the liver[22]. AdipoR1 and AdipoR2 may form both homo- and heteromultimers. Both of these receptors have been detected in almost every normal and malignant tissue, but one receptor usually prevails in each tissue. In obese individuals, AdipoR1 and AdipoR2 expression seems to be reduced[23], which thus leads

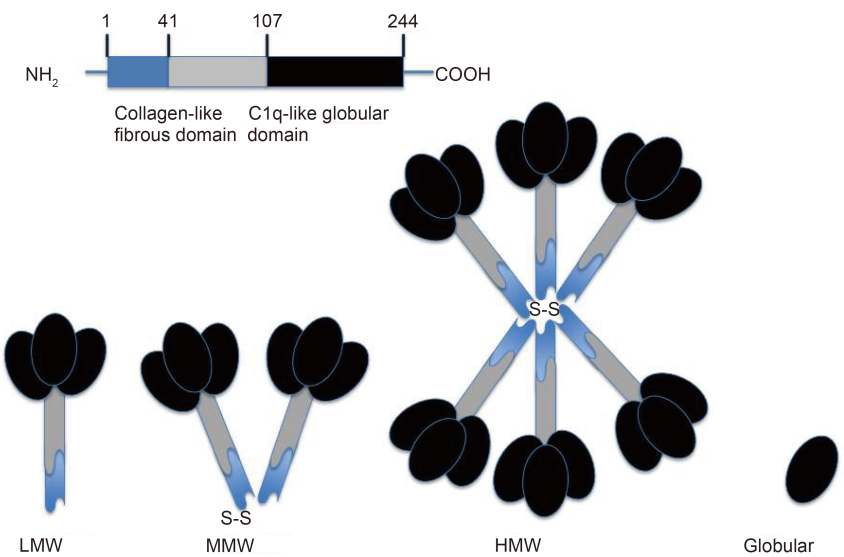

Figure 1 APN's structure. This figure depicts APN's structure molecularly and schematically.

to decreased sensitivity to APN.

In addition, the third non-classical receptor for APN is T-cadherin, which is a glycosylphospatidylinositol-anchored protein that lacks a transmembrane domain. This cell-surface receptor is found in endothelial, epithelial and smooth muscle cells. T-cadherin is encoded on the cadherin-13 gene and can bind MMW and HMW APN, but not trimeric or globular APN[24]. Calcium dependent mechanisms are seen to be crucial to T-cadherin signalling[24].

Genetic mutation of all receptors has been noted. For example, no missense or nonsense mutations in AdipoR1/R2 were detected in patients with severe insulin resistance. It was shown that none of the 24 polymorphisms (allele frequency of 2.3%-48.3%) tested was associated with the type 2 diabetes. It was concluded that genetic variation in AdipoR1/R2 is not a major cause of insulin resistance in humans, nor does it contribute in a significant manner to type 2 diabetes risks[25]. Of course, this is only a small study, and therefore further exploration on genetic mutation of APN or its receptor may offer better understanding on the interplay of disease and genetics.

APN signalling

APN binds to its receptors and subsequently modulates a plethora of signalling pathways, exerting a variety of complex metabolic and immunological effects. These effects are mostly mediated via AMPK[17,26-28], mitogen activating protein kinase (MAPK)[28,29], phospho inositide 3-Kinase (PI3K)/Akt[27,28], mammalian target of rapamycin (mTOR)[30], c-Jun N-terminal kinase (cJNK)[31,32], signal transducer and activator of transcription 3 (STAT-3), sphingolipids[33], Wnt[34], and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)[28] signalling. These anti-cancer signalling pathways are summarized in **Figure 2**.

A large proportion of APN's effects are exerted via the AMPK pathway[26,27]. A tumor microenvironment often exhibits certain features such as hypoxia, redox imbalance and nutrient starvation[35-37]. These features can lead to an increase in the AMP/ATP ratio and hence AMPK activation[38,39]. This has several pleiotropic metabolic effects, which generally restore cellular energy. AMPK also disrupts cellular growth signalling via mTOR and thus exerts its anti-cancer effects[40,41]. This inhibition of the mTOR pathway decreases translation via S6 kinase (S6K) and the eukaryotic translation initiation factor 4E binding protein-1 4EBP1 phosphorylation pathways via tuberous sclerosis 2 (TSC2) phosphorylation[30]. AMPK is also able to promote growth arrest and apoptosis via enhanced p53 and p21 expression[42].

APN also exerts its effects via the PI3K/Akt axis[26]. Activation of PI3K leads to a cascade of events resulting in cellular survival, growth and proliferation[43,44], and an

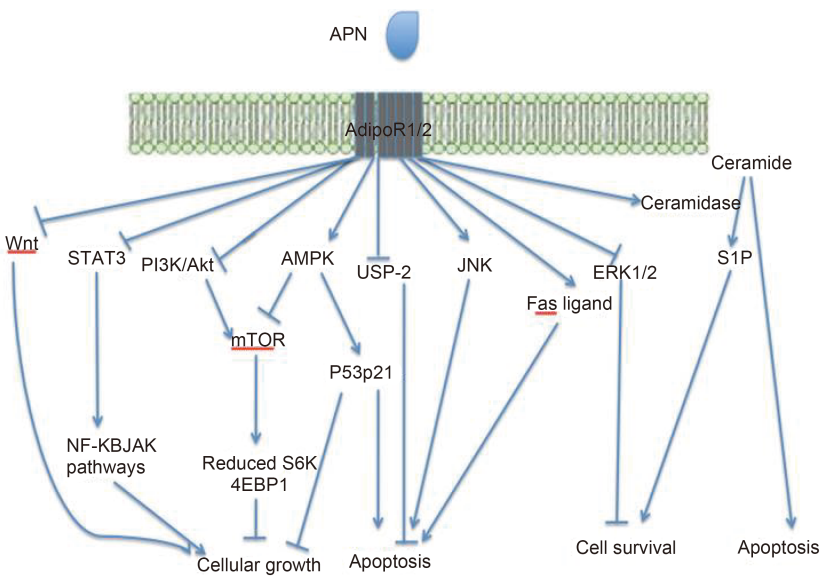

Figure 2 A summary of the cancer protective signalling pathways modulated by APN *in vivo*. APN may activate or inhibit these pathways either when it is presented directly or indirectly to AdipoR1/2. APN activates AMPK, Fas ligand and JNK, whereas it inhibits Wnt, STAT3, PI3K/Akt, USP-2, and ERK1/2. APN also promotes ceramidase activity, increasing the conversion of ceramide to S1P. Arrowheads: activating pathways; Blunt ends: suppressive pathways.

increase in glycolysis and fatty acid synthesis[45]. APN has been seen to have direct[46] and indirect[47] inhibitory effects on the PI3K/Akt pathway. Akt also has opposing effects to AMPK on TSC2, inhibiting its action[37,48,49].

Moreover, APN influences the MAPK cascade, which involves cJNK, MAPKp38 and extracellular signal-regulated kinases (ERK)1/2. cJNK and MAPKp38 are seen to have variable effects on cell proliferation and apoptosis, whereas ERK1/2 has largely mitogenic effects[50]. APN treatment has been seen to cause increased cJNK signalling and hence apoptosis via caspase 3 in a HC cell line[51]. Indeed, APN has also been shown to activate other caspases such as 8 and 9 in order to promote apoptosis[52]. APN has inhibitory effects on ERK1/2 signalling, which in BC[53], LC[54] and EC[55] cells has been shown to lead to reduced cell viability. APN treatment in BC cells led to an increase in p53 and Bax expression and a decrease in c-myc, cyclin D and Bcl-2 (B-cell CLL/Lymphoma 2) expression, which subsequently led to cell cycle arrest and apoptosis[56].

STAT3 has several cancer-causing effects including increasing tumor cell proliferation, survival, angiogenesis and invasion, as well as inhibiting anti-tumor immunity[57]. STAT3 can stimulate pro-oncogenic inflammatory pathways such as NF-κB and interleukin (IL)-6-Janus tyrosine kinase (GP130 JAK) pathways, and inhibit anti-tumor pathways such as STAT1- and NF-κB-mediated T-helper cell (Th1) pathways[57]. As well as its direct effects as a transcription factor, STAT3 is seen to have epigenetic effects on gene expression and also modulates mitochondrial functions[58]. gAcrp and flArcp have both been seen to inhibit STAT3 activation in PrC and HC lines[59, 60].

APN is also thought to have inhibitory effects on Wnt signalling[34]. Wnt binds to its receptor, frizzled, in order to inactivate glycogen synthase-3β (GSK3β) and to enhance nuclear accumulation of β-catenin[34]. Wnt signalling has positive effects on cellular growth and proliferation. APN has been shown to stimulate Wnt-inhibitory factor 1, which antagonises Wnt signalling and cancer progression[61]. APN has also been shown to modulate Wnt signalling in MDA-MB-231 BC cells[62].

Furthermore, APN was seen to decrease ubiquitin specific protease 2 (USP-2) expression in HC and BC cells[63] and thus this may be important in APN's anti-proliferative effects via cyclin D1 degradation[64]. USP-2 has also been seen to prevent apoptosis[65] and cause malignant transformation, via p53 regulation[66], in prostate cancer cells.

As well as decreasing cyclin D1 activity, gAcrp has been shown to increase p27 activity in HC (HepG2) and BC [Michigan Cancer Foundation-7 (MCF-7)] cells[67]. p27 has been considered as a tumor suppressor gene, with p27 dysfunction causing excess cell cycle activity and carcinogenosis[68]. In these HepG2 and MCF-7 cell lines, gAcrp induced Fas ligand activity and hence promoted apoptosis[67].

However, it must be remembered that APN has also been shown to have proliferative effects on cancer cells[69]. For example, APN binding to AdipoR1/R2 can also promote ceramidase activity, which subsequently acts to enhance ceramide catabolism to the proliferation enhancer and anti-apoptotic metabolite sphingosine-1-phosphate (S1P)[33]. In general, it is thought that higher APN concentrations may have a proliferative effect and lead to tumor growth, whereas lower concentrations are generally thought to have anti-carcinogenic effects. Furthermore, the presence of various isoforms of APN further complicates the picture and is a reason for the pleiotropic effects seen.

APN in cancer

Obesity is seen as a risk factor for several cancers and thus, it is thought that adipokines such as APN may act as crucial mediators in the pathogenesis of obesity-associated malignancies. Generally, serum APN levels are seen to be reduced in cancer. Here we will look at several examples of cancers where APN levels are seen to confer altered risk and prognosis for the patients affected.

Serial measurements of adipokines during cancer diagnosis and its treatments have elegantly demonstrated[70]. In children with acute lymphoblastic leukemia (ALL), low serum APN, and high serum leptin and resistin level were present at diagnosis[70]. Adipocytokines alterations are progressively restored during therapy, representing the success of treatment and good health. One should not undermine the complexity of disease and its treatment, these observations merely indicate the association of adipocytokines, cancer and cancer therapy.

Breast cancer (BC)

Miyoshi et al.[71] first highlighted the relationship between hypoadiponectinaemia and increased BC risk, where BC patients with lower APN levels being more likely to show a more aggressive phenotype. A recent meta-analysis of 8 observational studies found that low APN levels are associated with increased risk of BC in post-, but not pre-menopausal women[72]. The risk reduction from higher APN levels has been reported to be around 65%-80% in early BC patients[73].

However, some studies have produced inconsistent and confusing results, with one study showing no association between APN levels and BC risk[74]. This may in part be explained by the presence of different isoforms of APN. In particular, low levels of the HMW isoform may be predictive of increased BC risk, especially in post-menopausal women[75].

Although the mechanisms by which APN exerts its protective effects in BC are largely unknown, it has been proposed that one mechanism may involve APN altering the sensitivity of peripheral tissue to insulin. Insulin levels are generally increased when APN levels are lower and hence these increased insulin levels may induce BC cell proliferation via insulin and insulin-like growth factor 1 (IGF-1) receptor function[72].

Further work went on to establish that BC treatments might alter the balance of adipokines to favour anti-cancer state. A decreased leptin to APN ratio (LAR) were found in hormonal therapy groups[76]. These changes might have occurred through both mechanisms of hormonal therapy and body composition changes. It has been suggested that hormonal treatment may exert their protective effects for BC patients by decreasing LAR.

Our own work has also indicated that a normal serum APN was noted in the stage I and II BC, however, its level decreased with the progression of stages, to a level that was statistically significantly[28]. This work indicates that the disharmony of adipokines become very obvious when the disease advancing despite its treatments (either with chemotherapy or hormonal treatment). The treatment may try to restore the normal harmony of adipocytokine production, but ultimately the final stage of disease shapes the landscape of these adipocytokines. Therefore, many have argued that the serial measurement of adipocytokines maybe a good surrogate marker for the disease progression.

APN may also regulate the expression levels of various molecules such as MAPK, Bax, p53, Bcl2, AMPK, p42/p44 MAPK, cyclin D1 and β-catenin[72]. APN can also reduce the proliferation of BC cells independent of estrogen receptor status[62].

Furthermore, single nucleotide polymorphisms (SNPs) for ADIPOQ (rs2241766 and rs1501299) and ADIPOR1 (rs7539542) were significantly associated with BC risk[77,78]. The importance of this association may also be influenced by ethnicity[78]. However, one study did not find any significant association between ADIPOQ, ADIPOR1 and ADIPOR2 SNPs and BC risk[79].

Colorectal cancer (CRC)

Obesity, insulin resistance and hyperinsulinaemia have all been associated with CRC pathophysiology. A negative correlation between plasma APN levels and CRC risk has been shown by several studies and meta-analyses[80-83]. It has been suggested that APN interactions with AdipoR1 are more important to its protective effects than interactions with AdipoR2 as seen using AdipoR1 and 2 knockout mice models[84]. This group also found these protective effects to only be apparent under a high-fat but not basal diet. AdipoR1/R2 expression levels may also be increased in CRC, due to reduced APN levels[85].

APN interactions may be crucial at initial and later stages of CRC. It was seen that as APN levels decreased, the number and size of tumors increased[86]. Furthermore, APN receptor levels were seen to be significantly lower in CRC compared to adenomatous polyps[87]. AdipoR2 has also been positively linked with tumor, node and metastasis staging in CRC[88].

In vitro studies show that APN may directly affect cell proliferation, adhesion, invasion and colony formation as well as controlling metabolic (via AMPK/S6 signalling), inflammatory [via STAT3/VEGF (vascular endothelial growth factor)] and cell cycle (via p21/p27/p53/cyclins) processes in CRC cell lines[89].

It has also been suggested that certain gene polymorphisms may increase susceptibility of developing CRC. Variant rs1342387 of the ADIPOR1 gene and variants rs2241766 and rs1501299 may increase CRC risk at least in some populations[90-92].

Endometrial cancer (EC)

A significant inverse relationship has been found between APN levels and EC risk[93-97], as well as between the LAR ratio and EC risk[97]. In particular, one recent meta-analysis showed that higher APN levels were associated with a 53% reduction in EC risk[93]. This meta-analysis also identified this relationship to only be significant in post-menopausal women, whereas others argue that the relationship is stronger in pre-menopausal women[94]. Thus, clarification of these influences may be required in future studies.

APN may exert its protective effects on EC risk via several pathways and processes. One key mechanism may be via decreasing insulin levels[98] and hence reducing carcinogenesis through estrogen[99]. APN's anti-inflammatory actions may also be particularly relevant to EC[100]. Reduced MMW APN was identified as the only isoform that was an independent risk factor for EC[101], and thus may be particularly important for EC. However, the reason why this is the case is yet to be determined.

An increased frequency of ADIPOQ variant rs1063539C

was significantly associated with decreased EC risk in a recent study[102]. Another study found that ADIPOQ variants rs3774262, rs1063539 and rs12629945 were correlated with EC risk although not to a significant level[103]. No such relationship for ADIPOR1 and ADIPOR2 genes were found[103].

Gastric cancer (GC)

APN levels were seen to have a significant inverse correlation with GC risk[104,105]. GC cells lacking AdipoR1 had significantly higher lymphatic metastases and peritoneal dissemination compared to those that were AdipoR1 positive[106]. However, another study found no significant prognostic value in AdipoR1/2 expression in GC[107].

A recent study has shown that ADIPOQ variant rs266729 may be an independent prognostic risk factor for never-drinking GC patients receiving surgical treatment[108]. In addition, ADIPOQ variant rs16861205 and ADIPOR2 variants rs10773989 and rs1044471 were significantly associated with decreased risk of cardia GC[109]. However, rs16861205 was also significantly associated with increased risk of body GC[109].

Esophageal cancer (OC)

Low APN levels have been associated with increased risk of OC[110-113]. Low AdipoR1 expression was also an independent predictor for overall survival and AdipoR2 expression was inversely associated with tumor size[114].

Pancreatic cancer (PC)

An inverse relationship between APN levels and PC risk has been shown[115, 116]. However, a certain amount of heterogeneity exists in the literature, with reports of a positive correlation between APN levels and PC risk[117-119]. Thus, clarification of APN's role in the PC is needed as it may be that APN exerts unconventional roles in certain tissues. This elevation in APN concentrations seen in PC may also be a compensatory mechanism for weight loss and inflammation during cancer cachexia, and due to decreased expression of APN receptors[118].

One study also reported that the ADIPOQ SNP rs1501299 may be associated with PC risk[120].

Hepatic cancer (HC)

There appears to be significant heterogeneity in studies associating APN levels and HC risk. Higher APN levels have been associated with increased risk of primary HC in Japanese individuals with hepatitis[121]. These higher APN levels may also predict poorer survival in HC patients[122,123]. However, one study[124] found APN and AdipoR1/R2 expression levels to be significantly lower in HC patients compared to controls, and lower AdipoR1/R2 expression was associated with poor prognosis in HC patients. This proposed protective role might at least in part be mediated via thioredoxin protein-dependent apoptosis[125]. Thus, the exact role of APN in HC remains to be determined.

The rs1501299 variant of ADIPOQ may also predispose an increased risk of developing HC risk[126].

Renal cell carcinoma (RCC)

Serum APN levels have been negatively correlated with RCC, its tumor stage and its metastasis[127-129]. However, a more recent study found a positive association between APN levels and RCC risk, which appeared to vary with ethnicity[130]. This may highlight the complicated picture presented by different APN multimers in RCC. The rs182052 SNP for ADIPOQ has also recently been associated with RCC risk[131] and lower APN levels.

Prostate cancer (PrC)

Lower APN levels have been associated with increased PrC risk[132-134]. Furthermore, reduced APN levels were associated with tumor stage in obese and overweight men, but not in normal weight men or overall in all men[135]. Other studies have also found no significant association between APN levels and PrC risk[136,137]. Interestingly, APN was also seen to have anti-proliferative, but not anti-apoptotic effects on human PrC cells[138].

A study found four ADIPOQ SNPs (rs266729, rs182052, rs822391 and rs2082940) to be significantly associated with overall PrC risk[139]. However, this association may be influenced by ethnicity as it had a predominantly Caucasian population, whereas another study found no significant association between ADIPOQ and ADIPOR1 SNPs and PrC risk in African Americans[140].

Lung Cancer (LC)

Many studies have found no significant association between APN levels and lung cancer (LC) risk[141-143]. However, one study did find an increase in APN levels in LC patients compared to controls[144]. In contrast, one study[141] found

APN levels to be reduced in advanced disease patients compared to limited disease patients. Thus, the exact role of APN in LC remains to be determined.

Possible protective APN signalling interactions may be mediated via AdipoR1, as a study found AdipoR1, but not AdipoR2, expression to be positively associated with increased survival[145]. Rs266730, an APN promoter polymorphism, was also associated with LC risk in a recent study[146]. Another study found ADIPOQ variant rs2241766 to be associated with risk of non-small cell LC and its prognosis after surgery[147].

Haematological cancers

APN has been associated with various haematological cancers including leukemia, lymphoma and myeloma. APN levels were significantly lower in acute myeloid leukemia (AML) and ALL patients[148]. Hypoadiponectinaemia has also been associated with chronic myeloid leukemia (CML)[149]. Decreased levels of APN are also linked to an increased risk of myeloma[150]. APN levels were also lower in chronic lymphoid leukaemia (CLL) patients than controls[151]. In contrast, APN levels were higher in non-Hodgkin's lymphoma patients than controls[152].

The relationship between APN levels with the risk and prognosis of various cancers is summarized in **Table 1**. The altered risk of various malignancies conferred by ADIPOQ, ADIPOR1 and ADIPOR2 gene polymorphisms is summarized in **Table 2**.

APN and cancer metastasis

Metastasis is a complex and critical aspect of cancer from a clinical perspective, with it having been estimated to be the cause of around 90% of deaths from cancer[153]. However, despite its importance little is known about this process. APN has been seen to suppress many crucial metastatic processes such as adhesion, invasion and migration of BC cells[154]. This may occur in an liver kinase B1 (LKB1)-mediated manner[155]. LKB1 expression is seen to be inhibited in BC *in situ* cases associated with invasion, but not those without invasion and hence this pathway may be critical to metastasis[154]. APN's protective role against metastasis may also in part be mediated via the AMPK/Akt pathway[156].

Furthermore, APN has been seen to negatively impact upon angiogenesis and invasion in liver tumor nude mice models[157]. *In vitro* studies from this group showed that APN reduced the expression of the Rho-associated protein kinase (ROCK)/interferon gamma-induced protein 10 (IP10)/VEGF signalling and suppressed lamellipodia formation, which is required for cell migration[157].

APN was also seen to have metastatic suppressive effects in EC cells[158]. Here, APN was seen to inhibit leptin-mediated invasion, which required inactivation of JAK/STAT3 signalling and activation of the AMPK pathway. These anti-metastatic effects of APN are summarized in **Figure 3**.

How important is APN in malignancies?

Here, we present compelling evidence suggesting that APN may be a key molecule in the pathogenesis of several malignancies associated with obesity. However, it must be pointed out that this link is not a simple one, as the strength of this association seems to vary depending on factors such as tissue type, age, menopausal status, ethnicity and sex. In addition, it must be appreciated that several other important factors may also contribute to the link between obesity and malignancies. These include diet (calorie intake and specific components of the diet)[159], physical activity[160], altered insulin sensitivity[161], the action of insulin like growth factors (IGFs)[162], sex hormones[163], the NF-κB system[164], and the importance of genetics, oxidative stress and vascular growth factors independent of the action of APN. Thus, a goal of future studies will be to evaluate the relative importance of these mechanisms in cancer of different tissues and in different sub-groups.

In circumstances when the cancer is advanced, it often results in severe weight loss and cancer-related cachexia. Hyperadiponectinaemia may be noted as seen in cases with anorexia nervosa[165]. This transient and late increase in APN level has very little influence in the late phase of the pathogenesis of obesity-related cancers, as the disease modifying effects of APN has already altered the course of disease in the early phase. Moreover, it was recently reported that an increase in dendritic cell signalling of APN receptors, in particular AdipoR1/R2 following their engagement with APN can blunt the tumor-specific immune response in the patients with metastatic diseases[28]. This in fact results in a detrimental effect on ones' ability to control cancer[28]. Therefore the tempo of low or high APN level on the disease process can influence greatly the outcome of disease, depending on the stages of the cancer. The applicability of APN as a therapeutic tool to modify the disease outcome needs to take the stage of cancer into account when considering it.

Table 1 Summary of clinical data showing the association between APN and risk and prognosis of various cancers

Cancer type	Study outcome	Additional comments	Study type	Reference
BC	$P<0.005$ (for tumor size); $P<0.05$ (for grade)	>2 cm tumor and grade 2 and 3 BC cases were higher in lower tertile of serum APN	CC	71
	$P=0.001$	Total serum APN levels lower in BC patients, but APN levels not significantly associated with BC risk in premenopausal women ($P=0.829$)	Meta-analysis	72
	Adjusted OR=0.04 (0.071-0.99)	Lower APN in early BC *vs.* healthy controls	CC	73
	$P=0.43$ for linear trend	No association with risk	CC	74
	$P=0.024$	Negative correlation with HMW APN and BC risk	CC	75
CRC	$P=0.005$	CRC cases had significantly lower APN values than controls	Meta-analysis	80
	OR=0.91; $P=0.04$	Significant inverse association between APN and CRC	Meta-analysis	81
	$P=0.80$	No association between APN and CRC	CC	83
	$P<0.001$	Lower APN levels in CRC and adenoma patients	Meta-analysis	82
	$P<0.0001$	AdipoR1/R2 levels increased in CRC patients	CC	85
	OR=0.24; $P<0.001$	Lower APN in adenoma patients than controls, lower APN levels negatively associated with number and size of tumors	CC	86
	$P=0.009$ (tubular) $P<0.001$ (tubulovillous)	Lower AdipoR1/R2 levels in CRCs than colorectal adenomas	CC	87
	OR=0.72 (0.53-0.99) for CRC risk; $P=0.005$	Lower APN correlates to CRC risk; APN inversely correlates to tumor grade	CC	88
EC	Summary RR=0.40 (0.33-0.66)	High APN reduces EC risk	Meta-analysis	93
	OR=0.42 (0.19-0.94)	Inverse association with EC risk, association stronger in pre-menopausal than post-menopausal	CC	94
	OR=0.56 (0.36-0.86)	Inverse association independent of other obesity risk factors	CC	95
	OR=0.52 (0.32-0.83); $P<0.001$	Significant inverse association between EC risk and APN	CC	96
	Summary OR=0.47 (0.34-0.65) for APN Summary OR=0.45 (0.24-0.86) for APN/leptin ratio	Reduced EC risk with higher APN levels (18% risk reduction with 5 μg/mL increase in circulating APN	Meta-analysis	97
	Adjusted OR=4.89 (1.25-19.11); $P=0.022$	Lower MMW APN significantly associated with increased risk of EC	CC	101
GC	$P<0.05$	Inverse association with pathological findings e.g. tumor size, depth of invasion, tumor stage (only in undifferentiated GC)	CC	104
	$P>0.05$	No significant association between APN with GC risk and histopathological variables detected	CC	105
	$P=0.01$	Significantly longer survival time in AdipoR1 positive cases	CC	106
	$P>0.05$	No statistically significant relationship between AdipoR1/2 expression and tumor stage and survival	CC	107

Table 1 (*continued*)

Table 1 (*continued*)

Cancer type	Study outcome	Additional comments	Study type	Reference
OG (esophageal)	*P*<0.05	Significantly reduced APN in ESCC and EA patients than controls EA patients had lower APN than ESCC	CC	110
	P=0.01	Serum APN significantly reduced in patients than controls	CC	111
	P=0.043 (for T category) 0.56 (0.35-0.90); *P*=0.017 (for survival)	AdipoR2 expression was inversely associated with T-category). Low AdipoR1 was associated with improved overall survival	CC	114
PC	OR-0.55 (0.31-0.98); *P*=0.03	Higher APN negatively correlated with PC risk	CC	115
	Nonlinear relationship (*P*<0.01)	Low pre-diagnostic levels of APN associated with increased PC risk	CC	116
	P=0.0035	Median APN levels higher in PC than control group	CC	117
	OR=2.81 (1.04-7.59)	Higher APN associated with increased PC risk, no association with PC stage	CC	118
HC	Adjusted OR=3.30 (1.45-7.53); *P*<0.01 (for total APN Adjusted OR=3.41 (1.50-7.73); *P*<0.01 (for HMW APN)	Plasma total and HMW APN were higher in patients than controls serum APN was positively associated with HC risk	CC	121
	P=0.007	Increased APN staining was associated with poor survival	CC	122
	P=0.03	APN remained a significant predictor of time to death	CC	123
	P=0.005 (for APN) *P*<0.001 (for AdipoR1) *P*=0.003 (for AdipoR2)	APN and AdipoR1 levels were significantly lower in HCC cases than non-neoplastic controls AdipoR2 expression correlated with lower histological grade	CC	124
RC	OR=0.76 (0.57-1.00); *P*=0.05	Inverse association between serum APN and RCC risk	CC	127
	P<0.01 (tumor size); *P*=0.029 (non-metastatic vs metastatic)	Negative association between APN levels and tumor size Lower APN levels in metastatic cases	CC	128
	P=0.044 (for total APN); *P*=0.041 (for HMW APN)	Reduced APN levels in metastatic cases	CC	129
	OR=2.3 (1.1-4.6)	APN and RCC risk positively correlated in African American males	CC	130
PrC	Standard mean difference=-0.893 μg/mL (-1.345 to -0.440); *P*=0.000	Serum APN was lower in PrC cases than controls	Meta-analysis	132
	OR=0.29 (0.10-0.89)	Higher APN associated with reduced risk independent of various confounders	CC	133
	P<0.05	Significantly lower APN in PrC cases than controls	CC	134
	OR=0.62 (0.42-0.90); *P*=0.01	APN inversely associated with PrC stage in overweight and obese men	CC	135
	OR=0.70 (0.33-1.49); *P*=0.56	No significant association between APN and PrC risk	CC	136
LC	OR=1.13 (0.80-4.97) for cases *vs.* controls OR=0.25 (0.10-0.78) for advanced *vs.* limited	APN not significantly different between cases and controls APN significantly lower in advanced than limited diseases stage	CC	141

Table 1 (*continued*)

Table 1 (*continued*)

Cancer type	Study outcome	Additional comments	Study type	Reference
	$P>0.05$	No significant findings	CC	142
	OR=2.00 (0.80-4.97); $P=0.14$	Non significant findings	CC	143
	$P<0.0001$	Leptin: APN ratio significantly lower in patients than controls	CC	144
	$P<0.05$	AdipoR1/R2 expression higher in non-neoplastic than neoplastic tissues, patients with higher expression of AdipoR1 had longer survival	CC	145
HaemC	$P=0.00$	APN was significantly lower in AML and ALL cases than controls	CC	148
	$P<0.001$	APN levels significantly lower in CLL cases than controls	CC	151
	$P<0.05$	APN levels were higher in CLL cases than controls	CC	152

Therapeutic potential

Thus, due to its importance in the carcinogenesis and progression of several cancers, APN has been seen as a promising therapeutic target. APN may act as a possible prophylactic as well as a therapeutic. Nevertheless, efforts to engineer the APN protein have been troublesome, partly due to a lack of clarity on the effects of different APN isoforms. The requirement of post-translational modifications also further complicates the picture and means that mammalian cells are required. Hence, it may be more lucrative to screen for existing agonists or enhance endogenous APN levels.

The first APN receptor agonist that was produced is called ADP355 and it binds to both AdipoR1/R2, but with a greater affinity for AdipoR1[166]. This protein includes several non-natural amino acids, which stabilize the structure and protect it from proteolysis. *In vivo*, ADP355 inhibits orthotopic human BC xenograft growth by 31%, with an acceptable safety profile. It was also seen to regulate several signalling pathways including AMPK, PIK3/Akt, STAT3 and ERK1/2 in a manner similar to gAcrp.

More recently, this group aimed to modify ADP355 in order to potentially optimize its protective effects[167]. They showed that a substitution of the Gly4 and Tyr7 residues with Pro and Hyp led to a 5-10 fold increased agonistic activity. In addition, they also developed a chimera from ADP355 and the leptin receptor antagonist, Allo-aca. It is hypothesized that this chimera may offer the potential for combination therapy in a single chemical entity and thus, allowing a much lower dose than a physical mixture of the two individual drugs.

After screening several molecules[168], AdipoRon was seen to bind to AdipoR1/R2 at low micromolar concentrations. It was found to have similar effects to APN in muscle and liver, with downstream effects on AMPK and PPAR-α signalling[168].

Using a high throughput assay, 9 naturally occurring compounds were discovered[169]. The most active AdipoR1 ligands were matairesinol, arctiin, (-)-arctigenin and gramine, whereas the most active AdipoR2 ligands were parthenolide, taxifoliol, deoxyschizandrin and syringin. These compounds were seen to share some of the effects of APN including anti-proliferative, anti-inflammatory and anti-cancer properties.

In addition, it is also possible to augment endogenous APN levels. PPARγ ligands have been suggested as a promising means of exploiting this mechanism, with a group showing that thiazolidinediones (synthetic PPARγ ligands) can increase APN levels *in vitro* and *in vivo* in a dose- and time-dependent manner[170]. These PPARγ agonists can be either full or selective and can either augment circulating APN levels or activate APN signalling via its receptor interactions. Selective PPARγ agonists are however thought to be safer and thus show greater promise.

One such selective PPARγ agonist is efatutazone, which although it showed promise in phase 1 trials on metastatic cancer patients[171,172], failed to show sufficient efficacy in phase 2 trials and the study was thus terminated[173,174].

Other PPARγ agonists that show promise include rivoglitazone and troglitazone[175]. Rivoglitazone has been shown to have beneficial effects on the insulin resistance, type 2 diabetes and atherosclerosis *in vivo* partly through its substantial effects on APN[176,177]. However, its effects on cancer remain to be studied.

Troglitazone and its synthetic derivative Δ2-troglitazone were shown to enhance APN gene and protein expression in a dose- and time-dependent manner. Troglitazone has been

Table 2 Summary of the effects of gene polymorphisms on the risk of various cancers

Cancer type	SNP polymorphism	Outcome	Additional comments	Reference
BC	Rs2241766 (ADIPOQ)	OR=0.61 (0.46-0.80)	TG genotype significantly associated with reduced BC risk	77
	Rs1501299 (ADIPOQ)	OR=1.80 (1.14-2.85) HR=1.23 (1.059-1.43)	GG genotype significantly associated with higher BC risk	77,78
	Rs7539542 (ADIPOR1)	OR=0.51 (0.28-0.92)	CC significantly associated with reduced BC risk	77
CRC	Rs2241766 (ADIPOQ)	OR=1.433 (1.014-1.985)	TG and GG carriers significantly associated with higher CRC risk	75
	Rs1342387 (ADIPOR1)	OR=0.74 (0.57-0.97) for Ou et al study; OR=0.82 (0.72-0.94) for Ye et al study (homozygous model)	G/A and CT/TT genotypes significantly associated with reduced CRC risk	90,92
	Rs1501299 (ADIPOQ)	OR=0.723 (0.531-0.902)	GT and TT genotypes significantly associated with reduced risk of CRC	75
EC	Rs1063539 (ADIPOQ)	OR=0.39 (0.17-0.90)	CC and CG genotypes significantly associated with decreased risk	102
GC	Rs266729 (ADIPOQ)	HR=0.74 (0.56-0.97); *P*=0.032	GG/CG genotypes associated with significantly lower GC mortality	108
	Rs16861205 (ADIPOQ)	OR=0.61 (0.39-0.94)	Genotypes with minor allele A associated with decreased gastric cardia cancer risk	109
	Rs10773989 (ADIPOR2)	OR=0.70 (0.52-0.93)	Genotypes with minor allele C associated with decreased risk of gastric cardia cancer	109
	Rs1044471 (ADIPOR2)	OR=0.70 (0.52-0.95)	Genotypes with minor allele T associated with decreased risk of gastric cardia cancer	109
	Rs16861205 (ADIPOQ)	OR=1.82 (1.15-2.89)	Genotypes with minor allele A associated with increased risk of gastric body cancer	109
PC	Rs1501299 (ADIPOQ)	OR=1.86 (1.03-3.38)	CC genotypes associated with increased PC risk compared to AA genotypes	120
HC	Rs1501299 (ADIPOQ)	OR=4.33 (2.07-9.05); *P*<0.005	GG genotypes associated with increased risk of HCC compared to TT genotypes	126
RC	Rs182052 (ADIPOQ)	Adjusted OR=1.36 (1.07-1.74)	AA genotypes associated with increased risk of RCC compared to GG	131
PrC	Rs266729 (ADIPOQ)	*P*=0.049	Rare genotypes associated with increased risk	139
	Rs182052 (ADIPOQ)	*P*=0.04	Rare genotypes associated with increased risk	139
	Rs822391 (ADIPOQ)	*P*=0.04	Rare C allele associated with decreased risk	139
	Rs2082940 (ADIPOQ)	*P*=0.006	CT and TT genotypes associated with reduced risk	139
LC	Rs266730 (APN gene promoter)	*P*<0.05	G>A associated with NSCLC risk	146
	Rs2241766 (ADIPOQ)	*P*=0.012	TT genotype more prevalent in NSCLC patients than controls	147

shown to have beneficial effects *in vitro* including preventing tumor cell invasion[178]. Δ2-troglitazone was seen to be more potent at reducing cell proliferation in cancer cells[179] and may have a different side-effect profile to troglitazone[180]. However, similarly to efatutazone, phase 2 trials for troglitazone have been disappointing[181,182] uncovering little clinical value in this PPARγ ligand. There have also been some concerns regarding the risk of harmful cardiovascular effects of thiazolidinediones, especially for rosiglitazone[183]. Known agonists of AdipoR1/R2 and potential therapeutic strategies are summarized in **Table 3**.

APN may also be modulated with dietary or lifestyle factors. For example, daily intake of fish or omega-3 supplements led to increased APN levels in the range of 14%-

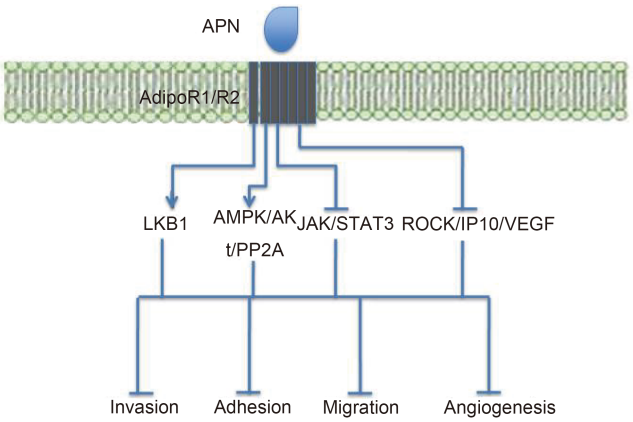

Figure 3 Summary of APN's anti-metastatic effects and the signalling pathways involved. The LKB1 and AMPK pathways inhibit metastasis, whereas JAK/STAT3 and the ROCK/IP10/VEGF pathways promote metastasis. APN activates LKB1 and AMPK signalling, and inhibits JAK/STAT3 and ROCK/IP10/VEGF signalling. These effects lead to inhibition of invasion, adhesion, cell migration and angiogenesis, overall reducing the likelihood of metastasis.

Table 3 Summary of known agonists of AdipoR1/R2 and molecules that could potentially be exploited clinically

Molecule	Comments	Reference
ADP355	Binds to both AdipoR1/R2 with greater affinity for AdipoR1. *In vivo*, ADP355 inhibits orthotopic human BC xenograft growth by 31%, with an acceptable safety profile. May activate signalling pathways similarly to gAcrp. The group tried to optimize ADP355's effects in 2015 and increased agonistic activity by a factor of 5-10	166,167
AdipoRon	Binds to AdipoR1/R2 at low micromolar concentrations. Has similar effects to APN on the muscle and liver	168
Naturally occurring compounds	Most active AdipoR1 ligands-matairesinol, arctiin, (-)-arctigenin and gramine. Most active AdipoR2 ligands- parthenolide, taxifoliol, deoxyschizandrin and syringin	169
Efatutazone	A selective PPARγ agonist showed promise in phase 1 trials, but phase 2 trials were disappointing with poor efficacy shown.	171-174
Rivoglitazone	Shown to have beneficial effects on insulin resistance, type 2 diabetes and atherosclerosis *in vivo* via APN modulation. Effects on cancer have not been studied to date	176,177
Troglitazone	Has been shown to prevent tumor cell invasion *in vivo*. Phase 2 trials have been disappointing showing little clinical value.	175,178,181,182
Δ2-Troglitazone	Synthetic derivative of troglitazone more potent than troglitazone. But not found to have any clinical value as of yet.	179,180

60%, whereas fiber supplementation led to an increase of 60%-115% in APN levels[184]. Moderately intense aerobic exercise has also been shown to elevate APN levels up to 260%[185]. Other dietary factors include coffee[186], deep yellow vegetables[187] and a Mediterranean diet[188].

However, it must be remembered that modifying these receptor interactions and thus the metabolic effects of APN receptor binding can also have important and dire effects on anti-cancer immunity[189]. Thus, we believe this will be an important consideration in future developments in APN-based anti-cancer therapies. In addition, several potential side-effects from chronic APN therapy have been proposed. These include infertility, cardiac damage and reduced bone density[190, 191].

Conclusions

Our understanding of cancer including obesity-associated malignancies is rapidly improving. APN has come under recent scrutiny as a key mediator between obesity and cancer. Hypoadiponectinaemia is often found in several cancers and associated with poor prognosis. Hence, various efforts aiming

to utilize the anti-cancer properties of APN therapeutically and prophylactically are being investigated. Furthermore, efforts to identify ADIPOQ, ADIPOR1 and ADIPOR2 SNPs that confer altered risk of cancer development may enable early screening and APN level augmentation.

We believe this field holds promise, but there remain several challenges to utilizing these treatments routinely. A deeper understanding of the cellular and molecular functions of APN in cancer is required in order for the development of effective therapies. The role of each isoform in distinct tissues and under tumor-specific conditions needs to be clarified. Furthermore, the molecular conditions under which APN acts as cancer suppressing or cancer promoting, anti-inflammatory or pro-inflammatory adipocytokine needs to be evaluated. The exact roles of each receptor and signalling pathway in different cancers also remain largely unknown. We believe these will be key steps in the pursuit of an effective APN-based cancer therapeutic. The complexity of APN influences the anti-tumor immune response and needs to be considered carefully when applying it as a therapeutic target.

Conflict of interest statement

Peng H. Tan's research activities (with Oxford University) used to be funded by Sir Peter Morris's Surgeon Scientist Programme. Currently he works full-time for the NHS (UK) trust with an honorary role with UCL.

References

1. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer. 2011; 11: 886-95.
2. Shibata R, Ouchi N, Murohara T. Adiponectin and cardiovascular disease. Circ J. 2009; 73: 608-14.
3. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med. 2001; 7: 941-6.
4. Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. Nat Med. 2001; 7: 947-53.
5. Fujimoto N, Matsuo N, Sumiyoshi H, Yamaguchi K, Saikawa T, Yoshimatsu H, et al. Adiponectin is expressed in the brown adipose tissue and surrounding immature tissues in mouse embryos. Biochim Biophys Acta. 2005; 1731: 1-12.
6. Delaigle AM, Jonas JC, Bauche IB, Cornu O, Brichard SM. Induction of adiponectin in skeletal muscle by inflammatory cytokines: in vivo and in vitro studies. Endocrinology. 2004; 145: 5589-97.
7. Piñeiro R, Iglesias MJ, Gallego R, Raghay K, Eiras S, Rubio J, et al. Adiponectin is synthesized and secreted by human and murine cardiomyocytes. FEBS Lett. 2005; 579: 5163-9.
8. Kaser S, Moschen A, Cayon A, Kaser A, Crespo J, Pons-Romero F, et al. Adiponectin and its receptors in non-alcoholic steatohepatitis. Gut. 2005; 54: 117-21.
9. Yokota T, Meka CS, Medina KL, Igarashi H, Comp PC, Takahashi M, et al. Paracrine regulation of fat cell formation in bone marrow cultures via adiponectin and prostaglandins. J Clin Invest. 2002; 109: 1303-10.
10. Kusminski CM, Mcternan PG, Schraw T, Kos K, O'hare JP, Ahima R, et al. Adiponectin complexes in human cerebrospinal fluid: distinct complex distribution from serum. Diabetologia. 2007; 50: 634-42.
11. Ayyildiz T, Dolar E, Ugras N, Adim SB, Yerci O. Association of adiponectin receptor (Adipo-R1/-R2) expression and colorectal cancer. Asian Pac J Cancer Prev. 2014; 15: 9385-90.
12. Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem. 1996; 271: 10697-703.
13. Wong GW, Wang J, Hug C, Tsao TS, Lodish HF. A family of Acrp30/adiponectin structural and functional paralogs. Proc Natl Acad Sci U S A. 2004; 101: 10302-7.
14. Rossi A, Lord J. Adiponectin inhibits neutrophil phagocytosis of Escherichia coli by inhibition of PKB and ERK 1/2 MAPK signalling and Mac-1 activation. PLoS One. 2013; 8: e69108.
15. 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. J Clin Invest. 2007; 117: 375-86.
16. Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature. 2003; 423: 762-9.
17. Shibata R, Sato K, Pimentel DR, Takemura Y, Kihara S, Ohashi K, et al. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. Nat Med. 2005; 11: 1096-103.
18. Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med. 2007; 13: 332-9.
19. 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 Res. 2008; 68: 1407-16.
20. Brochu-Gaudreau K, Rehfeldt C, Blouin R, Bordignon V, Murphy BD, Palin MF. Adiponectin action from head to toe. Endocrine. 2010; 37: 11-32.
21. Tanabe H, Fujii Y, Okada-Iwabu M, Iwabu M, Nakamura Y, Hosaka T, et al. Crystal structures of the human adiponectin receptors. Nature. 2015; 520: 312-6.
22. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors.

Endocr Rev. 2005; 26: 439-51.
23. Rasmussen MS, Lihn AS, Pedersen SB, Bruun JM, Rasmussen M, Richelsen B. Adiponectin receptors in human adipose tissue: effects of obesity, weight loss, and fat depots. Obesity (Silver Spring). 2006; 14: 28-35.
24. Hug C, Wang J, Ahmad NS, Bogan JS, Tsao TS, Lodish HF. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. Proc Natl Acad Sci U S A. 2004; 101: 10308-13.
25. Collins SC, Luan J, Thompson AJ, Daly A, Semple RK, O'rahilly S, et al. Adiponectin receptor genes: mutation screening in syndromes of insulin resistance and association studies for type 2 diabetes and metabolic traits in UK populations. Diabetologia. 2007; 50: 555-62.
26. Iwabu M, Yamauchi T, Okada-Iwabu M, Sato K, Nakagawa T, Funata M, et al. Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca(2+) and AMPK/SIRT1. Nature. 2010; 464: 1313-9.
27. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med. 2002; 8: 1288-95.
28. Tan PH, Tyrrell HE, Gao L, Xu D, Quan J, Gill D, et al. Adiponectin receptor signaling on dendritic cells blunts antitumor immunity. Cancer Res. 2014; 74: 5711-22.
29. Chang LF, Karin M. Mammalian MAP kinase signalling cascades. Nature. 2001; 410: 37-40.
30. Wendel HG, De Stanchina E, Fridman JS, Malina A, Ray S, Kogan S, et al. Survival signalling by Akt and eIF4E in oncogenesis and cancer therapy. Nature. 2004; 428: 332-7.
31. Wu Y, Song P, Zhang W, Liu J, Dai X, Liu Z, et al. Activation of AMPKα2 in adipocytes is essential for nicotine-induced insulin resistance in vivo. Nat Med. 2015; 21: 373-82.
32. Shibata R, Ouchi N, Ito M, Kihara S, Shiojima I, Pimentel DR, et al. Adiponectin-mediated modulation of hypertrophic signals in the heart. Nat Med. 2004; 10: 1384-9.
33. 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. Nat Med. 2011; 17: 55-63.
34. Karim RZ, Tse GM, Putti TC, Scolyer RA, Lee CS. The significance of the Wnt pathway in the pathology of human cancers. Pathology. 2004; 36: 120-8.
35. Svensson R, Shaw RJ. Cancer metabolism: Tumour friend or foe. Nature. 2012; 485: 590-1.
36. Pouysségur J, Dayan F, Mazure NM. Hypoxia signalling in cancer and approaches to enforce tumour regression. Nature. 2006; 441: 437-43.
37. Shaw RJ, Cantley LC. Ras, PI(3)K and mTOR signalling controls tumour cell growth. Nature. 2006; 441: 424-30.
38. Xiao B, Sanders MJ, Underwood E, Heath R, Mayer FV, Carmena D, et al. Structure of mammalian AMPK and its regulation by ADP. Nature. 2011; 472: 230-3.
39. O'Neill LA, Hardie DG. Metabolism of inflammation limited by AMPK and pseudo-starvation. Nature. 2013; 493: 346-55.
40. Majumder PK, Febbo PG, Bikoff R, Berger R, Xue Q, Mcmahon LM, et al. mTOR inhibition reverses akt-dependent prostate intraepithelial neoplasia through regulation of apoptotic and HIF-1-dependent pathways. Nat Med. 2004; 10: 594-601.
41. Engelman JA, Chen L, Tan X, Crosby K, Guimaraes AR, Upadhyay R, et al. Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. Nat Med. 2008; 14: 1351-6.
42. Motoshima H, Goldstein BJ, Igata M, Araki E. AMPK and cell proliferation-AMPK as a therapeutic target for atherosclerosis and cancer. J Physiol. 2006; 574: 63-71.
43. Yano S, Tokumitsu H, Soderling TR. Calcium promotes cell survival through CaM-K kinase activation of the protein-kinase-B pathway. Nature. 1998; 396: 584-7.
44. Cross DA, Alessi DR, Cohen P, Andjelkovich M, Hemmings BA. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature. 1996; 378: 785-9.
45. Gurumurthy S, Xie SZ, Alagesan B, Kim J, Yusuf RZ, Saez B, et al. The Lkb1 metabolic sensor maintains haematopoietic stem cell survival. Nature. 2010; 468: U75-659.
46. Habeeb BS, Kitayama J, Nagawa H. Adiponectin supports cell survival in glucose deprivation through enhancement of autophagic response in colorectal cancer cells. Cancer Sci. 2011; 102: 999-1006.
47. Lam JB, Chow KH, Xu A, Lam KS, Liu J, Wong NS, et al. Adiponectin haploinsufficiency promotes mammary tumor development in MMTV-PyVT mice by modulation of phosphatase and tensin homolog activities. PLoS One. 2009; 4: e4968.
48. Jia S, Liu Z, Zhang S, Liu P, Zhang L, Lee SH, et al. Essential roles of PI(3)K-p110beta in cell growth, metabolism and tumorigenesis. Nature. 2008; 454: 776-9.
49. Gan B, Hu J, Jiang S, Liu Y, Sahin E, Zhuang L, et al. Lkb1 regulates quiescence and metabolic homeostasis of haematopoietic stem cells. Nature. 2010; 468: 701-4.
50. Lee SH, Hu LL, Gonzalez-Navajas J, Seo GS, Shen C, Brick J, et al. ERK activation drives intestinal tumorigenesis in Apc(min/+) mice. Nat Med. 2010; 16: 665-70.
51. 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: 1762-73, 1773. e1-5.
52. 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. Proc Natl Acad Sci U S A. 2004; 101: 2476-81.
53. 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. J Clin Endocrinol Metab. 2007; 92: 1041-8.
54. Nigro E, Scudiero O, Sarnataro D, Mazzarella G, Sofia M, Bianco A, et al. Adiponectin affects lung epithelial A549 cell viability

counteracting TNFα and IL-1? toxicity through AdipoR1. Int J Biochem Cell Biol. 2013; 45: 1145-53.

55. 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. Endocr Relat Cancer. 2007; 14: 713-20.
56. Dieudonne MN, Bussiere M, Dos Santos E, Leneveu MC, Giudicelli Y, Pecquery R. Adiponectin mediates antiproliferative and apoptotic responses in human MCF7 breast cancer cells. Biochem Biophys Res Commun. 2006; 345: 271-9.
57. Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer. 2009; 9: 798-809.
58. Yu H, Lee H, Herrmann A, Buettner R, Jove R. Revisiting STAT3 signalling in cancer: new and unexpected biological functions. Nat Rev Cancer. 2014; 14: 736-46.
59. Miyazaki T, Bub JD, Uzuki M, Iwamoto Y. Adiponectin activates c-Jun NH2-terminal kinase and inhibits signal transducer and activator of transcription 3. Biochem Biophys Res Commun. 2005; 333: 79-87.
60. 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: 1713-22.
61. 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: 2195-202.
62. Wang Y, Lam JB, Lam KS, Liu J, Lam MC, Hoo RL, et al. Adiponectin modulates the glycogen synthase kinase-3beta/beta-catenin signaling pathway and attenuates mammary tumorigenesis of MDA-MB-231 cells in nude mice. Cancer Res. 2006; 66: 11462-70.
63. Nepal S, Shrestha A, Park PH. Ubiquitin specific protease 2 acts as a key modulator for the regulation of cell cycle by adiponectin and leptin in cancer cells. Mol Cell Endocrinol. 2015; 412: 44-55.
64. Shan J, Zhao W, Gu W. Suppression of cancer cell growth by promoting cyclin D1 degradation. Mol Cell. 2009; 36: 469-76.
65. Priolo C, Tang D, Brahamandan M, Benassi B, Sicinska E, Ogino S, et al. The isopeptidase USP2a protects human prostate cancer from apoptosis. Cancer Res. 2006; 66: 8625-32.
66. Stevenson LF, Sparks A, Allende-Vega N, Xirodimas DP, Lane DP, Saville MK. The deubiquitinating enzyme USP2a regulates the p53 pathway by targeting Mdm2. EMBO J. 2007; 26: 976-86.
67. Shrestha A, Nepal S, Kim MJ, Chang JH, Kim SH, Jeong GS, et al. Critical role of AMPK/FoxO3A axis in globular Adiponectin-Induced cell cycle arrest and apoptosis in cancer cells. J Cell Physiol. 2016;231:357-69.
68. Fero ML, Randel E, Gurley KE, Roberts JM, Kemp CJ. The murine gene p27Kip1 is haplo-insufficient for tumour suppression. Nature. 1998; 396: 177-80.
69. Chen MJ, Yeh YT, Lee KT, Tsai CJ, Lee HH, Wang SN. The promoting effect of adiponectin in hepatocellular carcinoma. J Surg Oncol. 2012; 106: 181-7.
70. Moschovi M, Trimis G, Vounatsou M, Katsibardi K, Margeli A, Damianos A, et al. Serial plasma concentrations of adiponectin, leptin, and resistin during therapy in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2010; 32: e8-13.
71. Miyoshi Y, Funahashi T, Kihara S, Taguchi T, Tamaki Y, Matsuzawa Y, et al. Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res. 2003; 9: 5699-704.
72. Ye J, Jia J, Dong S, Zhang C, Yu S, Li L, et al. Circulating adiponectin levels and the risk of breast cancer: a meta-analysis. Eur J Cancer Prev. 2014; 23: 158-65.
73. Mantzoros C, Petridou E, Dessypris N, Chavelas C, Dalamaga M, Alexe DM, et al. Adiponectin and breast cancer risk. J Clin Endocrinol Metab. 2004; 89: 1102-7.
74. Gaudet MM, Falk RT, Gierach GL, Lacey JV, Graubard BI, Dorgan JF, et al. Do adipokines underlie the association between known risk factors and breast cancer among a cohort of United States women? Cancer Epidemiol. 2010; 34: 580-6.
75. Guo MM, Duan XN, Cui SD, Tian FG, Cao XC, Geng CZ, et al. Circulating High-Molecular-Weight (HMW) adiponectin level is related with breast cancer risk better than total adiponectin: a Case-Control study. PLoS One. 2015; 10: e0129246.
76. Akyol M, Demir L, Alacacioglu A, Ellidokuz H, Kucukzeybek Y, Yildiz Y, et al. The effects of adjuvant endocrine treatment on serum leptin, serum adiponectin and body composition in patients with breast cancer: the izmir oncology group (IZOG) study. Chemotherapy. 2015; 61: 57-64.
77. Kaklamani VG, Sadim M, Hsi A, Offit K, Oddoux C, Ostrer H, et al. Variants of the adiponectin and adiponectin receptor 1 genes and breast cancer risk. Cancer Res. 2008; 68: 3178-84.
78. Kaklamani VG, Hoffmann TJ, Thornton TA, Hayes G, Chlebowski R, Van Horn L, et al. Adiponectin pathway polymorphisms and risk of breast cancer in African Americans and Hispanics in the Women's Health Initiative. Breast Cancer Res Treat. 2013; 139: 461-8.
79. Teras LR, Goodman M, Patel AV, Bouzyk M, Tang W, Diver WR, et al. No association between polymorphisms in LEP, LEPR, ADIPOQ, ADIPOR1, or ADIPOR2 and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2009; 18: 2553-7.
80. Xu XT, Xu Q, Tong JL, Zhu MM, Huang ML, Ran ZH, et al. Meta-analysis: circulating adiponectin levels and risk of colorectal cancer and adenoma. J Dig Dis. 2011; 12: 234-44.
81. Joshi RK, Kim WJ, Lee SA. Association between obesity-related adipokines and colorectal cancer: a case-control study and meta-analysis. World J Gastroenterol. 2014; 20: 7941-9.
82. An W, Bai Y, Deng SX, Gao J, Ben QW, Cai QC, et al. Adiponectin levels in patients with colorectal cancer and adenoma: a meta-analysis. Eur J Cancer Prev. 2012; 21: 126-33.
83. Joshi RK, Lee SA. Obesity related adipokines and colorectal cancer: a review and meta-analysis. Asian Pac J Cancer Prev. 2014; 15: 397-405.
84. 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: 1531-8.
85. Williams CJ, Mitsiades N, Sozopoulos E, Hsi A, Wolk A, Nifli AP, et al. Adiponectin receptor expression is elevated in colorectal carcinomas but not in gastrointestinal stromal tumors. Endocr Relat Cancer. 2008; 15: 289-99.
86. Otake S, Takeda H, Suzuki Y, Fukui T, Watanabe S, Ishihama K, et al. Association of visceral fat accumulation and plasma adiponectin with colorectal adenoma: evidence for participation of insulin resistance. Clin Cancer Res. 2005; 11: 3642-6.
87. Ayyildiz T, Dolar E, Ugras N, Eminler AT, Erturk B, Adim SB, et al. Adipo-R1 and adipo-R2 expression in colorectal adenomas and carcinomas. Asian Pac J Cancer Prev. 2015; 16: 367-72.
88. Gialamas SP, Petridou. Tseleni-Balafouta S, spyridopoulos TN, matsoukis IL, Kondi-Pafiti A, et al. Serum adiponectin levels and tissue expression of adiponectin receptors are associated with risk, stage, and grade of colorectal cancer. Metabolism. 2011; 60: 1530-8.
89. Moon HS, Liu X, Nagel JM, Chamberland JP, Diakopoulos KN, Brinkoetter MT, et al. Salutary effects of adiponectin on colon cancer: in vivo and in vitro studies in mice. Gut. 2013; 62: 561-70.
90. Ou Y, Chen P, Zhou Z, Li C, Liu J, Tajima K, et al. Associations between variants on ADIPOQ and ADIPOR1 with colorectal cancer risk: a Chinese case-control study and updated meta-analysis. BMC Med Genet. 2014; 15: 137.
91. Guo X, Liu J, You L, Li G, Huang Y, Li Y. Association between adiponectin polymorphisms and the risk of colorectal cancer. Genet Test Mol Biomarkers. 2015; 19: 9-13.
92. Ye J, Jiang L, Wu C, Liu A, Mao S, Ge L. Three ADIPOR1 polymorphisms and cancer risk: a Meta-Analysis of Case-Control studies. PLoS One. 2015; 10: e0127253.
93. Zheng Q, Wu H, Cao J. Circulating adiponectin and risk of endometrial cancer. PLoS One. 2015; 10: e0129824.
94. Dal Maso L, Augustin LS, Karalis A, Talamini R, Franceschi S, Trichopoulos D, et al. Circulating adiponectin and endometrial cancer risk. J Clin Endocrinol Metab. 2004; 89: 1160-3.
95. Cust AE, Kaaks R, Friedenreich C, Bonnet F, Laville M, Lukanova A, et al. Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. J Clin Endocrinol Metab. 2007; 92: 255-63.
96. Ma Y, Liu Z, Zhang Y, Lu B. Serum leptin, adiponectin and endometrial cancer risk in Chinese women. J Gynecol Oncol. 2013; 24: 336-41.
97. Gong TT, Wu QJ, Wang YL, Ma XX. Circulating adiponectin, leptin and adiponectin-leptin ratio and endometrial cancer risk: Evidence from a meta-analysis of epidemiologic studies. Int J Cancer. 2015; 137: 1967-78.
98. Lihn AS, Pedersen SB, Richelsen B. Adiponectin: action, regulation and association to insulin sensitivity. Obes Rev. 2005; 6: 13-21.
99. Dallal CM, Brinton LA, Bauer DC, Buist DS, Cauley JA, Hue TF, et al. Obesity-related hormones and endometrial cancer among postmenopausal women: a nested case-control study within the B~FIT cohort. Endocr Relat Cancer. 2013; 20: 151-60.
100. 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: 3203-10.
101. Ohbuchi Y, Suzuki Y, Hatakeyama I, Nakao Y, Fujito A, Iwasaka T, et al. A lower serum level of middle-molecular-weight adiponectin is a risk factor for endometrial cancer. Int J Clin Oncol. 2014; 19: 667-73.
102. Aminimoghaddam S, Shahrabi-Farahani M, Mohajeri-Tehrani M, Amiri P, Fereidooni F, Larijani B, et al. Epistatic interaction between adiponectin and survivin gene polymorphisms in endometrial carcinoma. Pathol Res Pract. 2015; 211: 293-7.
103. Chen X, Xiang YB, Long JR, Cai H, Cai Q, Cheng J, et al. Genetic polymorphisms in obesity-related genes and endometrial cancer risk. Cancer. 2012; 118: 3356-64.
104. Ishikawa M, Kitayama J, Kazama S, Hiramatsu T, Hatano K, Nagawa H. Plasma adiponectin and gastric cancer. Clin Cancer Res. 2005; 11: 466-72.
105. Seker M, Bilici A, Sonmez B, Ustaalioğlu BB, Gumus M, Gozu H, et al. The association of serum adiponectin levels with histopathological variables in gastric cancer patients. Med Oncol. 2010; 27: 1319-23.
106. Tsukada T, Fushida S, Harada S, Terai S, Yagi Y, Kinoshita J, et al. Adiponectin receptor-1 expression is associated with good prognosis in gastric cancer. J Exp Clin Cancer Res. 2011; 30: 107.
107. Ayyildiz T, Dolar E, Ugras N, Dizdar OS, Adim SB, Yerci O. Lack of any prognostic relationship between adiponectin receptor (Adipo R1/R2) expression for early/advanced stage gastric cancer. Asian Pac J Cancer Prev. 2014; 15: 4711-6.
108. Wu X, Chen P, Ou Y, Liu J, Li C, Wang H, et al. Association of variants on ADIPOQ and AdipoR1 and the prognosis of gastric cancer patients after gastrectomy treatment. Mol Biol Rep. 2015; 42: 355-61.
109. Ye L, Zhang ZY, Du WD, Schneider ME, Qiu Y, Zhou Y, et al. Genetic analysis of ADIPOQ variants and gastric cancer risk: a hospital-based case-control study in China. Med Oncol. 2013; 30: 658.
110. Yildirim A, Bilici M, Cayir K, Yanmaz V, Yildirim S, Tekin SB. Serum adiponectin levels in patients with esophageal cancer. Jpn J Clin Oncol. 2009; 39: 92-6.
111. Nakajima TE, Yamada Y, Hamano T, Furuta K, Oda I, Kato H, et al. Adipocytokines and squamous cell carcinoma of the esophagus. J Cancer Res Clin Oncol. 2010; 136: 261-6.
112. Konturek PC, Burnat G, Rau T, Hahn EG, Konturek S. Effect of adiponectin and ghrelin on apoptosis of Barrett adenocarcinoma cell line. Dig Dis Sci. 2008; 53: 597-605.
113. Alexandre L, Long E, Beales IL. Pathophysiological mechanisms linking obesity and esophageal adenocarcinoma. World J Gastrointest Pathophysiol. 2014; 5: 534-49.
114. Howard JM, Cathcart MC, Healy L, Beddy P, Muldoon C, Pidgeon GP, et al. Leptin and adiponectin receptor expression in oesophageal cancer. Br J Surg. 2014; 101: 643-52.
115. Stolzenberg-Solomon RZ, Weinstein S, Pollak M, Tao Y, Taylor

PR, Virtamo J, et al. Prediagnostic adiponectin concentrations and pancreatic cancer risk in male smokers. Am J Epidemiol. 2008; 168: 1047-55.

116. Bao Y, Giovannucci EL, Kraft P, Stampfer MJ, Ogino S, Ma J, et al. A prospective study of plasma adiponectin and pancreatic cancer risk in five US cohorts. J Natl Cancer Inst. 2013; 105: 95-103.
117. Chang MC, Chang YT, Su TC, Yang WS, Chen CL, Tien YW, et al. Adiponectin as a potential differential marker to distinguish pancreatic cancer and chronic pancreatitis. Pancreas. 2007; 35: 16-21.
118. Dalamaga M, Migdalis I, Fargnoli JL, Papadavid E, Bloom E, Mitsiades N, et al. Pancreatic cancer expresses adiponectin receptors and is associated with hypoleptinemia and hyperadiponectinemia: a case-control study. Cancer Causes Control. 2009; 20: 625-33.
119. Huang B, Cheng X, Wang D, Peng M, Xue Z, Da Y, et al. Adiponectin promotes pancreatic cancer progression by inhibiting apoptosis via the activation of AMPK/Sirt1/PGC-1α signaling. Oncotarget. 2014; 5: 4732-45.
120. Kuruma S, Egawa N, Kurata M, Honda G, Kamisawa T, Ueda J, et al. Case-control study of diabetes-related genetic variants and pancreatic cancer risk in Japan. World J Gastroenterol. 2014; 20: 17456-62.
121. Michikawa T, Inoue M, Sawada N, Sasazuki S, Tanaka Y, Iwasaki M, et al. Plasma levels of adiponectin and primary liver cancer risk in middle-aged Japanese adults with hepatitis virus infection: a nested case-control study. Cancer Epidemiol Biomarkers Prev. 2013; 22: 2250-7.
122. Wang SN, Yang SF, Tsai HH, Lee KT, Yeh YT. Increased adiponectin associated with poor survival in hepatocellular carcinoma. J Gastroenterol. 2014; 49: 1342-51.
123. Siegel AB, Goyal A, Salomao M, Wang S, Lee V, Hsu C, et al. Serum adiponectin is associated with worsened overall survival in a prospective cohort of hepatocellular carcinoma patients. Oncology. 2015; 88: 57-68.
124. Shin E, Yu YD, Kim DS, Won NH. Adiponectin receptor expression predicts favorable prognosis in cases of hepatocellular carcinoma. Pathol Oncol Res. 2014; 20: 667-75.
125. Xing SQ, Zhang CG, Yuan JF, Yang HM, Zhao SD, Zhang H. Adiponectin induces apoptosis in hepatocellular carcinoma through differential modulation of thioredoxin proteins. Biochem Pharmacol. 2015; 93: 221-31.
126. Cai X, Gan Y, Fan Y, Hu J, Jin Y, Chen F, et al. The adiponectin gene single-nucleotide polymorphism rs1501299 is associated with hepatocellular carcinoma risk. Clin Transl Oncol. 2014; 16: 166-72.
127. Spyridopoulos TN, Petridou ET, Skalkidou A, Dessypris N, Chrousos GP, Mantzoros CS, et al. low adiponectin levels are associated with renal cell carcinoma: a case-control study. Int J Cancer. 2007; 120: 1573-8.
128. Pinthus JH, Kleinmann N, Tisdale B, Chatterjee S, Lu JP, Gillis A, et al. Lower plasma adiponectin levels are associated with larger tumor size and metastasis in clear-cell carcinoma of the kidney. Eur Urol. 2008; 54: 866-73.
129. Horiguchi A, Ito K, Sumitomo M, Kimura F, Asano T, Hayakawa M. Decreased serum adiponectin levels in patients with metastatic renal cell carcinoma. Jpn J Clin Oncol. 2008; 38: 106-11.
130. Liao LM, Schwartz K, Pollak M, Graubard BI, Li Z, Ruterbusch J, et al. Serum leptin and adiponectin levels and risk of renal cell carcinoma. Obesity (Silver Spring). 2013; 21: 1478-85.
131. Zhang G, Gu C, Zhu Y, Luo L, Dong D, Wan F, et al. ADIPOQ polymorphism rs182052 is associated with clear cell renal cell carcinoma. Cancer Sci. 2015; 106: 687-91.
132. Liao Q, Long C, Deng Z, Bi X, Hu J. The role of circulating adiponectin in prostate cancer: a meta-analysis. Int J Biol Markers. 2015; 30: e22-31.
133. Michalakis K, Williams CJ, Mitsiades N, Blakeman J, Balafouta-Tselenis S, Giannopoulos A, et al. Serum adiponectin concentrations and tissue expression of adiponectin receptors are reduced in patients with prostate cancer: a case control study. Cancer Epidemiol Biomarkers Prev. 2007; 16: 308-13.
134. Arisan ED, Arisan S, Atis G, Palavan-Unsal N, Ergenekon E. Serum adipocytokine levels in prostate cancer patients. Urol Int. 2009; 82: 203-8.
135. Burton A, Martin RM, Holly J, Lane JA, Donovan JL, Hamdy FC, et al. Associations of adiponectin and leptin with stage and grade of PSA-detected prostate cancer: the ProtecT study. Cancer Causes Control. 2013; 24: 323-34.
136. Stevens VL, Jacobs EJ, Sun J, Gapstur SM. No association of plasma levels of adiponectin and c-peptide with risk of aggressive prostate cancer in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev. 2014; 23: 890-2.
137. Medina EA, Shi X, Grayson MH, Ankerst DP, Livi CB, Medina MV, et al. The diagnostic value of adiponectin multimers in healthy men undergoing screening for prostate cancer. Cancer Epidemiol Biomarkers Prev. 2014; 23: 309-15.
138. Gao Q, Zheng J. Adiponectin-induced antitumor activity on prostatic cancers through inhibiting proliferation. Cell Biochem Biophys. 2014; 70: 461-5.
139. Dhillon PK, Penney KL, Schumacher F, Rider JR, Sesso HD, Pollak M, et al. Common polymorphisms in the adiponectin and its receptor genes, adiponectin levels and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2011; 20: 2618-27.
140. Beebe-Dimmer JL, Zuhlke KA, Ray AM, Lange EM, Cooney KA. Genetic variation in adiponectin (ADIPOQ) and the type 1 receptor (ADIPOR1), obesity and prostate cancer in African Americans. Prostate Cancer Prostatic Dis. 2010; 13: 362-8.
141. Petridou ET, Mitsiades N, Gialamas S, Angelopoulos M, Skalkidou A, Dessypris N, et al. Circulating adiponectin levels and expression of adiponectin receptors in relation to lung cancer: two case-control studies. Oncology. 2007; 73: 261-9.
142. Karapanagiotou EM, Tsochatzis EA, Dilana KD, Tourkantonis I, Gratsias I, Syrigos KN. The significance of leptin, adiponectin, and resistin serum levels in non-small cell lung cancer (NSCLC). Lung Cancer. 2008; 61: 391-7.
143. Petridou ET, Sergentanis TN, Antonopoulos CN, Dessypris N,

Matsoukis IL, Aronis K, et al. Insulin resistance: an independent risk factor for lung cancer? Metabolism. 2011; 60: 1100-6.
144. Kerenidi T, Lada M, Tsaroucha A, Georgoulias P, Mystridou P, Gourgoulianis KI. Clinical significance of serum adipokines levels in lung cancer. Med Oncol. 2013; 30: 507.
145. Abdul-Ghafar J, Oh SS, Park SM, Wairagu P, Lee SN, Jeong Y, et al. Expression of adiponectin receptor 1 is indicative of favorable prognosis in non-small cell lung carcinoma. Tohoku J Exp Med. 2013; 229: 153-62.
146. Li Y, Yao Y, Qian X, Shi L, Zhou J, Ma Q, et al. The association of adiponectin gene promoter variations with non-small cell lung cancer in a Han Chinese population. PLoS One. 2015; 10: e0127751.
147. Cui E, Deng A, Wang X, Wang B, Mao W, Feng X, et al. The role of adiponectin (ADIPOQ) gene polymorphisms in the susceptibility and prognosis of non-small cell lung cancer. Biochemistry and Cell Biology. 2011; 89: 308-13.
148. Aref S, Ibrahim L, Azmy E, Al Ashary R. Impact of serum adiponectin and leptin levels in acute leukemia. Hematology. 2013; 18: 198-203.
149. Obeid S, Hebbard L. Role of adiponectin and its receptors in cancer. Cancer Biol Med. 2012; 9: 213-20.
150. Fowler JA, Lwin ST, Drake MT, Edwards JR, Kyle RA, Mundy GR, et al. Host-derived adiponectin is tumor-suppressive and a novel therapeutic target for multiple myeloma and the associated bone disease. Blood. 2011; 118: 5872-82.
151. Avcu F, Ural AU, Yilmaz MI, Bingol N, Nevruz O, Caglar K. Association of plasma adiponectin concentrations with chronic lymphocytic leukemia and myeloproliferative diseases. Int J Hematol. 2006; 83: 254-8.
152. Pamuk G, Turgut B, Demir M, Vural O. Increased adiponectin level in non-Hodgkin lymphoma and its relationship with interleukin-10. Correlation with clinical features and outcome. J Exp Clin Cancer Res. 2006; 25: 537-41.
153. Mehlen P, Puisieux A. Metastasis:a question of Life or death. Nat Rev Cancer. 2006; 6: 449-58.
154. Taliaferro-Smith L, Nagalingam A, Zhong D, Zhou W, Saxena NK, Sharma D. LKB1 is required for adiponectin-mediated modulation of AMPK-S6K axis and inhibition of migration and invasion of breast cancer cells. Oncogene. 2009; 28: 2621-33.
155. Saxena NK, Sharma D. Metastasis suppression by adiponectin: LKB1 rises up to the challenge. Cell Adh Migr. 2010; 4: 358-62.
156. Kim KY, Baek A, Hwang JE, Choi YA, Jeong J, Lee MS, et al. Adiponectin-activated AMPK stimulates dephosphorylation of AKT through protein phosphatase 2A activation. Cancer Res. 2009; 69: 4018-26.
157. 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. Clin Cancer Res. 2010; 16: 967-77.
158. Wu X, Yan Q, Zhang Z, Du G, Wan X. Acrp30 inhibits leptin-induced metastasis by downregulating the JAK/STAT3 pathway via AMPK activation in aggressive SPEC-2 endometrial cancer cells. Oncol Rep. 2012; 27: 1488-96.
159. Mcmillan DC, Sattar N, Mcardle CS. ABC of obesity. Obesity and cancer. BMJ. 2006; 333: 1109-11.
160. Brown JC, Winters-Stone K, Lee A, Schmitz KH. Cancer, physical activity, and exercise. Compr Physiol. 2012;2:2775-809.
161. Djiogue S, Nwabo Kamdje AH, Vecchio L, Kipanyula MJ, Farahna M, Aldebasi Y, et al. Insulin resistance and cancer: the role of insulin and IGFs. Endocr Relat Cancer. 2013; 20: R1-R17.
162. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst. 2000; 92: 1472-89.
163. Folkerd E, Dowsett M. Sex hormones and breast cancer risk and prognosis. Breast. 2013; 22: S38-43.
164. Moretti M, Bennett J, Tornatore L, Thotakura AK, Franzoso G. Cancer: NF-κB regulates energy metabolism. Int J Biochem Cell Biol. 2012; 44: 2238-43.
165. Tagami T, Satoh N, Usui T, Yamada K, Shimatsu A, Kuzuya H. Adiponectin in anorexia nervosa and bulimia nervosa. J Clin Endocrinol Metab. 2004; 89: 1833-7.
166. Otvos L, Haspinger E, La Russa F, Maspero F, Graziano P, Kovalszky I, et al. Design and development of a peptide-based adiponectin receptor agonist for cancer treatment. BMC Biotechnol. 2011; 11: 90.
167. Otvos L, Kovalszky I, Olah J, Coroniti R, Knappe D, Nollmann FI, et al. Optimization of adiponectin-derived peptides for inhibition of cancer cell growth and signaling. Biopolymers. 2015; 104: 156-66.
168. Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K, et al. A small-molecule AdipoR agonist for type 2 diabetes and short Life in obesity. Nature. 2013; 503: 493-9.
169. Sun Y, Zang Z, Zhong L, Wu M, Su Q, Gao X, et al. Identification of adiponectin receptor agonist utilizing a fluorescence polarization based high throughput assay. PLoS One. 2013; 8: e63354.
170. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, et al. PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. Diabetes. 2001; 50: 2094-9.
171. Murakami H, Ono A, Takahashi T, Onozawa Y, Tsushima T, Yamazaki K, et al. Phase I study of Efatutazone, an oral PPARγ agonist, in patients with metastatic solid tumors. Anticancer Res. 2014; 34: 5133-41.
172. Komatsu Y, Yoshino T, Yamazaki K, Yuki S, Machida N, Sasaki T, et al. Phase 1 study of efatutazone, a novel oral peroxisome proliferator-activated receptor gamma agonist, in combination with FOLFIRI as second-line therapy in patients with metastatic colorectal cancer. Invest New Drugs. 2014; 32: 473-80.
173. Boucher E, Davidenko I, Hadler D, von Roemeling R, Aprile G. PD-0008A randomized, placebo-controlled, phase 2 study of efatutazone maintenance therapy in patients with advanced colorectal cancer who have achieved disease control following first-line chemotherapy. Ann Oncol. 2014; 25(suppl 2): ii8.

174. Williams R. Discontinued in 2013: oncology drugs. Expert Opin Investig Drugs. 2015; 24: 95-110.
175. Tsai JS, Chuang LM, Chen CS, Liang CJ, Chen YL, Chen CY. Troglitazone and Δ2Troglitazone enhance adiponectin expression in monocytes/macrophages through the AMP-activated protein kinase pathway. Mediators Inflamm. 2014; 2014: 726068.
176. Kanda S, Nakashima R, Takahashi K, Tanaka J, Ogawa J, Ogata T, et al. Potent antidiabetic effects of rivoglitazone, a novel peroxisome proliferator-activated receptor-gamma agonist, in obese diabetic rodent models. J Pharmacol Sci. 2009; 111: 155-66.
177. Hiuge-Shimizu A, Maeda N, Hirata A, Nakatsuji H, Nakamura K, Okuno A, et al. Dynamic changes of adiponectin and S100A8 levels by the selective peroxisome proliferator-activated receptor-gamma agonist rivoglitazone. Arterioscler Thromb Vasc Biol. 2011; 31: 792-9.
178. Steffan JJ, Dykes SS, Coleman DT, Adams LK, Rogers D, Carroll JL, et al. Supporting a role for the GTPase Rab7 in prostate cancer progression. PLoS One. 2014; 9: e87882.
179. Wei S, Yang J, Lee SL, Kulp SK, Chen CS. PPARgamma-independent antitumor effects of thiazolidinediones. Cancer Lett. 2009; 276: 119-24.
180. Fu Y. Adiponectin signaling and metabolic syndrome. Prog Mol Biol Transl Sci. 2014; 121: 293-319.
181. Kulke MH, Demetri GD, Sharpless NE, Ryan DP, Shivdasani R, Clark JS, et al. A phase II study of troglitazone, an activator of the PPARgamma receptor, in patients with chemotherapy-resistant metastatic colorectal cancer. Cancer J. 2002; 8: 395-9.
182. Burstein HJ, Demetri GD, Mueller E, Sarraf P, Spiegelman BM, Winer EP. Use of the peroxisome proliferator-activated receptor (PPAR) gamma ligand troglitazone as treatment for refractory breast cancer: a phase II study. Breast Cancer Res Treat. 2003; 79: 391-7.
183. Lu CJ, Sun Y, Muo CH, Chen RC, Chen PC, Hsu CY. Risk of stroke with thiazolidinediones: a ten-year nationwide population-based cohort study. Cerebrovasc Dis. 2013; 36: 145-51.
184. Silva FM, De Almeida JC, Feoli AM. Effect of diet on adiponectin levels in blood. Nutr Rev. 2011; 69: 599-612.
185. Kriketos AD, Gan SK, Poynten AM, Furler SM, Chisholm DJ, Campbell LV. Exercise increases adiponectin levels and insulin sensitivity in humans. Diabetes Care. 2004; 27: 629-30.
186. Yamashita K, Yatsuya H, Muramatsu T, Toyoshima H, Murohara T, Tamakoshi K. Association of coffee consumption with serum adiponectin, leptin, inflammation and metabolic markers in Japanese workers: a cross-sectional study. Nutr Diabetes. 2012; 2: e33.
187. Tsukinoki R, Morimoto K, Nakayama K. Association between lifestyle factors and plasma adiponectin levels in Japanese men. Lipids Health Dis. 2005; 4: 27.
188. Fragopoulou E, Panagiotakos DB, Pitsavos C, Tampourlou M, Chrysohoou C, Nomikos T, et al. The association between adherence to the Mediterranean diet and adiponectin levels among healthy adults: the ATTICA study. J Nutr Biochem. 2010; 21: 285-9.
189. Katira A, Tan PH. Adiponectin and its receptor signaling: an anti-cancer therapeutic target and its implications for anti-tumor immunity. Expert Opin Ther Targets. 2015:1-21.
190. Ealey KN, Kaludjerovic J, Archer MC, Ward WE. Adiponectin is a negative regulator of bone mineral and bone strength in growing mice. Exp Biol Med (Maywood). 2008; 233: 1546-53.
191. Holland WL, Scherer PE. Cell biology. Ronning after the adiponectin receptors. Science. 2013; 342: 1460-1.

Cite this article as: Katira A, Tan PH. Evolving role of adiponectin in cancer-controversies and update. Cancer Biol Med. 2016; 13: 101-19. doi: 10.28092/j.issn.2095-3941.2015.0092