CHAPTER 5

Adiponectin-Based Therapeutics for Cancer Treatment

Dahui Li, Handi Cao, Jie Chen, Ming Liu and **Yu Wang**[*]

State Key Laboratory of Pharmaceutical Biotechnology and Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong, China

Abstract: Adiponectin is an adipokine predominantly produced from adipocytes and exerts potent growth inhibitory activity in a wide range of cancer cells. Decreased expression and/or function of adiponectin are associated with increased risks and aggressive development of cancers with poor prognoses. To restore the expression level of endogenous adiponectin and to activate its functional pathways represent promising strategies for the prevention and treatment of cancer, especially in obese patients. However, the development of recombinant adiponectin as a therapeutic agent has been hampered by the complexity of its structures and the highly diversified functionality of this magic molecule. Here, the application of different adiponectin-based prophylactics and therapeutics in cancer treatment will be thoroughly reviewed and scrutinized.

Keywords: Adiponectin, Adipokine, Cancer, Obesity, Glycosylation, Peptidomimetic, Tumor microenvironment, Angiogenesis, Therapeutics.

INTRODUCTION

Adiponectin (other names including adipocyte complement-related protein of 30 kDa (Acrp30) [1], AdipoQ [2], adipose most abundant gene transcript-1 (apM1) [3], and gelatin-binding protein of 28 kDa (GBP28) [4]) is a soluble matrix protein synthesized predominantly in the adipocytes of mammals [5 - 7]. It belongs to the expanding C1q/TNF-related protein (CTRP) family that contains 15 additional paralogs, designated as CTRP1–15 [8 - 10]. Most adiponectin paralogs are ubiquitously expressed in and secreted from multiple tissues [11]. Homologues of mammalian adiponectin have been found in plants [12 - 14], and bacteria [15 - 19]. The gene of human adiponectin (*ADIPOQ*) is located on chromosome 3q27 and encodes a 244-amino acid polypeptide [20, 21]. Polymorphisms of *ADIPOQ* affect circulating adiponectin concentration and/or

[*] **Corresponding author Yu Wang:** Department of Pharmacology and Pharmacy, Faculty of Medicine Building, 21 Sassoon Road, Pokfulam, Hong Kong, China; Tel: (852) 39176864; Fax: (852) 28170859; E-mail: yuwanghk@hku.hk

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function [22, 23], and modulates the metabolic phenotypes of obesity [24 - 26], the susceptibility to type 2 diabetes [27 - 29], the risks of coronary and cerebral artery diseases [30, 31], the severity of non-alcoholic fatty liver disease [32, 33], as well as the aggressive development of various cancers [34 - 38].

Unlike many other adipokines released from adipose tissue, adiponectin is abundantly present in the circulation and acts as a hormonal factor to regulate energy metabolism, immunity, and cellular homeostasis [39, 40]. In animals, replenishment of adiponectin decreases glucose production and restores insulin sensitivity [41 - 44], reduces visceral adiposity [45, 46], protects against hepatic steatosis and inflammatory liver diseases [47 - 51], attenuates the development of atherosclerotic vascular disease [52 - 56], and inhibits cancer development [57 - 62]. The diversified biological functions and therapeutic potentials of adiponectin have been thoroughly summarized by many excellent reviews [63 - 72]. The present chapter mainly focuses on the approaches, challenges and controversies as well as the future aspects in the development of adiponectin-based therapeutics for cancer diseases.

STUCTURAL POLYMORPHISM OF OLIGOMERIC ADIPONECTIN

The primary structure of adiponectin contains an NH_2-terminal signal peptide and a species-specific variable region, followed by a collagen-like domain with 22 Gly-X-Pro or Gly-X-Y repeats and a COOH-terminal globular domain (Fig. **1**); the latter exhibits similar three-dimensional folding topology with the pro-inflammatory cytokine, tumor necrosis factor alpha (TNF-α) [73, 74]. In adipocytes, adiponectin is synthesized as a monomeric subunit that undergoes oligomeric assembly to form trimers, hexamers, and high molecular weight (HMW) multimers (Fig. **1**) [75]. Trimerization of adiponectin is triggered by the hydrophobic interactions between the globular domains [74, 76, 77]. Two trimers are cross-linked to form hexamers *via* the disulfide bridges between the cysteine 39 residue of the variable region [78 - 80]. A number of chaperones, including endoplasmic reticulum protein 44 (ERp44), ER oxidoreductase 1-like protein alpha (Ero1-Lα) and disulfide-bond-A oxidoreductase-like protein (DsbA-L), interact with the variable region of adiponectin and facilitate the reduction of oxidized trimers and hexamers, thus assuring an efficient assembly and release of HMW oligomers [81 - 86]. Multiple trimers assemble to form the higher order structures of HMW adiponectin, resembling a “bouquet” of collagenous stalk and “blossoms” of the globular heads [87]. Hydroxylation and glycosylation of several conserved lysine residues within the collagen-like domain are indispensable for the formation of HMW adiponectin complexes (Fig. **1**) [6, 78 - 80, 88 - 90].

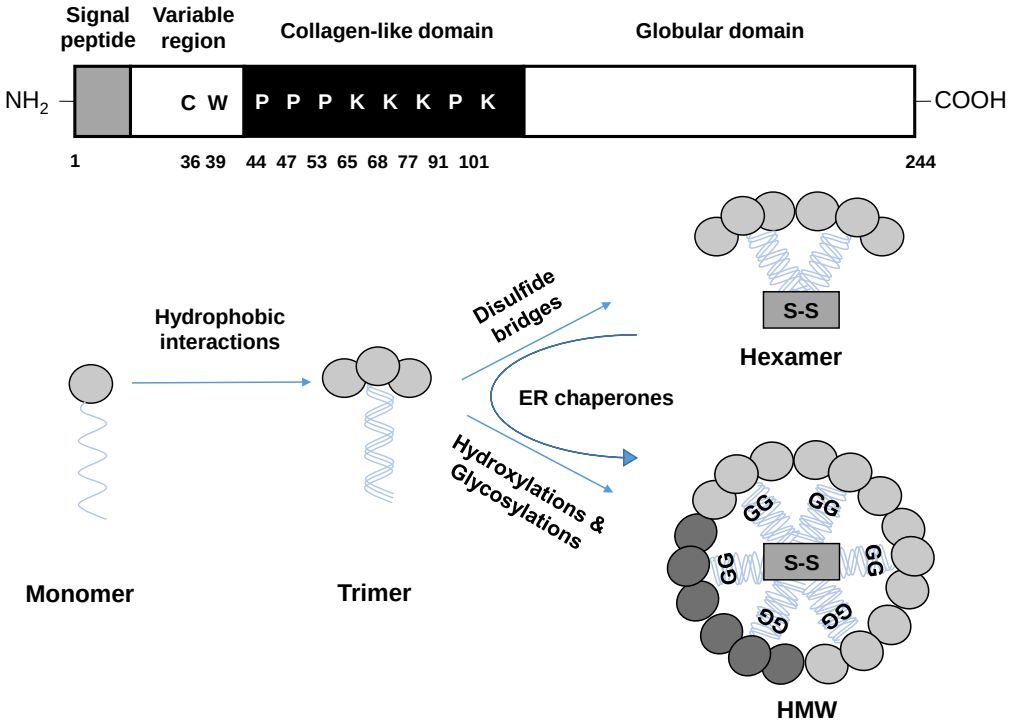

Fig. (1). Schematic illustrations of the primary structure (upper panel) and the oligomeric complex assembly (lower panel) of human adiponectin.

From the NH_2- to COOH-terminus, the primary sequence of adiponectin consists of a signal peptide, a variable region, a collagen-like domain and a globular domain. Adiponectin is extensively modified during the process of oligomeric assembly: The cysteine (C) 36 residue forms intra- and inter-trimer disulfide bridges, depicted as "S-S" [76]; The tryptophan (W) 39 residue modulates the interactions with ERp44 and the oxidative folding of trimers and hexamers [85]; A number of proline (P) and lysine (K) residues located within the collagen-like domain are post-translationally modified by hydroxylation [88 - 90]; Glycosylation of the hydroxylated lysines plays a crucial role in the formation of adiponectin HMW oligomers [6, 89]; A number of endoplasmic reticulum (ER) chaperones are responsible for the reduction of fully oxidized trimers and hexamers for HMW assembly [86].

Once released into the blood, the trimers, hexamers and HMW adiponectin oligomers do not spontaneously interconvert and exhibit non-overlapping biological activities by targeting distinct receptors and signaling pathways [73, 76, 78, 80, 91 - 97]. The circulating level of HMW adiponectin is considered the most relevant biomarker for disease-associated adipocyte dysfunctions [63, 98 - 101]. High levels of HMW adiponectin are associated with favorable metabolic profile [92, 102, 103]. The circulating concentration of adiponectin ranges from ~10 to 30 μg/ml, approximately 1000-fold higher than other hormonal factors and accounting for ~0.1% of total protein in human plasma [5, 102, 104, 105]. Under obesity and associated pathological conditions, the plasma levels of adiponectin are significantly decreased – a phenomenon referred to as hypoadiponectinaemia, which is caused by the reduced gene expression and/or protein assembly/secretion of this molecule in adipocytes [2, 104, 106 - 111]. Thus, the protective effects of adiponectin on the pathogenesis of insulin resistance, atherosclerosis, inflammation and cancers are significantly compromised by weight gain [112]. In animals, replenishment of adiponectin leads to remarkable remedial activities against various obesity-related medical complications [44, 113]. However, the structural polymorphism and the high abundancy of this molecule in circulation have posted major challenges to produce large amounts of homogenous and bioactive adiponectin for therapeutic applications in human.

RECEPTORS AND SIGNALING PATHWAYS OF ADIPONECTIN

Adiponectin receptors 1 (AdipoR1) and 2 (AdipoR2) are seven transmembrane domain receptors originally identified by molecular cloning strategies using the globular domain of adiponectin as a bait probe [114, 115]. Consequently, both receptors show relatively higher affinities to the COOH-terminal globular fragment than the full-length molecule of adiponectin [63, 94]. The two receptors share 67% identity in protein sequences and show an atypical topology different from the conventional G-protein-coupled receptor, with an internal NH_2-terminus and external COOH-terminus [63, 94]. Adiponectin stimulates the phosphorylation of AMP-activated protein kinase (AMPK) through AdipoR1, whereas its effects on peroxisome proliferator-activated receptor alpha (PPARα) are mediated by AdipoR2 [114, 116].

AdipoR1 and AdipoR2 are widely expressed in many organs/tissues but differ in the pattern of distribution and the relative abundance [114, 117]. For example, AdipoR1 is relatively more abundant in skeletal muscle whereas AdipoR2 is predominantly expressed in liver [117]. Moreover, the expression levels of AdipoR1 and AdipoR2 are affected by status of adiposity and diabetes [118], plasma insulin and adiponectin levels [118, 119], food intake (increase with fasting and decrease with feeding) [120, 121], physical activity [120, 122, 123],

and age [124]. Human and murine AdipoR share over 95% sequence homology [114, 116]. Genetic polymorphisms of human *ADIPOR1* and *ADIPOR2* do not display a significant correlation with the development of obesity-related metabolic abnormalities [125 - 133].

Disruption of AdipoR1 and/or AdipoR2 partially abolishes the metabolic actions of adiponectin, leading to the development of insulin resistance especially in skeletal muscle and adipose tissues [118, 134]. However, the phenotypes of adiponectin-deficient mice have not been thoroughly replicated by the AdipoR1/R2 dual-deficient mice [116]. Moreover, a number of studies have suggested a pro-inflammatory role of AdipoR1/R2 [135, 136]. AdipoR1 and AdipoR2, as well as other members of the progestin and AdipoQ receptor superfamily, possess potent ceramidase activities to produce ceramide and phosphorylated sphingoid, which are causatively involved in the development of insulin resistance, atherosclerosis and heart failure [137 - 140]. In this regard, a key question to be answered is whether or not by binding to AdipoR, adiponectin acts to inhibit their activities and if so, which oligomeric form(s) of adiponectin function as the antagonists.

T-cadherin (also known as CDH13, cadherin 13, and H-cadherin) is a "truncated" cadherin anchored on the plasma membrane of cells *via* a glycosylphosphatidylinositol linkage [141, 142]. It acts as an adiponectin receptor and binds to the hexamers and HMW multimers [143]. Due to the lacking of the transmembrane and intracellular domains, T-cadherin is considered to have no direct effects on adiponectin-mediated signal transduction in cells, but regulates the circulating levels and tissue distribution of this adipokine [144, 145]. Genetic studies have shown that single nucleotide polymorphisms in *CDH13*, the gene encoding human T-cadherin, contribute to low levels of adiponectin [146 - 151].

In T-cadherin-deficient mice, adiponectin accumulates in the circulation at higher than normal levels [145, 147 - 149, 152]. Meanwhile, a significant reduction in the tissue content of adiponectin leads to an increased susceptibility of these mice to injuries caused by inflammatory stimuli [145, 153]. Notably, T-cadherin is abundantly expressed in injured vascular endothelial and smooth muscle cells, such as those of the atherosclerotic plaques [141, 154, 155]. Without this molecule, heart and vascular tissues become insensitive to adiponectin, despite a constant expression of AdipoR1/R2 in T-cadherin-deficient mice [141]. Consistently, the vascular dysfunction and ischemia-induced heart problems have been observed in T-cadherin-deficient mice, similar to those of the adiponectin-deficient mice [154, 156, 157]. In human, genetic polymorphisms of *CDH13* are significantly associated with various cardiometabolic and vascular phenotypes [144, 146, 151, 154, 158, 159].

In summary, the evidence supports a synergistic role of T-cadeherin in adiponectin-mediated beneficial functions. However, without elucidating the detailed structural mechanisms underlying the interactions between adiponectin and T-cadeherin, further development of therapeutics based on this "third promising receptor" remain elusive.

ADIPONECTIN AND ITS RECEPTORS IN OBESITY-RELATED CANCER DISEASES

Excess adiposity is an independent risk factor for the development of cancer and closely associated with late-stage disease and poor prognosis [160 - 163]. Adipose tissue is the largest endocrine organ in human body [164]. During obesity, excessive expansion of the fat depots leads to chronic adipose tissue inflammation and the augmented productions of inflammatory adipokines, which act directly on tumor cells to promote their survival and proliferation [91, 165 - 169]. In addition, dysregulated metabolic homeostasis, characterized by hyperinsulinemia, hyperglycemia and dyslipidemia, indirectly enhances tumor growth and development in obese patients [170 - 172]. Increasing insulin and insulin-like growth factors (IGF) contribute to carcinogenesis [173, 174]. Moreover, adipose tissue located in proximity to or within the tumor microenvironment contributes to the local production of carcinogenic matrix proteins and the continuous supply of cancer stem cells [175, 176].

In obese subjects, hypoadiponectinaemia (<4 μg/ml) is associated with an increased risk of developing cancers including but not limited to those of the breast [177, 178], endometrium [179 - 182], prostate [183], colon [184 - 186], stomach [187 - 189], pancreas [190], liver [191, 192], kidney [193 - 195], leukemia [196, 197], lymphoma and myeloma [198 - 201]. Moreover, tumors from patients with low plasma adiponectin levels are larger, exhibiting higher histologic grade, more aggressive invasion and metastasis, as well as poorer prognosis [182, 183, 189, 202 - 211]. High plasma adiponectin levels, especially those of the HMW oligomers, are associated with a decreased cancer risk [180, 203, 212 - 216]. Genetic polymorphisms of the *ADN* gene affect its circulating levels, the tumor grade, clinical stage and aggressiveness in cancer patients [36, 126, 217 - 221]. Taken in conjunction, hypoadiponectinaemia not only represents a useful biomarker for early detection but also plays a causative role in the development of obesity-related cancer diseases.

The adiponectin receptors AdipoR1 and AdipoR2 are expressed in a plethora of malignant tissues including breast, endometrium, prostate, esophagus, stomach, colon, liver, pancreas, and lung [222 - 230]. Contrary to adiponectin, AdipoR1 and AdipoR2 exhibit an inconsistent pattern of change in both the expression and

distribution across different types of tumors and relative to the normal/benign tissues. For instance, the expression of AdipoR1 and AdipoR2 is downregulated in cancerous in comparison to healthy prostate tissues [220], but increased in tumor tissues of both non-small and small cell lung cancer [222 - 230]. In gastric cancer, the expression levels of AdipoR1 and AdipoR2 are lower in tumor than normal tissue and acts as a marker of better prognosis [231]. However, higher expression of AdipoR2 is associated with moderately differentiated when compared to well-differentiated gastric tumors [232]. Pancreatic cancer patients show positive or strong expression of AdipoR1/R2 in the tumor tissues [228]. Significantly increased or decreased expressions of AdipoR1 and AdipoR2 are found in colorectal cancer tissues *versus* normal colon epithelium [233 - 237]. A higher expression of AdipoR1 is found in tumor tissue and cell lines of breast cancer [225, 238, 239], and associated with a more invasive phenotype [239, 240]. In addition to the highly variable expression patterns of AdipoR1/R2 in tumor tissues, studies of their genetic polymorphisms in different populations of cancer patients preclude the application of these receptors as either biomarkers or suitable targets for therapeutic development in cancer diseases [126, 127, 231, 241 - 246].

ANTI-TUMORIGENIC ACTIVITY OF ADIPONECTIN

Unlike most of the inflammatory adipokines that are causally linked to obesity-related diseases, adiponectin possesses potent insulin-sensitizing, anti-inflammatory, anti-angiogenic and anti-tumorigenic activities [6, 47, 62, 63, 247 - 249]. Adiponectin prevents cancer development by improving the energy metabolism systemically and suppressing the actions of pro-inflammatory or pro-tumorigenic modulators in the tumor microenvironment locally [250 - 253]. It selectively binds to various carcinogenic growth factors to prevent their interactions with the respective receptors [247, 254]. Most importantly, adiponectin released from adipocytes acts as an endocrine and a paracrine factor to directly inhibit the survival, growth and invasion of cells in the tumor microenvironment, *via* both receptor-dependent and independent mechanisms [59, 191, 216, 248].

Inhibition of Tumor Cell Growth by Adiponectin

Adiponectin elicits potent cytostatic actions to suppress the proliferation of various types of cells, including endothelial and smooth muscle cells, myelomonocytic cells, hepatic stellate cells, satellite cell, myoblast and various different types of cancer or stem cells [57, 59, 247, 254 - 261]. Adiponectin inhibits the *in vitro* growth of human breast cancer MDA-MB-231, T47D MCF7 and SK-BR-3 cells, as well as the non-cancerous MCF10A and human mammary

epithelial cells [61, 238, 262 - 274]. Animal studies demonstrate that supplement therapy with mammalian adiponectin suppresses the tumor development in mice implanted with human breast cancer cells [61, 238, 275].

Adiponectin, in particular the HMW form at a sub-physiological concentration, inhibits leptin-, IGF-1- or dihydrotestosterone-stimulated proliferation of prostate cancer cells [276, 277]. It enhances the inhibitory effects of doxorubicin, a cytotoxic chemotherapy agent, on prostate cancer cell growth [276, 277]. Treatment with adiponectin reduces the viability and inhibits growth factor-induced proliferation and invasion of endometrial cancer cells [224, 276, 278, 279], hepatic carcinoma cells [280, 281], colorectal cancer cells [282], gastric cancer cells [189], esophageal cancer cells [283], pancreatic cancer cells [284], and lung cancer cells [227]. Prolonged exposure to adiponectin induces cell cycle arrest and apoptosis in multiple types of myeloma cells [285, 286]. It enhances the sensitivity of human chronic myelogenous leukemia cells to imatinib treatment [207, 287 - 290].

Depending on the experimental model, cytostatic/apoptotic effects of adiponectin are mediated by the increased activation of AMPK [230, 291, 292], the reduced signal transduction through extracellular-signal-regulated kinases 1 and 2, p38 or c-Jun N-terminal kinases [117, 270, 293], the inhibition of Wnt signaling or Akt and glycogen synthase kinase 3β/β-catenin pathways [61, 294, 295], and/or the enhanced expression of Bax, p53 and p21, which are important regulators of growth arrest and apoptosis [230, 274, 296, 297].

Inhibition of Tumor Angiogenesis by Adiponectin

In vascular endothelial cells, the cross-talks between adiponectin-mediated activation of AMPK (a cytostatic factor to inhibit both growth and death [298 - 301]) and inhibition of Akt/protein kinase B (a signal to promote survival and growth [302]) determine the outcome of vascularization or angiogenesis [303 - 306]. By activating endothelial nitric oxide synthase *via* AMPK, adiponectin elicits potent anti-apoptotic and anti-oxidant activities during ischemia-reperfusion injury, thus facilitating revascularization [6, 252, 255, 305, 307, 308]. In the setting of tumor development, a condition that differs significantly from tissue ischemia [309 - 311], adiponectin inhibits the activation, proliferation and migration of vascular endothelial cells, and prevents new blood vessel formation [57, 153, 252, 255, 305, 307, 308, 312 - 315]. By contrast, the globular domain of adiponectin increases endothelial activation, proliferation, migration and angiogenesis, largely through its binding to AdipoR1 or AdipoR2 [306, 307, 316 - 322]. In human vascular endothelial cells, globular adiponectin stimulates the formation of capillary-like structures and acts as a chemoattractant [306]. It also

restores the function of endothelial progenitor cells under high glucose conditions [318]. While the evidence support certain pharmacological properties of the globular domain, the existence and presence of this adiponectin fragment *in vivo* has not been confirmed under both physiological and pathological conditions [1, 3, 4, 321, 323, 324].

T-cadherin plays a role in the crosstalks between adiponectin and vasculogenic factors as well as AdipoR in the tumor microenvironment [311, 325 - 327], and enhances endothelial barrier function [328]. It may act as a co-receptor by competing with AdipoR1 and AdipoR2 receptors for adiponectin binding or interfering with adiponectin signal transduction [329]. Nevertheless, the role of T-cadherin in tumor angiogenesis remain to be elucidated.

ADIPONECTIN-DERIVED ANTI-CANCER THERAPEUTICS

Despite that adiponectin elicits potent activities against obesity-related pathologies [43, 44, 330], it is extremely challenging to convert the full-length molecule into a peptidomimetic drug for the therapeutic applications in human [331, 332]. Therefore, efforts have been directed towards the identification and testing of the active moieties on adiponectin. Based on earlier studies [52, 333 - 335], Otvos *et al*. designed a series of overlapping peptides across the entire globular domain of adiponectin and tested their agonistic effects on AdipoRs [336]. A lead peptidomimetic, ADP355 (H-DAsn-Ile-Pro-Nva-Leu-T-r-DSer-Phe-Ala-DSer-NH2) with four non-natural amino acid replacements, was generated to elicit cytostatic and anti-oncogenic activities primarily through AdipoR1 [337]. Subsequently, a number of derivatives of ADP355 were designed for testing the anti-proliferative activities in MCF-7 breast cancer cells and K562 chronic myeloid leukemia cells [331, 338]. A bell-shaped dose-response curve was observed for all the ADP adiponectin peptidomimetics, *i.e*. the growth inhibition reversed at high dose [338]. The variable activities of the ADP peptidomimetics are probably due to cell type-specific mechanisms and involve additional signaling biopolymers apart from AdipoRs [331]. Although multimerization of the peptide ligands enhances the cellular activities, none of the ADP peptidomimetics exerts favorable effects on the inhibition of endothelial cell mitogenesis [339].

While the pharmacological properties of the ADP355 derivatives are worthwhile further exploration, the rationale for their applications in cancer treatment needs to be thoroughly re-reviewed. First of all, although there is evidence that activation of AdipoR receptors limits the proliferation of cancer cell lines *in vitro* [222, 230, 238], studies have not been able to demonstrate any robust inhibitory effects of the globular domain on the proliferation of breast, colorectal, prostate

and leukemia cancer cells [238, 263, 264, 269, 270, 274, 277, 340 - 342]. On the other hand, the globular form of adiponectin has been reported to be associated with the development of colorectal and breast cancer [324, 343]. Second, most of studies have utilized bacterially-produced recombinant protein representing the globular domain, which is not detected under pathophysiological conditions; thus its roles in cancer development are insufficiently connected to the *in vivo* functions of the properly glycosylated adiponectin [323, 333]. Third, the structural similarity between the globular domain and TNF-α may not necessarily be translated into the anti-tumor but rather the pro-tumor and inflammatory activities, partly through the stimulation of AdipoR1/R2 [139, 173, 324, 329, 344 - 346]. The latter is associated with an increased ceramidase activity and production of the anti-apoptotic metabolites, sphingolipid ceramide [139, 347].

A recent study attempted to identify non-peptidic AdipoR agonists from a natural product library, using ADP355 as a reference compound [348]. The most active agonists are matairesinol, arctiin, (-)-arctigenin and gramine for AdipoR1, parthenolide, taxifoliol, deoxyschizandrin and syringing for AdipoR2. Most of the hit compounds possess potent anti-oxidative and anti-proliferative properties [112, 349]. However, as the involvement and role of AdipoR in cancer cell proliferation and tumor growth remain to be established [139, 350], results derived from the receptor-based screening experiment need to be carefully scrutinized to differentiate the agonistic or antagonistic effects [348]. AdipoR1 and AdipoR2 form homo- and hetero-multimers, which influence the ligand binding and thus drug compound screening [63, 91, 351]. Multimerization by binding with different ligands may activate distinct signaling pathways, *via* modulating the alternative interactions with the intracellular adaptor protein, APPL1 (adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1) [352 - 354]. The latter mediates the signaling of AdipoR to promote the proliferation and migration of cancer cells [329, 355].

Okada-Iwabu *et al.* screened a compound library and identified several small-molecule AdipoR agonists [356]. One of them, AdipoRon, binds to AdipoR1 and AdipoR2 at low micromolar concentrations and activates AMPK as well as the transcriptional coactivator, peroxisome proliferator–activated receptor gamma (PPARγ) coactivator 1–alpha [115, 357]. Like adiponectin, AdipoRon improves energy metabolism and insulin sensitivity, in turn extending life span in obese animals [357]. Meanwhile, AdipoR- or adiponectin-independent effects of AdipoRon have been identified and reported [357 - 363]. Nevertheless, the effects of the low molecular weight agonists of AdipoR on tumor development remain to be explored.

ALTERNATIVE STRATEGIES FOR ADIPONECTIN REPLACEMENT THERAPIES

Despite the existing controversies on AdipoR and their agonists, there are compelling evidence supporting a key role of hypoadiponectinaemia in the pathogenesis of malignant diseases associated with obesity [216, 279, 349, 364]. Increasing circulating adiponectin levels counteracts metabolic dysfunction and slows cancer progression in experimental models [286, 365]. Given that it is difficult to convert the full-length adiponectin protein into a viable drug, restoring the balanced production and mimicking the cancer-protective effects of adiponectin have attracted significant interests for potential clinical applications. For example, metformin, a biguanide derivative and first-line oral medication for type 2 diabetes mellitus, stimulates AMPK to inhibit a number of anabolic/mitogenic pathways activated by growth factors and nutrients, thus eliciting similar anti-tumorigenic effects as adiponectin [366 - 379].

Circulating adiponectin levels are modulated by lifestyle, dietary components and pharmacological agents [380 - 386]. Body weight loss, particularly in the form of visceral fat reduction, is effective in boosting the plasma adiponectin levels [387, 388]. Calorie restriction induces AMPK signaling in tumor tissues and exerts anticancer effects, concurrent with an augmented adiponectin levels [389]. Specific dietary components for cancer prevention, such as omega-3 and vitamin D, increase adiponectin expression and secretion [390 - 392]. Astragaloside II and isoastragaloside I, the active ingredients of anticancer medicinal herb Radix Astragali, increase adiponectin production from adipocytes [393]. The molecular mechanisms underlying the modulation of adiponectin levels by body weight reduction or dietary components remain unclear. Nevertheless, it is suggested that obesity-induced endoplasmic reticulum stress leads to a decreased production of adiponectin, especially the HMW form [394, 395]. Thus, targeting the machinery responsible for adiponectin assembly and secretion represents an attractive strategy for elevating the circulating levels of this molecule [396].

Adiponectin is secreted from adipocytes into the bloodstream as three oligomeric isoforms. Both clinical and animal studies suggest that the HMW is the predominant isoform mediating the beneficial effects of adiponectin [79, 397, 398]. L-4F, an apolipoprotein A-I mimetic peptide, increases serum concentrations of HMW adiponectin in obese mice [399], and reduces tumor burden through induction of myeloma cell apoptosis [400]. Administration of the PPARγ agonist thiazolidinediones (TZDs, a class of drugs used to improve lipid and glucose metabolism in type 2 diabetes [401]) in both diabetic patients and rodents results in a selective elevation in serum levels of the HMW oligomer *via* stimulating the biosynthesis and secretion pathways of adiponectin [109, 391,

402, 403]. *In vitro* and *in vivo* treatment with TZDs inhibits the growth, migration and invasion of cancer cells [403 - 408]. Leuprolide, a gonadotropin-releasing hormone agonist, increases plasma adiponectin levels in nondiabetic men with prostate cancer when combined with androgen blockade, bicalutamide [409]. While the above evidence suggest that pharmacological intervention is feasible to modulate circulating adiponectin levels, a specific target to effectively sustain the expression and/or production of adiponectin remain to be identified.

Adiponectin shares homology with collagen VIII and X, complement factor C1q and TNF-α [73, 261]. Adiponectin may act as soluble defense collagen by negatively regulating the functions of inflammatory cells [261]. Apart from the globular domain, there are other pharmacological moieties of adiponectin remain to be explored and examined. For example, a number of groups have adopted chemical synthetic approaches to produce non-globular adiponectin fragments. Among them, the adiponectin variable domain [410], and the post-translationally modified collagen-like domain [411], might prove beneficial for the treatment of obesity-related malignant diseases. A full uncover of the structure/function relationships of different domains of adiponectin will facilitate the conversion of this magic molecule into a viable drug.

CONCLUDING REMARKS

Obesity is a global epidemic problem with widespread health consequences, including an increase in the incidence and death of many lifestyle-related malignant diseases. The need for cancer prevention and therapies is of upmost importance. Adiponectin represents a critical link between obesity and many types of cancer development. Epidemiological, genetic, and animal studies have demonstrated the protective effects of adiponectin against a cluster of obesity-related metabolic, cardiovascular and malignant complications. Various strategies to increase the circulating level and function of adiponectin have been successfully applied in animals and proved to be effective in enhancing the insulin sensitivity and energy homeostasis, alleviating the obesity-associated inflammatory injuries, as well as preventing the formation and development of various cancers. However, the direct translation of animal studies to human turns out to be a challenge. Unlike other metabolic hormones (such as insulin), adiponectin is a highly abundant plasma protein in humans. Long-term replacement of bioactive adiponectin is not cost-effective and feasible at this stage. Different oligomeric forms of adiponectin and the quality of the preparation significantly affect experimental outcome and have impeded the clinical use of adiponectin. For the same reason, our current understanding of the mode of adiponectin function at the molecular level has been compromised. Considering the highly dynamic and complexed structural-signaling mechanisms, approaches

to up-regulate the endogenous adiponectin levels are more appealing for cancer prevention and treatment. Alternatively, the identification of the true functional moieties of adiponectin will greatly enhance the process of future drug discovery and development, especially in therapeutic applications for obesity-related medical complications.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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