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INVITED REVIEW

Adiponectin action from head to toe

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Abstract Adiponectin, the most abundant protein secreted by white adipose tissue, is known for its involvement in obesity-related disorders such as insulin resistance, type 2 diabetes mellitus and atherosclerosis. Moreover, modulation of the circulating adiponectin concentration is observed in pathologies that are more or less obesity-related, such as cancer and rheumatoid arthritis. The wide distribution of adiponectin receptors in various organs and tissues suggests that adiponectin has pleiotropic effects on numerous physiological processes. Besides its well-known insulin-sensitizing, anti-inflammatory and antiatherosclerotic properties, accumulating evidence suggests that adiponectin may also have anticancer properties and be cardioprotective. A beneficial effect of adiponectin on female reproductive function was also suggested. Since adiponectin has numerous beneficial biological functions, its use as a therapeutic agent has been suggested. However, the use of adiponectin or its receptors as therapeutic targets is complicated by the presence of different adiponectin oligomeric isoforms and production sites, by multiple receptors with differing affinities for adiponectin isoforms, and by cell-type-specific effects in different tissues. In this review, we discuss the known and potential roles of adiponectin in various tissues and pathologies. The therapeutic promise of administration of adiponectin and the use of its circulating levels as a diagnostic biomarker are further discussed based on the latest experimental studies.

Keywords Adiponectin · Metabolic syndrome · Cancer · Inflammation · Heart disease · Reproduction

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Introduction

White adipose tissue (WAT) was, until recently, regarded only as a major site of energy storage with important roles in the control of energy homeostasis. However, WAT is now considered to be a major endocrine organ in humans, secreting a wide range of biologically active molecules, including numerous "adipokines" [1]. Many of these adipokines have the ability to modulate metabolic and inflammatory processes and are believed to contribute to the pathophysiology of obesity-linked diseases [2]. Among these, adiponectin has gained considerable attention because of its antidiabetic, antiatherogenic and anti-inflammatory properties. Interest in adiponectin has increased significantly with demonstration that it has an important protective role in carcinogenesis [3]. The identification of adiponectin receptors (AdipoR1, AdipoR2 and T-cadherin) as well as their wide distribution in peripheral tissues and organs further suggests that adiponectin exerts pleiotropic effects on whole-

body metabolism [4, 5]. The present review summarizes current knowledge on the role of adiponectin in various tissues and in the development of metabolic and other diseases, with the aim of providing a more global picture of its action in the entire organism. The potential therapeutic benefits associated with the administration of adiponectin and the use of its circulating levels as a diagnostic biomarker of various disorders are further discussed based on the latest clinical and experimental studies.

Adiponectin: an overview

Adiponectin, also called Acrp30, apM1, GBP28 and AdipoQ, was first identified in the mouse and humans by four research groups [6–9]. This 30-kDa protein is secreted mainly by the adipose tissue and reaches a plasma concentration of 2 to 10 μg/ml in humans [10]. Adiponectin is a 244-amino-acid protein composed of an amino-terminal signal peptide followed by a species-specific variable domain, a collagenous domain of 22 Gly-X-Y repeats, and a carboxyl-terminal globular domain that is similar to the complement factor C1q and structurally similar to tumor necrosis factor-α (TNFα) [6, 7, 11]. The adiponectin collagene-like domain allows oligomerization of the protein via disulfide bonds and, more importantly, the hydroxylation and glycosylation of four conserved lysine residues, which are required for the formation of its high molecular weight (HMW) oligomeric complex [12–15]. As with other collagen-domain proteins, the basic form of circulating adiponectin is a trimer, and trimers can associate into hexamers and finally into multimers of HMW species [15]. In serum, adiponectin can be found in its full-length version or as a proteolytic fragment that corresponds to the globular domain of the protein (gAdiponectin) [16]. The hexamers and HMW species are the two major oligomeric forms of adiponectin that can be found in plasma [9], whereas low plasma concentrations of trimers and globular species may be explained by their shorter half-life [13]. Recent studies demonstrated that those different multimeric forms can, in turn, determine the activity of adiponectin, as the HMW form is highly active in liver [17] and endothelial [18] cells, whereas the trimers and full-length monomeric forms provoke responses in various tissues [19].

Although adiponectin is secreted mainly by WAT, it was recently demonstrated that the pituitary gland, liver, diencephalon, skeletal muscle, ovary, spleen and kidney can express adiponectin in the chicken [20]. In humans, its expression was also found in bone marrow, osteoblasts, fetal tissue, myocytes, cardiomyocytes and salivary gland epithelial cells [4]. This suggests an autocrine/paracrine complementary role for adiponectin in various tissues. In addition, Wong et al. [21] identified seven adiponectin paralogs (complement-C1q tumor necrosis factor-related proteins, CTRP1 to 7) that share a similar structural organization and are widely expressed in different mouse tissues. Interestingly, at least one of them, mouse CTRP2 (mCTRP2), exhibits similar biological activity to adiponectin, raising the possibility of functional redundancy and/or compensatory mechanisms for adiponectin.

The serum concentrations of adiponectin, unlike most of the other adipokines, are inversely correlated with body mass index (BMI) [22, 23] and, most importantly, with visceral fat accumulation [24]. Circulating adiponectin levels are reduced in obesity and type 2 diabetes [25], and mice lacking adiponectin develop insulin resistance, glucose intolerance, hyperglycemia and hypertension, all characteristics of metabolic syndrome (MS) [26–28]. The regulation of adiponectin expression has yet to be fully determined. Analysis of the promoter region of the human adiponectin gene revealed several regulatory elements including three potential CCAAT-enhancer-binding protein (C/EBP) elements, two stimulating protein 1 (SP1) and seven activating protein 1 (AP1) sequence motifs [29]. It was also recently reported that SIRT1, an NAD+-dependent protein deacetylase known to be involved in adipogenesis [30] can up-regulate adiponectin gene expression by enhancing the formation of a FOXO1-C/EBPα transcription complex, which is recruited to the adiponectin promoter [31]. As FOXO1 and SITR1 protein levels were found to be reduced in fat tissues of obese and type 2 diabetic mouse models, it was further hypothesized that the decreased expression of SIRT1 and FOXO1 might play a causal role in the diminished adiponectin expression associated with obesity [31]. Circulating adiponectin concentrations can be regulated by various hormonal, nutritional and pharmacological factors. Moreover, treatment of 3T3-L1 adipocytes with insulin or TNFα reduces adiponectin messenger RNA (mRNA) abundance in a time- and dose-dependent fashion [32]. Adiponectin production can be downregulated by prolactin, growth hormone (GH) and glucocorticoids [33]. Insulin-sensitizing peroxisome proliferator-activated receptor (PPAR) agonists, such as thiazolidinediones and fibrates, can increase circulating adiponectin levels in mice and humans [34].

Interestingly, transgenic mice overexpressing adiponectin show a paradoxical 30% decrease in adiponectin mRNA, measured in inguinal and gonadal adipose depots, when compared to wild-type mice [35]. A concomitant decrease in AdipoR2 mRNA expression was also observed in the same tissues. Those findings suggest that adiponectin can control its own production and AdipoR2 mRNA expression through a regulatory feedback loop.

Adiponectin receptors

To date, three putative adiponectin receptors have been identified based on their capability to bind adiponectin: adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2) and, more recently, T-cadherin. AdipoR1 and AdipoR2 are seven-transmembrane domain receptors with an extracellular carboxy terminus and an intracellular amino terminus, a structure that is opposite to that of all other G-coupled protein receptors [36]. The AdipoR1 gene encodes for a 375-amino-acid protein with a predicted molecular mass of 42.4 kDa, whereas AdipoR2 encodes for a 311-amino-acid protein of 35.4 kDa. Those two receptors are structurally highly related, as their protein sequence shares 67% identity. They are also highly conserved in that they share 95 and 97% identity between mice and humans for the AdipoR1 and AdipoR2 proteins, respectively.

The suppression of AdipoR1 and AdipoR2 expression using small-interfering RNA (siRNA) revealed that AdipoR1 is a high-affinity receptor for globular adiponectin and a low-affinity receptor for full-length adiponectin, whereas AdipoR2 has an intermediate affinity for both the full-length and globular species [36]. These receptors are ubiquitously expressed, with the highest AdipoR1 expression in human and mouse skeletal muscle and the highest AdipoR2 expression in mouse liver and human skeletal muscle and liver [36–38].

The regulation of AdipoR1 and AdipoR2 expression differs in the receptor responses to different stimuli. For example, GH upregulates AdipoR2 expression in 3T3-L1 preadipocytes but has no effect on AdipoR1 expression [32, 39]. In response to fasting, mouse AdipoR1 mRNA is upregulated in brown adipose tissue and epigonadal fat and downregulated in subcutaneous fat, whereas AdipoR2 gene expression is only upregulated in epigonadal adipose tissue [40]. The modulation of gene expression can also be species-specific, as fasting in pigs had no effect on the expression of AdipoR1 but increased the AdipoR2 mRNA level in subcutaneous adipose tissue [41], whereas the gene expression of AdipoR1, but not of AdipoR2, was lower in the subcutaneous adipose tissue of fasted mice than in that of fed mice [40].

Discrepancies also exist between AdipoR1 and AdipoR2 with regard to their regulation by insulin. For example, Sun et al. [42] recently reported that insulin is able to repress AdipoR1 transcription but has no effect on AdipoR2 in C2C12 myocytes. Similarly, Inukai et al. [43] reported that AdipoR1 mRNA was increased in the skeletal muscle of streptozotocin (STZ)-induced diabetic mice and that normal AdipoR1 levels were restored by insulin administration. In contrast, hepatic AdipoR2 gene expression was not affected in STZ-induced diabetic mice.

Using AdipoR1 and AdipoR2 gene knockout mice, it was clearly demonstrated that both receptors are involved in energy metabolism, although they have opposing effects [44]. AdipoR1$^{-/-}$ mice become obese and glucose-intolerant and have decreased energy expenditure. In contrast, AdipoR2$^{-/-}$ mice are lean and resistant to high-fat-diet-induced obesity and show increased energy expenditure [44].

A third putative adiponectin receptor, T-cadherin, was recently isolated by Hug et al. [5]. T-cadherin, also called H(heart)-cadherin or cadherin 13 (CDH13), is a unique cadherin molecule that lacks the transmembrane and cytoplasmic domains and is bound to the surface membrane through a glycosylphosphatidylinositol (GPI) anchor [5]. In humans, T-cadherin is ubiquitously expressed, with the highest expression found in the heart and the aortic, carotid, iliac and kidney arteries [45]. This receptor can bind the hexameric and HMW forms of adiponectin but not the globular or trimeric forms [5]. Although T-cadherin is a truncated receptor that lacks the intracellular domain needed for signal transduction, it can participate in intracellular signaling cascades by competing with AdipoR1 and AdipoR2 receptors for adiponectin binding. For example, the reduction of T-cadherin mRNA abundance, using siRNA, was associated with an increase in the adiponectin-stimulated phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) [46]. Those results suggest that T-cadherin can compete with AdipoR1 and AdipoR2 for adiponectin binding or that it can interfere with adiponectin signal transduction.

Little information is available concerning the regulation of T-cadherin expression. Bromhead et al. [47] previously reported that the addition of progesterone and epidermal growth factor to human osteosarcoma cells results in an increase in T-cadherin mRNA abundance. Oxidative stress can also upregulate T-cadherin expression in endothelial cells. That was demonstrated in a culture of human umbilical vein endothelial cells (HUVECs) submitted to various oxidative stress conditions such as serum deprivation and the addition of hydrogen peroxide (H_2O_2) [48]. Moreover, in the rat carotid artery, the expression of T-cadherin is upregulated after injury caused by a balloon catheter [49] and, interestingly, T-cadherin and adiponectin are found in the same location in injured vessel walls [45]. Finally, the transcription of T-cadherin was found to be downregulated in skeletal muscles of 24-h-fasted pigs, suggesting a putative nutritional regulation of T-cadherin expression [50].

Adiponectin signaling

Adiponectin primarily mediates its insulin-sensitizing effects through the sequential activation of adenosine

monophosphate (AMP)-activated protein kinase (AMPK), p38 mitogen-activated protein kinase (MAPK) and PPARα [51]. AMPK is a ubiquitously expressed cellular energy sensor that is activated by an increase in the intracellular AMP/adenosine triphosphate (ATP) ratio [52]. Strong evidence of AMPK implication in adiponectin signaling was provided by the suppression of adiponectin-induced acetyl-coenzyme A carboxylase (ACC) phosphorylation, fatty-acid oxidation, glucose uptake and lactate production in cultured myocytes of AMPK dominant-negative mutants [53].

Recently, the characterization of the interaction between adiponectin receptors and the adaptor protein containing a pleckstrin homology domain, a phosphotyrosine domain, and a leucine zipper motif (APPL1) shed some light on our understanding of adiponectin signaling [51]. To date, 14 proteins are known to bind APPL1; they include membrane receptors (e.g. the androgen receptor) and various signaling molecules with key roles in apoptosis [54], cell proliferation, chromatin remodeling [55] and cell survival [56]. The interaction of APPL1 with the androgen receptor [51] may account for the effect of sex hormones on adiponectin signaling. Furthermore, APPL1 is now recognized as a key player in regulating insulin sensitivity through the activation of the adiponectin signaling cascade. Overexpression of APPL1 in C2C12 myocytes increases the phosphorylation of AMPK and p38 MAPK, whereas its suppression by siRNA abrogates the adiponectin-mediated activation of AMPK and p38 MAPK [57]. It was further demonstrated that adiponectin stimulates interaction between APPL1 and the RAS-associated protein Rab5, a small guanine triphosphatase (GTPase) known to be involved in glucose transporter 4 (GLUT4) translocation, and that the disruption of that interaction blocks adiponectin-mediated translocation of GLUT4 to the membrane [57]. Moreover, the activation of p38 MAPK seems to be dependent on the APPL1-Rab5 interaction, as the overexpression in L6 myoblasts of dominant-negative Rab5 leads to inhibition of the adiponectin-mediated activation of p38 MAPK [57]. The involvement of APPL1 in the adiponectin signaling cascade is further supported by decreases in adiponectin-stimulated fatty-acid oxidation, glucose uptake, and AMPK, ACC and p38 MAPK phosphorylation in APPL1-deficient myocytes [57]. Adiponectin activation of the ERK1/2-MAPK pathway is also mediated through the APPL1 protein, as the downregulation of APPL1 by RNA interference (RNAi) reduces adiponectin-stimulated ERK1/2 activation in human embryonic kidney 293 (HEK293) cells [46]. As the activation of the ERK1/2-MAPK pathway is known to be essential for cell cycle initiation and to play key roles in cell growth and survival [58], it is believed that the proliferative effects of adiponectin are mediated through that pathway [46]. Finally, Chandrasekar et al. [59] recently reported that the anti-inflammatory and cytoprotective effects of adiponectin are mediated, at least in part, through an APPL1-dependent AMPK activation of the phosphatidylinositol 3-kinase (PI3K)-v-akt murine thymoma viral oncogene homolog (Akt) signaling pathway.

As mentioned above, the T-cadherin receptor lacks a cytoplasmic domain and thus probably acts as a coreceptor. Nevertheless, it was recently reported that the binding of adiponectin to T-cadherin appears to limit AdipoR1 and AdipoR2 signaling, as the reduction of T-cadherin mRNA by siRNA resulted in a marked increase in adiponectin-stimulated ERK1/2 phosphorylation in HEK293 cells [46].

A schematic model of the known and assumed pathways for adiponectin signal transduction is depicted in Fig. 1.

Adiponectin and tissue functions

Reproductive tissues

Female reproductive functions are closely related to nutritional status. Underweight women have delayed menarche [60] and are at higher risk for premature delivery [61]. Reproductive functions can also be inhibited with a 10–15% bodyweight loss [61]. In contrast, overweight and obese women have early menarche [60] and are prone to polycystic ovary syndrome (PCOS), miscarriage, gestational diabetes mellitus, stillbirth and pre-eclampsia [61].

Adipokines such as leptin, resistin and ghrelin are known to be implicated in reproductive functions at different levels, including central effects on the hypothalamus and pituitary, peripheral effects on the ovary and reproductive tract and direct effects on the oocyte and embryo [62]. Circulating adiponectin levels are higher in females than in males at attainment of puberty [63–65]. This sexual dimorphism may be explained, in part, by a much higher proportion of the HMW form in females [13, 66]. The contribution of gonadal hormones may also account for that sexual dimorphism. Indeed, it was demonstrated that testosterone administration decreases adiponectin levels in human serum, whereas exogenous estrogen treatment or ovariectomy does not affect serum adiponectin levels [67–69]. The following sections summarize the adiponectin effects on female reproduction.

Ovary

Adiponectin, AdipoR1 and AdipoR2 mRNA and proteins are present in theca and granulosa cells, oocytes and the corpus luteum [70, 71]. AdipoR2 mRNA and protein are weakly expressed in human KGN granulosa cells, whereas AdipoR1 is clearly present [70, 71]. In sows, adiponectin is also

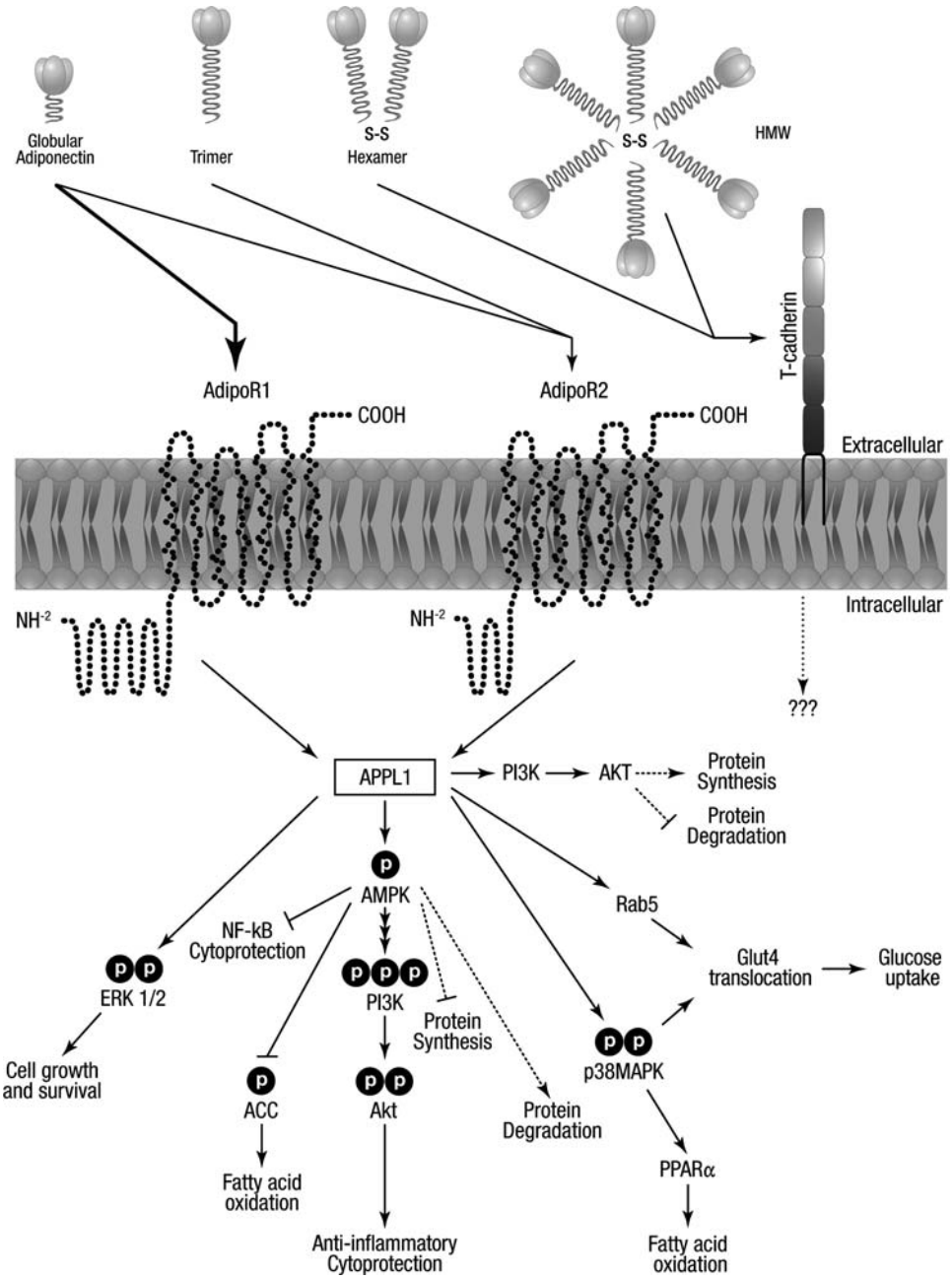

Fig. 1 Schematic representation of known and assumed pathways for adiponectin signal transduction. Adiponectin receptor 1 (AdipoR1) has a high affinity for globular adiponectin and a low affinity for full-length adiponectin, whereas adiponectin receptor 2 (AdipoR2) has an intermediate affinity for full-length and globular adiponectin. T-cadherin is a truncated receptor that can bind the hexameric and high molecular weight (HMW) oligomeric forms of adiponectin. AdipoR1 and AdipoR2 interact with the adaptor protein containing a pleckstrin homology domain, a phosphotyrosine domain and a leucine zipper motif (APPL1), which binds the N-terminal intracellular domains of the receptors. The binding of adiponectin to its receptors provokes the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), and the activation of various signaling molecules such as p38 mitogen-activated protein kinase (p38 MAPK), peroxisome proliferator-activated receptor-α (PPARα), the RAS-associated protein Rab5, phosphatidylinositol 3-kinase (PI3K) and the v-akt murine thymoma viral oncogene homolog (Akt). Activation of AMPK can also block the nuclear factor κ B (NFκB) signaling, known to be a mediator of inflammation in endothelial cells. *ACC* acetyl coenzyme-A carboxylase; Ⓟ indicates phosphorylation

present in follicular fluid at a concentration that is estimated to be 80–90% of the concentration in serum [72]. The treatment of porcine granulosa cells with adiponectin induces a periovulatory pattern of gene and protein expression that includes increased expression of the COX-2, VEGF and PGES genes [72]. It is interesting to note that combining

adiponectin and insulin and/or luteinizing hormone (LH) produces an additive effect on COX-2 mRNA abundance in granulosa cells [72]. Those results are consistent with the increase in adiponectin and AdipoR1 proteins observed in immature rat ovaries treated with pregnant mare serum gonadotropin (PMSG)-human chorionic gonadotropin (hCG) to mimic periovulatory conditions [70]. In terms of ovarian steroidogenesis, contradictory results were reported. In chicken granulosa cells, adiponectin alone increased insulin-like growth factor 1 (IGF-1)-induced progesterone secretion, but in combination with LH or follicle-stimulating hormone (FSH), adiponectin reduced progesterone secretion in cultured granulosa cells [71]. Adiponectin alone was also able to increase the IGF-1-induced production of progesterone and estradiol in rat granulosa cells [70]. On the opposite, adiponectin had little or no effect on granulosa cell functions in cows, instead decreasing insulin- and LH-induced progesterone and androstenedione production by theca cells [73]. Those discrepancies could result from species differences or the different analytical methods used.

In the ovary, most of the adiponectin-induced modulations in gene and protein expression reported above are mediated by an AMPK- [60, 70, 71] or ERK1/2-MAPK-dependent pathway [60, 70, 72]. As reviewed in Dupont et al. [74], in the ovary, the association between adiponectin and the fuel sensor AMPK suggests that adiponectin may act as a key signal regulating the amount of energy required for the growth of follicles and oocytes. The missing element explaining adiponectin effects on ovarian cells was found in the action of PPARγ. Peroxisome proliferator-activated receptors are transcription factors that are structurally similar to steroid hormone receptors. They are known to play a role in the regulation of genes involved in steroidogenesis, ovulation, oocyte maturation and corpus luteum maintenance. The kinase AMPK can phosphorylate PPARγ, leading to the repression of its transactivating functions [75]. Mounting evidence suggests that adiponectin, AMPK and PPARγ work in concert to regulate energy homeostasis in the ovary and ensure proper growth of ovarian follicles and oocytes [74].

Interestingly, mice with null mutations for adiponectin, AdipoR1 or AdipoR2 genes are fertile, suggesting that adiponectin is not absolutely essential for ovarian function. In fact, adiponectin effects on the ovary are believed to be mediated through its insulin-sensitizing effects [74, 76] and through its effect on the action of IGF-1, which is known to be implicated in follicular development [77].

Pregnancy

Pregnancy requires great energy uptake and mobilization by the mother. To ensure proper fetal development, the first half of pregnancy is associated with acute fat mass accretion, whereas the second half involves the development of an insulin-resistant state in the mother in order to increase hepatic gluconeogenesis and decrease glucose uptake in maternal muscle and adipose tissue, thus channeling maximum glucose to the fetus [78, 79].

Adiponectin was observed in the secretory granules of rat oviductal epithelial cells, suggesting that adiponectin could have a key role during the first stages of embryo development [80]. In the rat oviduct, the maximal expression of adiponectin protein occurs during proestrous and estrous periods [80]. The expression of AdipoR1 and AdipoR2 was detected in the human and pig uterus [37, 81] and these receptors are equally expressed in endometrial epithelial and stromal cells, as revealed by in situ hybridization [81]. In women, AdipoR1 and AdipoR2 mRNA expression in glandular and luminal endometrial epithelium and in the underlying stroma is higher during the mid-secretory phase of the menstrual cycle, suggesting that adiponectin is implicated in endometrial changes in preparation for embryo implantation [81]. Adiponectin protein is expressed in the endometrial epithelium and stroma of rabbits and mice during the peri-implantation period [82], and adiponectin can inhibit IL-1β-induced secretion of pro-inflammatory cytokines IL-6, IL-8 and monocyte chemoattractant protein-1 (MCP-1) by endometrial stromal cells in humans through an AMPK-dependent signaling pathway [81]. Collectively, those results suggest a beneficial effect of adiponectin on the implantation process. Moreover, adiponectin receptors are also present in oocytes and early developing pig, rabbit and mice embryos in both trophoblastic and embryoblastic cells [82, 83]. It has also been demonstrated that adiponectin can improve porcine embryo development up to the blastocyst stage by means of accelerated meiosis mediated through a p38-MAPK-dependent signaling pathway [83]. The presence of adiponectin and adiponectin receptor mRNA and proteins in the human placenta, particularly in the syncytiotrophoblast, further suggests a role for adiponectin in placentation and supports the hypothesis of maternal-fetal crosstalk involving adiponectin [84]. During fetal development, adiponectin is found in a variety of nonadipose tissues such as the epidermis, smooth muscle fibers, small intestine wall, major arterial vessels and ocular lens, suggesting a potential role in fetal growth and development [85]. The wide expression of adiponectin in fetal tissues, combined with the lower and differently distributed fat mass of newborns compared to adults (e.g. mostly subcutaneous in newborns, more visceral in adults), could explain why adiponectin concentrations found in cord blood and the plasma of newborns are two to three times greater than those observed in the plasma of adults [60, 85–90]. The high concentrations of adiponectin found in the fetal circulation further suggest a role for adiponectin in fetal

growth. In humans, adiponectin concentrations in the fetal circulation are 20 times higher at term than at 24 weeks of gestation [86]. The findings that fetal adiponectin levels do not correlate with those of the mother, correlate with gestational age, present sexual dimorphism [91, 92] and cannot pass through the placental barrier [90] further suggest that fetal adiponectin is of fetal origin.

In the mother, circulating adiponectin levels increase in the first half of pregnancy [93, 94] and then decrease proportionally to the increase in BMI, insulin resistance and hemodilution observed in the second half of pregnancy [94–96]. Therefore, it was suggested that hypoadiponectinemia could play a role in the development of the insulin-resistant state observed in late pregnancy.

In a recent study, specific SNPs and haplotypes identified in the adiponectin, AdipoR1 and AdipoR2 genes were found to be associated with reproductive traits in the pig model [97]. For example, heterozygous females for the adiponectin c.178G>A SNP were associated with a lower number of stillborn piglets and with shorter weaning-to-oestrus intervals. Moreover, haplotype analyses of AdipoR2 SNPs suggested that pig breeders might be able to increase the number of live-born piglets and decrease weaning-to-oestrus intervals by selecting in favor of the [A;C] haplotype and against the [A;C] haplotype. Nevertheless, further analyses are needed to validate these results as associations varied across parities and homozygous mutant animals were lacking for specific SNPs (Adiponectin c.178G>A; AdipoR1 c.*129A>C and AdipoR2 c.*112G>A).

Gestational diabetes mellitus is a common complication that is observed in 2–8% of pregnancies [98]. Women with gestational diabetes have lower serum concentrations of total, HMW, medium and low molecular weight adiponectin compared to those with normal pregnancy [99]. Moreover, circulating adiponectin levels measured in early pregnancy were found to be lower in women who developed gestational diabetes later in pregnancy compared to women who did not [100]. Those observations suggest a possible role for adiponectin in the development of this pathology.

Pre-eclampsia is another pregnancy-related complication. It is characterized by a sudden onset of maternal hypertension and placental dysfunction [101], which are often accompanied by the development of insulin resistance [91], and constitutes a risk of maternal and fetal mortality. The role of adiponectin in pre-eclampsia remains unclear as its circulating level was found to be higher [91, 95], lower [102] or similar [103] in women with pre-eclampsia than in women with normal pregnancies. Nevertheless, these discrepancies might be explained by the time of sampling as plasma adiponectin concentrations were lower in the first-trimester, but higher at delivery in women with pre-eclampsia than in the normal pregnancy group [102]. Interestingly, first-trimester circulating adiponectin values were lower in women who later became hypertensive than in those who had a normal pregnancy [104]. In this study, a strong association was observed between the low plasma adiponectin concentrations, observed in first-trimester, and the risk of developing hypertensive disorders in late pregnancy.

Polycystic ovary syndrome

Polycystic ovary syndrome is the most common endocrine disorder in women. It affects 10–15% of women of reproductive age [105] and accounts for 70% of cases of anovulatory infertility [106]. The diagnostic features associated with PCOS are chronic anovulation, menstrual dysfunction, clinical or biochemical hyperandrogenism and the presence of polycystic ovaries [107]. Moreover, metabolic complications such as insulin resistance, impaired glucose resistance and type 2 diabetes mellitus are often associated with PCOS [108, 109], with or without obesity [110, 111]. Because hypoadiponectinemia is found in subjects with most of the abovementioned symptoms, it was suggested that this adipokine may affect the ovary, leading to the development of PCOS. Although this topic has been investigated by many research groups, there is still no clear evidence of a direct relationship between hypoadiponectinemia and PCOS. A number of studies showed an independent decrease in adiponectin levels in PCOS patients [108, 112–118], but others failed to demonstrate a direct link between hypoadiponectinemia and PCOS [119–129]. Whether hypoadiponectinemia is or is not directly implicated in the development of PCOS, it surely participates in the insulin-resistant state observed in those patients, and there has been speculation that hypoadiponectinemia could be used to identify women with PCOS who are at higher risk for the future development of type 2 diabetes [130] and coronary artery diseases (CAD) [117].

This syndrome tends to cluster in families, but the source and mode of inheritance of PCOS are still unknown. Adiponectin gene single nucleotide polymorphisms (SNPs) T45G and G276T were investigated in PCOS patients. For the T45G SNP, a higher prevalence of the G allele was found in PCOS women [122, 131, 132]. Similar results were observed for the G276T adiponectin gene SNP, in that decreased circulating adiponectin levels were observed in individuals carrying the G allele [132, 133]. Collectively, those studies report that particular adiponectin gene SNPs are associated with a higher risk of PCOS development. It is increasingly obvious that PCOS development has an important genetic basis. First-degree relatives of PCOS patients are more prone to develop glucose intolerance and

insulin resistance as well as hypertension and hyperlipidemia [134, 135]. Moreover, their circulating levels of adiponectin are lower than those of normal individuals. Overall, relatives are at risk for developing type 2 diabetes and cardiovascular disorders. Interestingly, prepubertal daughters of PCOS mothers show hypoadiponectinemia and hyperinsulinemia compared to control individuals, and that observation is independent of obesity. At puberty, those girls begin to develop hyperandrogenism and elevated triglyceride (TG) levels [134]. Those metabolic derangements are not gender-specific, as sons of PCOS mothers also develop insulin resistance independent of obesity during childhood and through adulthood [136].

Liver

The liver is the principal storage and release organ of glucose and fatty acids and is responsible for an important part of energy metabolism. Interestingly, adiponectin mRNA and protein were detected in healthy mice liver and its expression was up-regulated in ConA-mediated acute liver failure [137]. Moreover, Yoda-Murakami et al. [138] reported that adiponectin can be induced in mouse liver undergoing carbon tetrachloride (CCl_4)-induced hepatic fibrosis. These results suggest that adiponectin has autocrine/paracrine action in that tissue, being induced in damaged liver and in acute inflammation conditions. Adiponectin mRNA was also detected in db/db mice livers [139] but was absent in liver samples from healthy, steatotic or nonalcoholic steatohepatitis (NASH) patients [140]. It therefore seems that adiponectin can be synthesized by the liver under appropriate conditions and in some species. AdipoR1 and AdipoR2 transcripts were both detected in mouse liver [138] and hepatocytes [141], the expression of AdipoR2 mRNA being greater than AdipoR1. In the liver, adiponectin activates AMPK and PPARα, leading to an increase in fatty-acid oxidation and the suppression of fatty-acid synthesis [36, 53, 142, 143]. Moreover, adiponectin increases insulin sensitivity in isolated primary hepatocytes, resulting in decreased glucose production [144].

The association between low circulating adiponectin levels and liver disease is well documented, and a protective effect of adiponectin against fatty liver disease was suggested. For example, reduced levels of circulating adiponectin were reported in a rodent model of fatty liver disease [145]. Moreover, adiponectin was found to prevent the development of alcohol-induced steatosis and to ameliorate fatty liver disease in ob/ob mice [129], an effect partly explained by an increase in hepatic fatty-acid oxidation coupled with a reduction in fatty-acid synthesis. Reduced serum adiponectin levels were also observed in patients suffering from chronic hepatitis with liver steatosis [146]. Moreover, serum adiponectin levels were negatively correlated with steatosis grade [146]. In two recent studies, genetic variations in the adiponectin (GG genotype of the +45 SNP) and AdipoR2 (rs767870) genes were found to be associated with the progression of liver fibrosis and liver fat content, respectively [147, 148]. However, further analyses are needed to clarify how these variations may contribute to the occurrence and progression of various fatty liver diseases. Further details on the role of adiponectin in liver disease are available in [149].

Skeletal muscle

In addition to the liver, skeletal muscle is an important target of adiponectin in the regulation of energy metabolism. Although expressed and secreted mainly in WAT, adiponectin is also expressed and secreted in avian [20], human [150–152] and rodent skeletal muscle [151, 153, 154], suggesting paracrine/autocrine action in this tissue.

As shown with rodent models, adiponectin regulates lipid metabolism in skeletal muscle via the activation of AMPK, p38 MAPK and PPARα, leading to higher glucose utilization and fatty-acid oxidation, thereby directly regulating glucose metabolism and insulin sensitivity [16, 36, 53, 142, 155, 156], with the involvement of GLUT4 translocation [157, 158]. Mouse knockout studies linked AdipoR1 more closely to the activation of the AMPK pathway, whereas AdipoR2 is more tightly involved in the PPARα pathway [159]. The role of APPL1 in mediating adiponectin signaling and function was specifically demonstrated using rodent C2C12 and L6 myoblasts [57] (see above). The functional significance of local production of adiponectin in skeletal muscle cells was recently addressed in Liu et al. [160]. In this study, treating L6 muscle cells with rosiglitazone increased adiponectin mRNA and protein expression by ~2.5-fold and enhanced insulin-induced glucose uptake. A significant decrease in adiponectin mRNA and HMW-to-total protein expression was observed in the gastronemius muscle of rats fed a high-fat high-sucrose obesity-promoting diet, whereas there was no change in circulating adiponectin level [160]. Moreover, treatment of these rats with rosiglitazone fully corrected muscle adiponectin mRNA and protein levels while improving whole body insulin sensitivity. These results demonstrate that locally produced adiponectin can mediate real metabolic effects on the whole body.

AdipoR1 and AdipoR2 transcripts and proteins are both detected in mice skeletal muscle with a predominant expression of the AdipoR1 gene over AdipoR2 [50, 141, 158, 161]. Moreover, the expression of AdipoR1/R2 in the skeletal muscle appears to be inversely regulated by insulin in physiological and pathophysiological states such as fasting/refeeding, insulin deficiency and hyperinsulinemia

models and therefore correlates with adiponectin sensitivity. Evidence for this assertion can be found in studies of various rodent models, where fasting, undernutrition and insulin deficiency lead to greater adiponectin sensitivity via increases in AdipoR expression [43, 141, 162]. In young growing pigs, fasting decreased the expression of T-cadherin but not AdipoR1/R2 in skeletal muscle [50]. On the other hand, adiponectin resistance resulted from decreased AdipoR expression under hyperglycemic and hyperinsulinemic conditions, in response to high-fat or high-sucrose feeding in rodent muscle and in genetically obese mice [141, 158, 161]. Interestingly, the incubation of myocytes with insulin reduced the expression of AdipoR1 and/or AdipoR2 via the PI3K/forkhead box O1 (Foxo1)-dependent pathway [42, 141]. Globular adiponectin resistance seems to develop independently of impaired insulin-stimulated glucose transport and precedes the accumulation of skeletal muscle lipids and insulin resistance [163, 164]. In contrast to results obtained with rodent muscle, similar AdipoR1 and AdipoR2 expression was observed in isolated muscle strips of type 2 diabetic and nondiabetic men [165]. A recent human study [166] revealed that circulating adiponectin concentrations were higher with increasing skeletal muscle capillary density and in individuals with higher proportions of slow oxidative muscle fibers, and that adiponectin could be a partial mediator of the relationship between skeletal muscle morphology and insulin sensitivity.

Adiponectin has been hypothesized to be involved in the regulation of skeletal muscle growth. To date, there are few data addressing the regulation of myogenic cell proliferation and protein metabolism by adiponectin in skeletal muscle or any other tissue or cell type. Adiponectin is potentially able to stimulate protein synthesis and inhibit protein degradation via the stimulation of the insulin signaling pathway, as Yamauchi et al. [142] showed that, in human skeletal muscle, adiponectin activates insulin receptor substrate 1 (IRS-1), which in turn activates the PI3K-Akt cascade. Consequently, the mammalian target of rapamycin (mTOR) pathway and protein synthesis may be stimulated, whereas protein degradation by the proteasome may be attenuated. On the other hand, AMPK was reported to interfere with the mTOR pathway by activating tuberous sclerosis 2 (TSC2), also known as tuberin, or directly inhibiting mTOR [167], and to stimulate myofibrillar protein degradation by activating ubiquitin ligases [168]. Thus, adiponectin may link energy and protein metabolism through its potential to stimulate both the AMPK and the PI3K signaling pathways, which act antagonistically in terms of protein metabolism. Moreover, there are early indications that nutrients themselves (free fatty acids, amino acids) may play an important role in the regulation of protein metabolism by adiponectin [167, 169]. Initial results show that high circulating adiponectin levels in mice are associated with less muscle proteolysis [170] and that accelerated protein degradation induced by free fatty acids is inhibited by adiponectin [169]. The authors concluded that the balance between fatty acids and adiponectin impacts proteolysis in insulin-resistant conditions and suggested a role for adipose tissue-muscle crosstalk in diabetes and obesity. Recently, Fiaschi et al. [154] provided the first evidence that gAdiponectin is able to induce muscle gene expression and cell differentiation in murine C2C12 cells. Globular adiponectin induced the expression of specific skeletal muscle markers and provoked cell fusion into myotubes through the redox-dependent activation of p38 MAPK, Akt and AMPK pathways. Moreover, adiponectin was shown to be expressed in differentiated cells, suggesting an autocrine function in the coordination of the myogenic differentiation program.

Very little information is available on the implication of adiponectin in inflammatory processes in skeletal muscle tissue. Inflammatory cytokines and pro-inflammatory conditions were shown to upregulate adiponectin in human and rodent myotubes, which may be viewed as local inflammatory protection by adiponectin [151, 154]. In a recent proteome study, Ikegami et al. [171] observed that NFκB activation was involved in the adiponectin-mediated upregulation of ferritin heavy chain in primary murine skeletal muscle cells, a finding that is in contrast to the anti-inflammatory effects observed in other cell types (see above). Other NFκB target genes, namely manganese superoxide dismutase (MnSOD) and inducible nitric oxide synthase (iNOS), were also increased by adiponectin treatment. Thus, ferritin heavy chain elevation may partially explain how adiponectin protects against oxidative stress in skeletal muscle.

Pancreas

It was reported earlier that adiponectin-deficient mice (Adipo$^{-/-}$) are insulin-resistant and present lower plasma insulin levels after glucose loading than do wild-type mice do. Those findings suggest that adiponectin may have a direct effect on insulin secretion [172]. It was previously reported that human and rat pancreatic β-cells express AdipoR1 and AdipoR2 to a similar extent and at a level comparable to that of the liver, thus suggesting a direct role for adiponectin in pancreatic cells [172]. Interestingly, pancreatic AdipoR1 mRNA levels were found to be lower in two strains of congenitally obese mice (ob/ob and Db/Db) relative to lean mice, whereas there was no difference for AdipoR2 transcript levels [173]. The addition of recombinant adiponectin to glucose-induced isolated islets increased insulin secretion, and intravenous injection of

adiponectin into C57BL/6 mice significantly increased plasma insulin levels compared to mice that received saline [174]. A similar observation was made by Gu et al. [175], who reported an increase in insulin secretion from purified rat islets incubated with adiponectin and glucose. Those authors also reported an increase in AMPK phosphorylation with adiponectin treatment at high glucose concentrations.

Interestingly, it was demonstrated earlier that adiponectin can counteract free-fatty-acid-induced apoptosis in the pancreatic β-cell line INS-1, suggesting a putative protective effect of adiponectin on the pancreas [176]. Using a cannabinoid receptor-1 antagonist, which increases circulating adiponectin levels, Zyromski et al. [177] demonstrated that the attenuation of acute pancreatitis in obese mice was mediated through adiponectin signaling. In a murine model of obesity, an inverse association was observed between circulating adiponectin levels and the severity of acute pancreatitis [178]. Although the above results suggest a protective effect of adiponectin on the pancreas, further work is needed before adiponectin can be used as a marker of pancreatitis, given that two recent studies reported that adiponectin has no effect on the etiology of acute and chronic pancreatitis in humans [179, 180].

Central nervous system and the pituitary gland

Accumulating evidence suggests that adipose-derived hormones such as adiponectin may act as key neuromodulators of food intake, energy expenditure and reproductive functions. In mice, intracerebroventricular injection of adiponectin increased energy expenditure and decreased body weight, but had no effect on food intake [181]. In contrast, Kubota et al. [182] reported that adiponectin stimulates food intake and decreases energy expenditure. Those authors also reported that adiponectin-deficient mice are protected from high-fat-induced obesity and have reduced food intake and increased energy expenditure [182]. Those conflicting results demonstrate the need for further investigation to establish the exact role of adiponectin in the brain. There is also disagreement about whether or not this adipokine crosses the blood–brain barrier. Indeed, adiponectin in cerebrospinal fluid (CSF) either is not detectable [183] or is present at very low concentrations [184] in humans, whereas it corresponds to 1–4% of plasma adiponectin in mice [181]. However, Qi et al. [181] recently reported a rise in CSF adiponectin after intravenous injection of full-length adiponectin to C57Bl/6J mice, which is consistent with a real serum-to-CSF transport. Interestingly, adiponectin, AdipoR1 and AdipoR2 transcripts and proteins were detected in the rat and human pituitary glands, revealing a potential autocrine/paracrine role played by locally produced adiponectin at the pituitary level [185, 186].

Furthermore, the addition of adiponectin to rat pituitary cell cultures resulted in the inhibition of the release of GH and LH, suggesting a putative role for adiponectin in controlling the release of somatotrophs and gonadotrophs [185].

AdipoR1 and AdipoR2 receptors are widely distributed throughout the central nervous system (CNS), with expression detected in regions of the hypothalamus and brainstem that are involved in the control of feeding behavior and energy expenditure [181, 182, 187]. Moreover, it was recently demonstrated that adiponectin can influence the excitability of different groups of neuron in the paraventricular nucleus, including neuroendocrine-CRH, preautonomic-TRH and preautonomic-oxytocin neurons [188]. These results show that adiponectin can affect neuroendocrine and autonomic functions in the CSN.

As obesity and obesity-linked diseases are well-documented risk factors for ischemic stroke, it was further investigated whether or not hypoadiponectinemia could be considered a predictor of cerebrovascular diseases. Few manuscripts have been published so far on that topic, and conflicting results were reported, with hypoadiponectinemia being associated [189] or not [190, 191] with ischemic cerebrovascular diseases. Recently, Nishimura et al. [192] provided evidence that adiponectin has a cerebroprotective action, which seems to be mediated through the endothelial nitric oxide synthase (eNOS) signaling pathway. Finally, adiponectin may also participate in the vasodilatation and inflammation associated with the development of migraines, as reviewed in Peterlin et al. [193].

Clearly, the abovementioned studies demonstrate that there is a need to conduct further investigation before a conclusion can be reached regarding the exact role of adiponectin in the brain. Nevertheless, the wide distribution of adiponectin receptors, the local production of adiponectin, and the release of somatotrophs and gonadotrophs from rat pituitary cell cultures strengthen the hypothesis that adiponectin has a real effect in the brain.

Adiponectin in diseases and disorders

Inflammation

A growing body of evidence suggests that adiponectin exerts anti-inflammatory effects. First, Yokota et al. [194] demonstrated that recombinant adiponectin can indirectly inhibit the differentiation of early B lineage progenitors in long-term bone marrow cell cultures. Moreover, in macrophages and other monocyte-derived cells, adiponectin

increases the expression of the anti-inflammatory cytokines interleukin (IL)-10 and IL-1 receptor agonist (IL-1RA) and decreases the pro-inflammatory IL-6, TNFα and interferon-γ (IFNγ)/lipopolysaccharide (LPS)-induced expression via inhibition of the nuclear factor κ B (NFκB) pathway [195–197]. Similar effects on cytokine expression and secretion in pig adipocytes [198] and human endothelial cells [199] were observed, suggesting a local and general anti-inflammatory effect for adiponectin. In addition, adiponectin was shown to reduce the phagocytic activity of macrophages [195]. Most interestingly, the effects of adiponectin on cytokine production seem to differ according to the specific adiponectin isoforms and the type and activation status of the target cells [197]. For example, low molecular weight adiponectin suppresses lipopolysaccharide (LPS)-induced IL-6 secretion and increases IL-10 release in differentiated THP-1 macrophage cells, whereas HMW adiponectin had no effect on the production of these cytokines [197]. In the same study, HMW adiponectin induced the secretion of IL-6 in human monocytes and THP-1 cells but had no significant effect on LPS-induced IL-6 secretion. On the other hand, pro-inflammatory cytokines can also modify adiponectin expression. For example, the TNFα suppression of adiponectin transcription may explain the lower circulating levels of adiponectin observed in obesity, since adipose tissue seems to be the principal source of TNFα [200].

Tsatsanis et al. [201] demonstrated that the addition of gAdiponectin to the culture medium of macrophages increases IL-6 and TNFα secretion. However, prolonged exposure to high levels of adiponectin renders macrophages tolerant to adiponectin restimulation and inhibits the secretion of those pro-inflammatory cytokines. Those observations suggest that adiponectin is not pro-inflammatory per se, but its constant high circulating levels, found in lean individuals, may render macrophages resistant to pro-inflammatory stimuli [201].

The possible implication of adiponectin in inflammatory processes was recently reported in clinical cases of rheumatoid arthritis (RA), a disorder in which infiltrating leukocytes create a constant inflammatory state leading to premature joint degradation. Serum [202, 203] and synovial fluid [203, 204] adiponectin levels are significantly higher in patients with this form of arthritis than in healthy or osteoarthritis patients. In addition, the serum adiponectin concentration correlates with the degree of severity of RA [202]. Adiponectin mRNA is also present in synovial fibroblasts and articular adipose tissue [205], contributing to the elevated synovial fluid adiponectin levels observed in inflammatory joint diseases. Moreover, AdipoR1 and AdipoR2 mRNA and protein are present in rheumatoid synovial fibroblasts (RSF) [206], suggesting a paracrine action of adiponectin in joints. It should be noted that the treatment of synovial fibroblasts with adiponectin induces the production of IL-6 and pro-matrix metalloproteinase-1 (pro-MMP-1), the precursor of the matrix-degrading enzyme MMP-1, through the p38 MAPK pathway [205], whereas it has no effect on other pro-inflammatory cytokines such as IL-1, TNFα, vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β). Another group observed a dose-dependent increase in IL-8 production in RSF treated with recombinant adiponectin. Interestingly, the treatment of RSF with AdipoR2 RNAi, but not with AdipoR1 RNAi, blocked IL-8 expression [206]. Adiponectin intracellular signaling in RSF is expected to involve the NFκB and MAPK pathways, as demonstrated by the increase in adiponectin-mediated nuclear translocation of p50 and p65 NFκB and by the reduction in adiponectin-induced IL-8 production when MAPK inhibitors are used [206]. Collectively, those results demonstrate that adiponectin has a key role in the pathogenesis of chronic inflammatory joint diseases. Since serum adiponectin levels correlate with the severity of joint damage, this parameter could constitute a better indicator of the spreading of joint destruction in RA patients than BMI [202].

Cardiovascular diseases

Cardiovascular disease prevalence in industrialized countries has been on the rise for the last several decades. It is well known that coronary artery disease (CAD) risk is associated with visceral obesity [207]. Since serum adiponectin levels are also highly correlated with visceral adiposity, the possible implication of adiponectin in the pathogenesis of cardiovascular disease was suggested. In fact, circulating adiponectin levels were found to be lower in patients with CAD [60, 208–210]. Interestingly, it was reported that a reduction in the HMW form of adiponectin is associated with CAD, whereas hexamer and trimer species are unchanged or increased, respectively [209]. It was also demonstrated that hypoadiponectinemia is associated with the number and complexity of coronary lesions and thus represents a significant risk factor in CAD patients [210]. Shibata et al. [211] reported that adiponectin may have a key role in myocardial remodeling in response to acute injury. Indeed, ischemia-reperfusion in adiponectin-deficient mice resulted in a 78% increase in myocardial infarct size and was associated with elevated TNFα levels, decreased AMPK activation and an increase in myocyte and stromal cell apoptosis. The administration of adiponectin to those mice reduced infarct size and TNFα production through the activation of the cyclooxygenase-2 (COX-2)-prostaglandin E synthase (PGES)-prostaglandin E receptor 4 (EP4)-dependent pathway in an AMPK-independent manner [211]. Ikeda et al. [212] later reported

that adiponectin acts as a physiological regulator of COX-2 signaling in the mouse heart, as demonstrated by the reduction of COX-2 production in adiponectin-deficient hearts submitted to ischemia-reperfusion. They further demonstrated that the adiponectin-induced expression of COX-2 in neonatal rat cardiomyocytes is mediated through a sphingosine kinase (SphK)-dependent pathway [212]. Those results support a cardioprotective role for adiponectin through its direct effect on COX-2 expression.

It is worth noting that other studies were unable to find any association between circulating adiponectin levels and the development of cardiovascular disease [213, 214]. However, it was later argued that those discrepancies may be explained by the fact that the serum samples had been stored for a long period (16 years) at −20°C and by differences in statistical analysis methods [215].

Recent studies also demonstrated the possible involvement of adiponectin in the development of atherosclerosis, a phenomenon in which activated macrophages adhere to the vascular wall and differentiate into foam cells that accumulate lipid droplets and recruit other macrophages, thus maintaining local inflammation. Interestingly, it was recently reported that adiponectin inhibits TNFα-induced monocyte adhesion on human aortic endothelial cells (HAECs) by decreasing the surface expression of vascular cell adhesion molecule-1 (VCAM-1), E-selectin and intercellular adhesion molecule-1 (ICAM-1) in HAECs [208]. In addition, it was shown that adiponectin can bind types I, III and V collagen, which are present in the vascular wall. It should be noted that binding was seen only in injured vessels, suggesting a putative role of adiponectin in the repair of injured vessels [216]. Furthermore, adiponectin treatment suppresses the transformation of human monocyte-derived macrophages into foam cells through the inhibition of the class A macrophage scavenger receptor, known to be a key player in foam cell formation [217]. Other evidence of the involvement of adiponectin in atherosclerosis was provided by its capacity to inhibit the binding of low-density lipoprotein (LDL) to biglycan, a vascular proteoglycan, thus decreasing subendothelial lipid accumulation, which leads to atherosclerotic plaque formation [218]. Another way in which adiponectin can influence vasculature is by increasing the production of nitric oxide (NO) in endothelial cells, as NO production is known to increase vasodilatation and blood flow [219]. The above findings can be summarized as follows: adiponectin can accumulate in injured vascular walls, reduce the ability of macrophages to develop into foam cells, limit subendothelial lipid accumulation, and promote vasodilatation and increased blood flow, all actions that strengthen the antiatherosclerotic effect of adiponectin.

Interestingly, associations were found between the adiponectin gene variant +276G>T and the risk of developing coronary artery disease, with the T/T homozygotes having a decreased risk of coronary artery disease compared with the G/G or G/T genotypes [220]. Moreover, the −11377C>G promoter variant of the adiponectin gene was found to be associated with the presence of coronary atherosclerosis and the prevalence of coronary stenoses [221]. If confirmed, these SNPs may help in the identification of patients who are at higher risk of developing coronary artery diseases.

It is interesting to note that T-cadherin is preferentially expressed in athero-resistant mammary arteries compared to athero-prone coronary arteries [222] and that its expression is associated with the progression of atherosclerosis [223]. Further, adiponectin and T-cadherin were found in the same location in injured vessels, suggesting a role for those two proteins in atherosclerosis. However, a clear demonstration of a link between adiponectin and T-cadherin in the development of atherosclerosis is still pending.

Finally, other studies reported that adiponectin can inhibit the development of acute viral myocarditis, through an increase in AdipoR1 immunoreactivity [224], and attenuates angiotensin-II-induced cardiac hypertrophy [225]. Those findings extend our understanding of adiponectin action on the heart metabolism.

Obesity-related diseases and eating disorders

Obesity has been rising dramatically worldwide for the last 30 years. Adipose tissue is more than a simple energy storage organ, and it is well accepted that it acts as a true endocrine organ with a key role in maintaining energy homeostasis and hormone balance [226]. As a consequence, both an excess of adipose tissue in obesity and its paucity in anorexia result in various medical complications such as type 2 diabetes, hypertension or reproductive failure. As mentioned before, adiponectin is negatively correlated with body fat mass, suggesting a negative feedback of adiponectin on its own production. More precisely, BMI, waist and hip circumference [227], waist-to-hip ratio and intra-abdominal fat are inversely correlated with plasma adiponectin, with the waist-to-hip ratio having the highest correlation [23]. Moreover, AdipoR1 and AdipoR2 expression in subcutaneous fat is also downregulated by more than 30% in obese individuals compared to normal subjects [228]. Weight loss usually recapitulates the expression of adiponectin and adiponectin receptors in fat tissue [228]. Accumulating evidence suggests that adiponectin is directly implicated in obesity-related disorders such as insulin resistance and type 2 diabetes mellitus, hypertension, dyslipidemia and MS. The following sections address the putative role of adiponectin in those diseases.

Insulin resistance and type 2 diabetes mellitus

One of the most studied and possibly most important features of adiponectin is its insulin-sensitizing effect. Plasma levels of adiponectin are lower in diabetic men and women across different ethnic groups [25, 229, 230]. Moreover, high circulating adiponectin levels were associated with a lower risk of subsequent development of type 2 diabetes [230], and adiponectin was found to negatively correlate with plasma glucose and insulin levels [25, 229, 230]. Recently, it was reported that total and HMW adiponectin and the HMW ratio all negatively correlate with the homeostasis model assessment (HOMA) insulin resistance index [13, 231]. In addition, the HMW ratio seems to be a better predictive factor of insulin resistance than total plasma adiponectin levels [231]. That finding is also supported by the observation that humans with mutations affecting the multimerization of adiponectin are more likely to develop a diabetic phenotype [232].

To determine whether adiponectin has a causal role in the development of insulin resistance or whether its downregulation is a consequence of the disorder, the development of adiponectin knockout mice was a helpful step. Adiponectin knockout mice have normal circulating insulin concentrations, but the glucose-lowering effect of insulin was found to be significantly impaired in those mice, suggesting that adiponectin has a direct effect on glucose tolerance in vivo [26]. Similarly, lipoatrophic mice, in which adiponectin is absent from serum, are hyperinsulinemic and hyperglycemic. Continuous systemic injection of recombinant adiponectin into those mice significantly ameliorated their hyperglycemia and hyperinsulinemia [142]. Such a beneficial effect of adiponectin was also observed in db/db obese mice, where adiponectin reversed insulin resistance [142, 233]. The same effect was observed in diabetic pigs [234]. Studies on adiponectin and insulin resistance and/or type 2 diabetes have accumulated over the years and all tend towards the conclusion that hypoadiponectinemia is highly associated with the development of those disorders and that it could be considered a risk factor in predicting the occurrence of those disorders in individuals.

Finally, genetic association studies have examined the role of several adiponectin (reviewed in [235]), AdipoR1 and AdipoR2 polymorphisms on indices of insulin sensitivity and glucose tolerance, as well as on type 2 diabetes predisposition. Among the most common SNPs, the +45G-allele of the adiponectin gene was found to be associated with glucose tolerance and insulin sensitivity [236] and with lower adiponectin circulating levels compared with non-carriers [237]. Moreover, the C allele of the AdipoR1 −3882T>C polymorphism was found to be associated with reduced insulin resistance and lower fasting glucose levels [236]. Although accumulating literature highlights the influence of adiponectin, AdipoR1 and AdipoR2 SNPs on the development of type 2 diabetes, the mechanisms by which these polymorphisms affect glucose tolerance and insulin sensitivity remains to be determined,

Hypertension

The three main risk factors associated with the development of hypertension are hyperactivation of the sympathetic nervous system, imbalance of the renin-angiotensin system and endothelial dysfunction. It is well accepted that obesity and hypertension are closely interrelated disorders. For example, it was demonstrated that systolic blood pressure increases with waist-to-hip ratio in both men and women [238]. Given that circulating adiponectin levels decrease with obesity, the involvement of adiponectin in the progression of hypertension was suggested. Initial evidence came from clinical studies showing that exposure to angiotensin II receptor blockers increases circulating levels of adiponectin. Moreover, the induction of hypertension with angiotensin II injection leads to a decrease in plasma adiponectin concentration concomitant with blood pressure elevation [239]. Further, Tanida et al. [240] reported that adiponectin dose-dependently decreases renal sympathetic nerve activity and blood pressure in rats and that its action may be mediated through the hypothalamic suprachiasmatic nucleus. Collectively, those findings suggest that adiponectin can have an immediate effect on blood pressure and that hypoadiponectinemia could also be considered an independent risk factor for hypertension. Moreover, circulating adiponectin levels could be used to predict the development of that disorder in normotensive subjects. Nevertheless, further studies are needed to elucidate the exact role of adiponectin in angiotensin-II-induced hypertension, and the use of adiponectin knockout animals with angiotensin II infusion should help underline the mechanisms involved. Further information on this topic can be found in two recent reviews that took a more detailed look at how adiponectin is involved in the development and progression of hypertension [241, 242].

Dyslipidemia

Dyslipidemia is considered to be a set of disorders of lipoprotein metabolism, including lipoprotein overproduction or deficiency. In the context of obesity, they are often associated with an increase in plasma triglycerides, free fatty acids and small LDL particles as well as a decrease in high-density lipoprotein (HDL) cholesterol levels in the blood.

It was demonstrated earlier that circulating adiponectin levels positively correlate with HDL cholesterol and LDL

particle size and show an inverse association with triglycerides [243–247]. In addition, adiponectin is an independent predictor of very low-density lipoprotein (VLDL), LDL and HDL profiles, and hypoadiponectinemia is usually associated with an atherosclerotic lipid profile [245]. The association of adiponectin levels with plasma HDL cholesterol and triglyceride levels becomes more obvious with increasing adiposity [246]. Interestingly, the positive link between adiponectin and HDL cholesterol may lie in the strong negative correlation observed between this adipokine and apolipoprotein A-I (apoA-I) kinetics in humans, as apoA-I is the major apolipoprotein of HDL particles. Moreover, as the association between adiponectin and apoA-I kinetics is independent of obesity, insulin resistance and the HDL triglyceride content, it becomes more evident that adiponectin may have a direct role in HDL catabolism [247].

Metabolic syndrome

Metabolic syndrome, also known as syndrome X, visceral fat syndrome or the deadly quartet, is a cluster of risk factors that include elevated blood pressure, dyslipidemia and obesity and are associated with various biological manifestations, including hyperglycemia and insulin resistance [248]. Interestingly, hypoadiponectinemia is a common denominator for all of those diseases. Various studies investigated the potential association between biological variables related to MS and circulating adiponectin levels. For instance, Lara-Castro et al. [24] reported that circulating HMW adiponectin is highly correlated with multiple parameters of metabolic syndrome. Indeed, they reported that HMW adiponectin is negatively correlated with abdominal fat accumulation (independently of total body fat), insulin resistance and dyslipidemia (low HDL cholesterol and high triglyceride levels). However, there was no association between total, low molecular weight or HMW adiponectin levels and blood pressure. Similarly, Seino et al. [249] reported that a decrease in HMW adiponectin is a good predictor of progression to metabolic syndrome in a 6-year follow-up study of Japanese men. Those results strengthen the hypothesis that adiponectin levels could be considered an important biomarker of metabolic syndrome.

Eating disorders

Weight loss in anorexia nervosa occurs mainly at the expense of body fat, and the endocrine functions of the adipose tissue are markedly affected in individuals with this condition [250]. In most studies, mean serum adiponectin levels were found to be higher in anorexic patients than in normal-weight individuals and to be associated with an increase in insulin sensitivity [251–254]. The opposite was also reported, however, with a decrease in circulating adiponectin concentration in individuals with anorexia nervosa and bulimia nervosa relative to normal-weight controls [255]. The physiological relevance of the high adiponectin levels observed in anorexia nervosa remains unclear, and further work is needed to determine whether those high levels may be caused by adipose tissue depletion or whether they precede it.

Cancer

There is now sufficient evidence to support a link between obesity and the development of cancer [256]. It has also been suggested that adipose-tissue-derived adipokines such as leptin and adiponectin may be involved in tumorigenesis [256].

Interestingly, in vitro studies demonstrated the ability of adiponectin to inhibit fibroblast growth factor-2 (FGF-2)-stimulated endothelial cell proliferation and to decrease VEGF-induced endothelial cell migration [257]. Moreover, intralesional injection of recombinant murine adiponectin into hypervascularized murine fibrocarcinomas led to a 60% reduction in tumor volumes and weights accompanied by an increase in tumor apoptosis mediated through caspase-3 activation [257]. The above results suggest that adiponectin could act as a potent angiogenesis inhibitor that can activate apoptosis, and thus inhibit tumor growth.

Recent studies also reported that adiponectin may be involved in breast cancer development. In the mammary gland, epithelial cells are exposed to both circulating and locally produced adiponectin from adjacent adipocytes. The close association between mammary epithelial cells and adipocytes may favor a more direct action of adipokines on that tissue. Korner et al. [258] recently reported that low circulating adiponectin levels (total and HMW) are associated with a higher risk of breast cancer development and that this association is independent of age, BMI and hormonal and reproductive factors. In T47D breast cancer cell lines, adiponectin inhibits cell proliferation, an effect partially mediated through an increase in ERK1/2-MAPK activation [258]. In another study, Wang et al. [259] demonstrated that adiponectin considerably reduces xenograft tumor progression in athymic nude mice. They also reported that the ability of adiponectin to inhibit the proliferation of breast cancer cell lines is cell-type-dependent. Indeed, in mesenchymal-like MDA-231 cells, adiponectin inhibits proliferation and induces apoptosis, whereas it has little effect on the proliferation of luminal epithelial-like T47D cells stimulated by various concentrations of fetal bovine serum (FBS) [259]. Similarly, the cell-type dependency of adiponectin action was further investigated by Grossman et al. [260], who reported that

low adiponectin concentrations can inhibit the proliferation of estrogen receptor-α (ERα)-positive breast cancer cell lines, whereas high adiponectin concentrations are necessary to inhibit the proliferation of ERα-negative cell lines. Recently, variants of the adiponectin and AdipoR1 genes were found to be associated with breast cancer risk [261]. In this study, women with the adiponectin rs2241766 (+45 T → G) TG genotype had a 39% decreased risk for breast cancer, whereas those having the adiponectin rs1501299 (+276 G → T) TG and GG genotypes were associated with a 59 and 80% increased risk for breast cancer, respectively. Interestingly, the rs2241766 TG genotype is also associated with increased circulating levels of adiponectin, whereas the rs1501299 TG and GG genotypes had decreased levels of circulating adiponectin. In the same study, the AdipoR1 rs7539542 (+10225 C → G) CC and CG genotypes were both associated with a 43% lower risk of developing breast cancer.

An exhaustive European study investigating whether obesity-related markers are involved in the development of endometrial cancer recently reported that circulating adiponectin levels could be used as a predictor of endometrial cancer risk, independently of obesity [262]. In that study, women in the highest quartile of adiponectin concentration had a 50% reduced risk of developing endometrial cancer when compared to women with the lowest concentrations [262]. Circulating levels of adiponectin are also lower in patients with prostate cancer than in controls [263] and are negatively associated with the histologic grade and disease stage [264, 265]. The expression of adiponectin receptors was also detected in prostate cancer cell lines, and it was demonstrated that recombinant full-length human adiponectin can inhibit prostate cancer cell growth in a dose-dependent manner [266].

Finally, the induction of colorectal cancer in wild-type and adiponectin knockout mice resulted in an increase in the number, volume and aggressiveness of, as well as in the occurrence of metastasis from, colorectal tumors in adiponectin knockout mice when compared to wild-type mice [267]. Moreover, COX-2 expression in the colorectal tumors of adiponectin-deficient mice was higher relative to wild-type mice. Given that COX-2 is a well-established pathogenic factor in colorectal carcinogenesis, those findings further suggest that adiponectin may play a protective role against colorectal cancer development [267]. Working on two independent case–control studies, Kaklamani et al. [268] recently reported that individuals with the adiponectin rs266729 (−11365 C → G) GG and GC genotypes have a 27% decreased risk of developing colorectal cancer than those having the CC genotype. However, further work is needed to confirm these results as Carvajal-Carmona et al. [269] were unable to replicate the association between rs266729 genotypes and colorectal cancer risk.

Taken collectively, the above findings provide evidence supporting the involvement of adiponectin in cancer development. However, further studies are needed to delineate the molecular basis for the association between obesity, adiponectin and cancer development.

Conclusion

Recent experimental and clinical investigations have enhanced our understanding of adiponectin action on whole-body metabolism. As demonstrated in Fig. 2, adiponectin has pleiotropic effects on numerous organs and tissues. The protective action of adiponectin in obesity-linked diseases has been reported in numerous published articles, and it is now well-accepted that adiponectin can have antiatherogenic, anti-inflammatory, insulin-sensitizing and cardioprotective effects. Moreover, preclinical studies have demonstrated that adiponectin is a reliable biomarker for the metabolic syndrome and its associated diseases (reviewed in [270] and [271]). Accumulating evidence suggests that adiponectin is also an important regulator of reproductive events and may have a protective role in cancer development owing to its antiangiogenesis and proapoptotic effects. Pharmacological approaches (ex. Statins, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, PPAR agonist, fibrates and cannabinoid Type 1 receptor blockers) that either increase circulating adiponectin levels or enhance adiponectin signaling through its receptors have become attractive therapeutic modalities for obesity-linked disorders and cardiovascular diseases (reviewed in [270] and [272]). However, many questions need to be addressed before adiponectin can be used as a potent therapeutic target. For example, the presence of different adiponectin oligomeric isoforms and production sites, the sexual dimorphism in adiponectin concentration and oligomeric isoform distribution, and the identification of multiple receptors with differing affinity for adiponectin oligomers all add to the complexity of adiponectin's action across and array of physiological processes and diseases. Nevertheless, experiments conducted in animal models of diabetes, obesity and atherosclerosis clearly demonstrated that adiponectin can indeed have beneficial effects on those disease states. Those findings suggest that adiponectin is a promising therapeutic option in obesity-related diseases. Moreover, recent investigations demonstrated that medical monitoring of adiponectin and its oligomeric isoforms could eventually be helpful in the diagnostic and prognostic determination of various disorders.

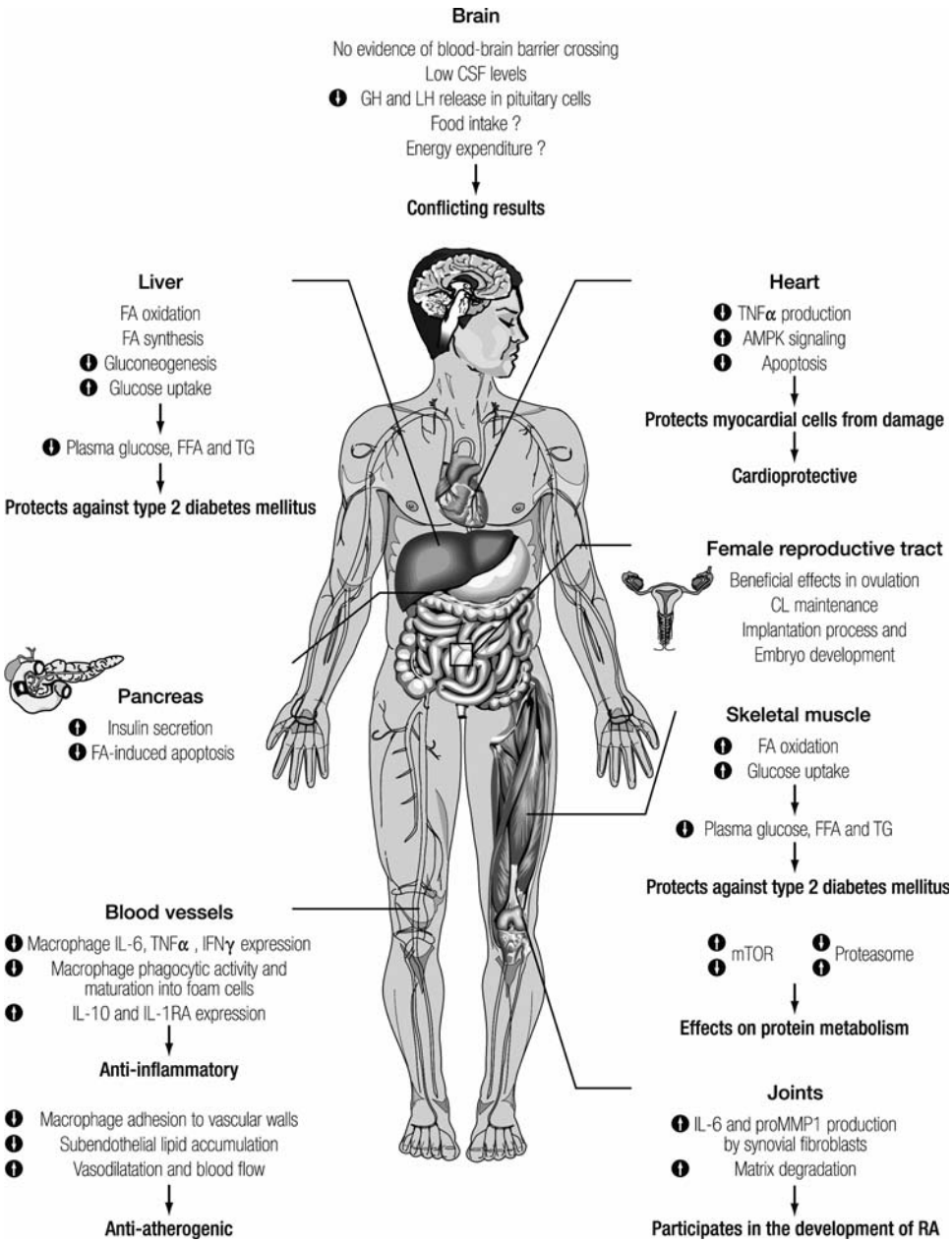

Fig. 2 Adiponectin's actions in major tissues and organs. *CSF* cerebrospinal fluid, *FA* fatty acid, *FFA* free fatty acids, *TG* triglycerides, *RA* rheumatoid arthritis

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