COMMENTARY

Adiponectin: no longer the lone soul in the fight against insulin resistance?

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Adiponectin is one of the most effective adipokines in the context of correcting obesity-induced insulin resistance. However, adiponectin-deficient animal models show a relatively modest phenotype unless metabolically challenged. This suggests that potent compensatory mechanisms are in place. In this issue of the Biochemical Journal, Wong et al. characterize new members of the CTRPs [C1q-TNFα (tumour necrosis factor α)-related proteins]. They establish that some CTRPs are produced primarily in the stromal vascular fraction of adipose tissue, and that expression of CRTP1, in particular (like adiponectin), is induced by PPARγ (peroxisome-proliferator-activated receptor γ) agonists. Moreover, injection of recombinant CTRP1 displays glucose-lowering effects. These observations suggest that CTRP1 may have partially overlapping functions and, along with other paralogues, may effectively compensate for the chronic loss of adiponectin function.

Key words: adipocyte complement-related protein 30 (Acrp30), adipokine, adipose tissue, C1q/TNF (tumour necrosis factor α)-related protein (CTRP), insulin sensitizer, oligomerization.

The study of adipose tissue as an endocrine organ is a highly active area of research in light of the increasing obesity pandemic. In the 15 years since the discovery of the leptin gene [1], the list of adipose-secreted factors (adipokines) has expanded to include almost 100 proteins [2]. Although white adipose tissue has long been appreciated to be a depot for the storage of triacylglycerols during states of excess energy supply, its endocrine function is now recognized to be important for central and peripheral metabolic homeostasis. One of the most studied yet enigmatic adipokines to date is adiponectin/Acrp30 (adipocyte complement-related protein 30). Adiponectin is a 30 kDa protein produced almost exclusively from adipocytes in multimeric complexes that have been demonstrated to exert distinct biological functions [3–5]. Assembled in the ER (endoplasmic reticulum), adiponectin exists in at least three different forms: as a trimer, hexamer and 18-mer (or occasionally even a 36-mer), the 18-mer being designated ‘HMW’ (high molecular mass) [6]. Once assembled and secreted from the adipocyte, adiponectin is widely acknowledged as an insulin sensitizer: an activity that is primarily attributed to the HMW adiponectin acting on the liver to suppress hepatic glucose output [7,8].

In both humans and rodent models, adiponectin levels have been shown to correlate inversely with obesity. This is unique in that circulating levels of essentially all other adipokines change in proportion to adipose mass, i.e. increase in the obese state. Moreover, several studies suggest that the reduction in circulating adiponectin is one of the first events to occur during the onset of obesity, leading to the decreased insulin sensitivity frequently seen associated with weight gain [9]. Normalizing circulating adiponectin levels, by either transgenic overexpression [10,11] or injection of recombinant protein [7,8], is sufficient to correct the obesity-induced metabolic phenotype. Moreover, adiponectin has been implicated in PPARγ (peroxisome-proliferator-activated receptor γ) agonist-induced insulin sensitization. To this end, the insulin-sensitizing action of PPARγ agonists is significantly diminished in diabetic mice lacking adiponectin [12].

In light of the abundance of data on the insulin-sensitizing effects of adiponectin, its significant repression in states of impaired metabolic homeostasis and the capacity of adiponectin to normalize even the most severe states of diabetes, one would postulate that mice lacking adiponectin would suffer from severe metabolic complications. Indeed, several studies have demonstrated that mice with a disruption of the adiponectin locus are more susceptible to metabolic challenges, such as diet-induced insulin resistance [12–14]. Clamp studies have further demonstrated that the reduced insulin sensitivity results from the impaired ability to suppress hepatic glucose output [12]. Surprisingly, the phenotype in unchallenged adiponectin-null mice is minimally apparent, and still relatively mild under diet- or genetically induced metabolic challenges. Generally, adiponectin gain-of-function approaches lead to unambiguous and strong improvements in the metabolic phenotype that are easily apparent [7,10,11]. This discrepancy between gain-of-function and loss-of-function phenotypes suggests that compensatory mechanisms within adipose tissue may exist that partially counterweigh the congenital absence of adiponectin.

Adiponectin belongs to a family of proteins characterized by a common TNFα (tumour necrosis factor α)-like globular domain [15–17]; furthermore, these proteins share a less conserved N-terminal domain containing collagen-like repeats. Members of this family also include complement factor C1q, hibernation proteins 20, 25 and 27, a number of collagens and CTRPs (C1q/TNFα-related proteins). The function and tissue distribution of the various family members differ extensively, with proteins such as C1q being involved in the innate immune response [18], in contrast with adiponectin and hibernation proteins, which have been implicated in metabolism [8,19,20].

In this issue of the Biochemical Journal, Wong et al. [21] report the expression patterns and metabolic functions of several additional CTRPs (Figure 1). These proteins are highly conserved paralouges of adiponectin, containing an N-terminal signal peptide, a hypervariable region, a cluster of collagen-like repeats

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produced exclusively in adipocytes, whereas expression of CTRPs these proteins share a biosynthetic pathway. Adiponectin is among the CTRPs and adiponectin may only be possible when mixed oligomers. Therefore heterotrimeric complex formation oligomer formation outside the cell, but failed to demonstrate any given time outside the adipocyte. This also makes it very unlikely that mixed trimers could form with other CTRPs that do not share structural studies, one could strongly predict that monomers that form the globular domain. On the basis of these observations, combined with the high degree of structural conservation, offer the attractive possibility that CTRPs and adiponectin may function in concert by forming mixed complexes. In fact, the sequence similarity among the CTRPs is so close that most of them could theoretically form hetero-oligomers. Moreover, co-expression experiments in vitro in the present study [21] demonstrate that this does occur if these proteins are expressed within the same cell type.

The high-resolution structure of the globular head domain of adiponectin has been published previously [16]. This study highlighted for the first time the close structural relationship between the C1q/adiponectin superfamily of proteins and the TNFα superfamily of cytokines. It also revealed the presence of a very strong hydrophobic trimer interface between the three subunits that form the globular domain. On the basis of these structural studies, one could strongly predict that monomers should be highly stable and are likely not to be found at any given time outside the adipocyte. This also makes it very unlikely that mixed trimers could form with other CTRPs that do not share an assembly pathway within the same cell. Indeed, consistent with that prediction, the authors tested the possibility of hetero-oligomer formation outside the cell, but failed to demonstrate any mixed oligomers. Therefore heterotrimeric complex formation among the CTRPs and adiponectin may only be possible when these proteins share a biosynthetic pathway. Adiponectin is produced exclusively in adipocytes, whereas expression of CTRP proteins is restricted predominantly to the stromal vascular fraction. In light of their differential biosynthetic origin, it is unlikely that adiponectin hetero-oligomerizes with any CTRPs in vivo. However, it cannot be excluded that very low (but significant) levels of these CTRPs may be expressed in adipocytes. Further analysis of serum complexes will therefore need to be performed in order to determine whether hetero-oligomerization can occur in vivo. This is very reminiscent of the situation described for another adipokine, resistin. Resistin is the founding member of a family of proteins termed RELMs (resistin-like molecules) [23,24]. Members of this family of cytokines form hexamic complexes and are structurally closely related. Similar to the situation described for adiponectin, they can be co-assembled into hetero-hexameric complexes provided they are co-transfected into the same cell [25]. However, none of these proteins are co-expressed in the same cell types in vivo, and evidence for bona fide hetero-hexamer formation is lacking to date.

The assembly of higher-ordered adiponectin complexes in the ER involves the formation of disulfide bonds by sequential transfer of oxidizing equivalents between proteins in the thiol–disulfide exchange reaction. This process is highly dependent on two ER-resident proteins, ERP44 and Ero1-Lα [26,27]. In fact, deletion of either of these proteins dramatically alters adiponectin secretion. Moreover, it is thought that the ability of the insulin-sensitizing PPARγ agonists to enhance serum adiponectin levels is due mostly to the induction of the Ero1-Lα/ERP44 machinery and not to a substantial increase in transcription of the adiponectin gene. CTRP1 mRNA, like adiponectin, is slightly elevated on rosiglitazone treatment; however, it is not known whether this increased expression translates into elevated circulating levels. To this end, there are no published data describing the mechanism of CTRP assembly and secretion from adipose tissue. It is likely that the multimeric complexes require a similar thiol-mediated retention mechanism as adiponectin, and that they may also be subject to PPARγ agonist induced up-regulation.

Similar to adiponectin, several CTRPs appear to exhibit expression patterns that are regulated by both sex and metabolic status. Some CTRP proteins show a modest elevation in females as compared with male littermates. Interestingly, CTRP6, which shows the highest degree of sexual dimorphic expression, is, however, one of the least abundant CTRPs to be expressed in adipose tissue. In contrast, analysis of serum suggests that CTRP5 levels are 6-fold higher in females as compared with males (adiponectin levels, in comparison, are 2–3-fold higher in females).

Increased circulating adiponectin, either by transgenic overexpression or injection of recombinant protein, results in significant glucose-lowering effects [7,8,10,11]. These effects are primarily due to the capacity of adiponectin to suppress hepatic glucose output [12]. However, some studies using recombinant protein suggest that adiponectin can also stimulate phosphorylation of AMPK (AMP-activated protein kinase) in skeletal muscle, and the resulting increase in glucose uptake and β-oxidation contributes to the glucose-lowering effects of adiponectin [19]. Wong et al. [21] have shown that addition of recombinant CTRP1 to the culture medium of C2C12 myotubes induces an up-regulation of phosphorylated Akt, as well as p44/p42 MAPK (mitogen-activated-protein kinase), but has no effect on the AMPK phosphorylation state. They demonstrated further that injections of recombinant CTRP1 significantly lower circulating glucose levels; however, the mechanism by which this occurs is not yet known. Interestingly, CTRP5, which circulates at much higher levels in females, displays no glucose-lowering effects and its function still remains to be determined.

Taken together, these data are consistent with the notion that at least a subset of the CTRP family members may have an
important function in metabolism. Specifically, CTRP1 displays impressive glucose-lowering effects in vivo, comparable with that of adiponectin. In light of the relatively mild phenotype of the adiponectin-null mouse models, one might postulate that CTRP1 may compensate partially for the lack of adiponectin. CTRP1 is indeed up-regulated in serum from adiponectin-null mice, suggesting that a feedback mechanism may be in place for adiponectin and CTRP1, even though they are expressed in different cell types. Furthermore, it will be of interest to determine whether CTRPs can bind the established adiponectin receptors. Future studies should elucidate whether some of these CTRPs are as potent as adiponectin in correcting obesity-induced insulin resistance.

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