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Review Article

Adiponectin in inflammatory and immune-mediated diseases

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ABSTRACT

Circulating levels of adiponectin (APN) are reduced in obesity and associated comorbidities, with inflammation playing an important role in downregulating APN production. In contrast to obesity and metabolic disease, elevated systemic and local levels of APN are present in patients with inflammatory and immune-mediated diseases, including autoimmune and pulmonary conditions, heart and kidney failure, viral hepatitis, organ transplantation and perhaps critical illness. A positive association between inflammation and APN is usually reported in inflammatory/immune pathologies, in contrast with the negative correlation typical of metabolic disease. This review discusses the role of APN in modulation of inflammation and immunity and the potential mechanisms leading to increased levels of APN in inflammatory/immune diseases, including modification of adipose tissue physiology; relative contribution of different tissues and adipose depots; hormonal, pharmacological, nutritional and life style factors; the potential contribution of the microbiota as well as the role of altered APN clearance and release from T-cadherin-associated tissue reservoirs. Potential reasons for some of the apparently contradictory findings on the role of APN as a modulator of immunity and inflammation are also discussed, including a comparison of types of recombinant APN used for *in vitro* studies and strain-dependent differences in the phenotype of APN KO mice.

1. Introduction

The adipokine adiponectin (APN) has been extensively studied for its involvement in obesity and associated morbidities, particularly cardiovascular disease (CVD), the metabolic syndrome and Type 2 diabetes. A massive amount of data accumulated over the past 20 years strongly supports the notion of reduced production of APN from adipocytes in the above-mentioned conditions. Inflammation is the common thread generally invoked to explain suppressed production of APN in obesity and its co-morbidities, with strong evidence supporting these claims. Briefly, expansion of adipose tissue in obesity, with or without additional contributions from CVD and/or insulin resistance, leads to development of chronic inflammation, which in turn contributes to inhibition of APN. Excellent and numerous reviews discussing the regulation of production and role of APN in the context of metabolic disease have been published (see for example [1–4]). On the other hand, a less extensive – although growing – body of evidence points to paradoxical upregulation of APN in several types of inflammatory and immune-mediated conditions [5–12]. Here, after an introduction about APN and its effects on modulation of inflammatory and immune responses, I discuss evidence on the association between APN and inflammatory/immune diseases and potential factors contributing to this association.

Adipocytes are the most important source of APN, but other cell types – including skeletal and cardiac myocytes, airway epithelial cells and lymphocytes – can also produce this adipokine [3,13–16]. Although extra-adipocyte sources of APN may be important modulators of the local microenvironment, they are unlikely to significantly contribute to the circulating pool of APN under physiological conditions. Activation of the transcription factors PPARα and γ and FOXO1 is critical in regulating production of APN in adipocytes [17]. The complex structure of APN, its receptors ADIPOR1, ADIPOR2 and T-cadherin, the signaling pathways activated by APN as well as its effects on metabolism have been described in detail in several excellent reviews [1–4]. A plethora of beneficial effects of APN have been reported in metabolic disease, as reviewed in [1–4], even though the occasional conflicting result has also been reported [18,19].

2. Effects of APN on inflammation and immunity

2.1. Inflammation: in vitro

There is ample evidence for multiple anti-inflammatory activities of APN, ranging from inhibition of pro-inflammatory cytokines

Abbreviations: APN, adiponectin; BMI, body mass index; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; GVHD, graft-versus-host disease; LPS, lipopolysaccharide; MW, molecular weight; PPAR, peroxisome proliferator-activated receptor; TLR, toll-like receptor.

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to induction of anti-inflammatory ones, downregulation of adhesion molecule expression, antagonism of toll like receptors (TLR) and their ligands, such as lipopolysaccharide (LPS), and others (reviewed in [1–4]). At least part of the anti-inflammatory effects of APN are likely due to its ability to activate ceramidase, reducing intracellular levels of pro-inflammatory ceramides while increasing the concentration of sphingosine-1-phosphate, a molecule with important immunoregulatory and anti-inflammatory effects [20].

In contrast with the above-mentioned results, studies also report an apparently conflicting pro-inflammatory role for this adipokine [5,6,8,9,21]. The effect of APN on activation of the prototypic inflammatory transcription factor, NFκB, is a good example of these controversial findings. As listed in Table 1, several groups investigated the effect of APN on NFκB activation *in vitro,* obtaining widely divergent results [22–36]. These contradictory findings extend to other inflammatory pathways [5,6,8,9,21]. As a consequence of the avid binding of APN to LPS [37], some of the reported pro-inflammatory effects of APN, particularly those obtained using recombinant APN obtained from *E. coli*, may be the result of contamination with LPS. However, no clear pattern emerges from the published studies as to which form of APN (bacterial versus mammalian, globular versus full-length) has activating versus inhibitory effects on inflammation (Table 1). No cell-specific pattern emerges either. Furthermore, APN forms oligomers (trimer, hexamer and high MW forms) and circulates in blood as truncated fragments that correspond to its globular domain and are bound to positively-charged proteins [38]. Data suggest that the different MW and truncated forms of APN exert differential activities [1–4]. Therefore, some of the discrepancies in the reported activities of APN as pro- or anti-inflammatory may result from use of different MW and/or truncated forms of APN. For example, two studies reported differential effects of the various MW forms of APN in modulation of NFκB. However, one report indicates that hexameric and high MW APN activate NFκB while trimeric and globular APN do not [33], whereas the other study demonstrates activation of NFκB by globular APN (bacterially derived) but not by the full-length form (of mammalian origin) [23]. Finally, it has also been suggested that exposure to APN induces a limited inflammatory program that eventually results in desensitization of cells to additional inflammatory stimuli [39]. Therefore, a careful parallel comparison of the various forms of APN under highly controlled experimental conditions coupled with confirmation of the findings through complementary approaches, such as use of neutralizing antibodies, receptor-deficient cells, etc., appears necessary to settle this issue.

2.2. Immunity

The apparently contradictory effects of APN extend to its role in modulation of immune responses. Thus, one study reports that APN activates dendritic cells, leading to enhancement of Th1 and Th17 responses [40]. In contrast, other reports demonstrate that APN instead downregulates expression of co-stimulatory molecules while increasing expression of inhibitory ones on dendritic cells, leading to upregulation of T regulatory cells [41,42].

Activation of T lymphocytes results in translocation of APN receptors from the intracellular compartment to the cell membrane, with APN negatively regulating generation and function of antigen-specific CD8 T cells through induction of apoptosis and inhibition of proliferation [43]. As a result of the suppressive effect of APN, higher numbers of antigen-specific T cells are present in APN KO mice infected with Coxsackie virus [43]. However, APN can also reportedly upregulate production of interferon γ by antigen-specific human CD4 and CD8 T cells in response to hepatitis C virus, thus possibly helping to control infection by this virus [44]. On the other hand, APN inhibits production of interferon γ by natural killer cells, although the effect on cytotoxicity is more subtle and may be activation-dependent [45,46]. Increased levels of natural killer cell-derived interferon γ and reduced viral titers have been reported in APN KO mice infected with coxsackie virus compared to WT mice [46]. As these examples illustrate, the effect of APN in modulation of immune responses is likely highly context-dependent and needs to be further clarified.

2.3. Inflammation and immunity: use of APN KO mice

As described in more detail in Section 3, discrepant results have been reported *in vivo* in studies using APN KO mice in models of immune/inflammatory diseases [14,47–65]. Different groups independently generated APN KO mice; three of these strains have been used to study immune/inflammatory diseases [18,66,67]. As indicated in Table 2, divergent outcomes have been observed with these strains of APN KO mice. Thus, mice generated by Maeda et al. [66] always had a worse outcome when compared to WT mice, irrespective of the experimental model used [14,49,51–53,55,57,59–63,65,68]. The opposite results have been obtained

Table 1
Effects of different types of recombinant APN on NFκB activation *in vitro.*

Cell type	Dose APN	Type APN	Effect on NFκB	Refs.
Myocytes	2–4 μg/ml	All MW forms, bacterial and mammalian	Hexamers and HMW activate, globular and trimeric do not	[33]
Macrophages	1–10 μg/ml	Not indicated	Inhibits	[35]
Adipocytes	30 μg/ml	Not indicated	Inhibits	[24]
Endothelial cells	3–30 μg/ml	Bacterial full-length (Biovendor)	Inhibits	[28]
Macrophages	5–30 μg/ml	Bacterial globular	Inhibits	[36]
Synovial fibroblasts	0.1–30 μg/ml	Mammalian full-length (R&D systems)	Activates	[30]
Macrophages	1 μg/ml	Bacterial globular (Peprotech)	Activates	[29]
Endothelial cells	10 μg/ml	Bacterial globular and full-length (Peprotech)	Inhibits	[26]
Hepatocytes	10 μg/ml	Mammalian full-length (R&D systems)	Activates	[34]
Endothelial cells	10 μg/ml	Bacterial globular (Peprotech)	Activates	[32]
Macrophages	25 μg/ml	Not indicated	Activates	[25]
Endothelial cells	5 μg/ml	Mammalian full-length (Alexis)	Globular activates, full-length does not	[23]
Angiogenic cells	2–30 μg/ml	Bacterial full-length	Activates	[22]
Macrophages	5–10 μg/ml	Mammalian full-length (Biovendor); Bacterial globular (Peprotech)	Inhibits	[31]
Renal tubular cells	50–100 ng/ml	Bacterial full-length (Biovision)	Inhibits	[27]

Survey of manuscripts reporting the effect of APN on NFκB activation *in vitro*. The cell type, as well as the dose, type (globular or full-length, bacterial or mammalian) and source of APN used is reported together with the effect on NFκB activation.

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