Published in final edited form as:
Cytokine. 2013 October ; 64(1): 1–10. doi:10.1016/j.cyto.2013.06.317.

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.

Keywords

adipose tissue; adipokines; inflammation; immunity; disease

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

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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 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 by researchers using APN KO mice generated by Ma et al. [18], that either fared better or the same compared to their WT counterpart [47, 48, 50, 56, 64, 69]. Finally, mice generated by Nawrocki et al. [67] had improved outcome in a model of pulmonary disease, but developed more severe disease in a model of kidney damage [54, 70]. Although some of these discrepancies may be due to use of different experimental procedures, a clear pattern of strain-dependent responses emerges from this analysis. A side-by-side comparison of different strains would be a valuable tool to clarify whether these conflicting results are due to the gene targeting strategy employed to generate the mice, to environmental factors such as housing conditions and use of littermates that impact the microflora (see section 4) or to the presence of only minor metabolic alterations in the Ma strain compared with the other two [18, 66, 67]. More consistent findings have been reported by investigators that used the approach of increasing APN levels, either through exogenous administration or APN overexpressing mice. Although only few studies employed this strategy to study immune/inflammatory diseases, with the exception of a single study, increasing APN invariably resulted in improved outcomes [71–76].

3. Adiponectin in human inflammatory and immune-mediated diseases

Convincing evidence indicates that inflammation suppresses production of APN in adipocytes; chronic inflammation is thus often considered a causal factor in the reduced APN levels observed in obesity, CVD and type 2 diabetes [1–4]. If inflammation is indeed the most important mechanism regulating production of APN, one would expect to observe reduced levels of this adipokine in diseases characterized by elevated inflammation. However, data indicate a complex association between inflammation and APN outside the realm of metabolic disease. Recent reviews detail the specifics of this association for various categories of diseases [5–12, 21, 77]. Therefore, only a discussion of selected issues is presented below.

3.1 Autoimmunity

Elevated circulating levels of APN have been reported in patients with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, active autoimmune idiopathic recurrent pericarditis and type 1 diabetes, though not all reports are in agreement [5, 21, 77–80]. Upregulation of APN is also present locally in the inflamed joints of rheumatoid arthritis patients [21, 77], with data indicating a direct pro-inflammatory role of APN in chondrocytes [81, 82].

The presence of elevated levels of APN - specifically the high MW form that is protective against insulin resistance [83] - is particularly intriguing in Type 1 diabetic patients, given that opposite findings are reported for Type 2 diabetes [1–4]. In Type 1 diabetics the expected correlation between APN and age, gender, adiposity, arterial stiffness and degree of insulin sensitivity are present [83, 84]. However, unexpectedly, serum APN levels predict progression of renal damage and are positively, rather than negatively, associated with CVD in Type 1 diabetes [85, 86]. Deregulated production of APN is also observed in experimental models of Type 1 diabetes, with NOD mice at risk for developing autoimmune diabetes having significantly elevated levels of APN compared with mice not at risk [87]. In this model, APN is positively, rather than negatively, correlated with gonadal adipose tissue weight [87]. Whether APN contributes to the pathophysiology of Type 1 diabetes and other autoimmune diseases is still unknown.

3.2 Heart failure

Although APN levels are low in CVD and this adipokine exerts potent vascular and cardioprotective effects [3], circulating levels of APN are high and associated with adverse outcome in patients with chronic heart failure, who also develop APN resistance [11]. Although, as discussed below, this may be the result of changes in body composition in patients with chronic heart failure, it should be noted that levels of APN are positively correlated with cardiac inflammatory infiltrate and systemic markers of inflammation in patients with dilated inflammatory cardiomyopathy [13]. Furthermore, induction of autoimmune myocarditis in mice leads to elevated circulating and cardiac levels of APN; however, APN gene transfer reduces inflammation and cytokine production *in vivo* and *in vitro* in cardiomyocytes [13]. Since several studies indicate an anti-inflammatory effect of APN in the heart, upregulation of APN in chronic heart failure may represent a failed attempt at controlling disease [11].

3.3 Kidney failure

A complex association between APN and disease is also present in chronic kidney failure, as discussed in detail in [9, 88]. To summarize, circulating levels of APN are high in patients with chronic kidney failure, particularly in end-stage renal disease. Elevated levels of APN in this population are positively correlated with markers of systemic inflammation and

associated with higher risk of death [89]. Although clearance of APN is mostly mediated by the liver [90], reduced renal excretion - rather than suppressed production by adipocytes - has been proposed as the mechanism for the elevated circulating levels of APN in chronic kidney disease [9, 88]. Evidence about regulation of APN expression by adipocytes in patients with kidney failure is contradictory, with studies demonstrating either upregulated, downregulated or unchanged APN mRNA expression in visceral and subcutaneous adipose tissue in patients with end-stage renal disease [91–93]. Controversial results also exist for the potential pathogenetic role of APN in kidney failure, with animal models demonstrating that APN deficiency protects against acute kidney injury but instead worsens renal failure in models of podocyte injury or ischemia-reperfusion [69, 70, 94], though the fact that these results were obtained using different strains of APN KO mice should be taken into account, as discussed above. To conclude, the relative contribution of APN's reduced clearance *versus* increased adipose tissue expression as well as the role of APN in the pathophysiology of chronic kidney disease remain to be elucidated.

3.4 Liver disease

Reduced levels of APN are present in patients with non-alcoholic fatty liver disease, a condition often associated with obesity and insulin resistance [1–4]. However, subjects with chronic viral hepatitis have elevated serum levels of APN that are positively associated with viral load and systemic inflammation [95–98]. High levels of APN are also present in chronic alcoholics and in patients with hepatocellular carcinoma, particularly those infected with hepatitis C virus [99, 100]. Interestingly, the expected association between APN and hepatic steatosis, overweight/obesity and sex, but perhaps not with insulin resistance, is maintained in these populations [100, 101]. Circulating levels of APN are reduced, as expected, in rat models of non-alcoholic fatty liver disease, but are elevated in a mouse model of cirrhosis induced by bile duct ligation [102]. As mentioned above, APN is mostly cleared by the liver [90]. Therefore, the relative contribution of clearance *versus* dysregulated production and the exact role of APN in the pathophysiology of the different types of liver disease mentioned above remain unclear.

3.5 Lung disease

Unorthodox levels of APN have been reported in several types of lung disease, with the strongest evidence available for chronic obstructive pulmonary disease (COPD) (reviewed in [6, 10]). Briefly, elevated circulating and local levels of APN have been consistently reported in COPD: high APN is associated with worse lung function and greater disease severity in this population. Furthermore, systemic levels of APN increase during acute exacerbations of COPD and are positively correlated with markers of inflammation [103]. Gene variants of APN have been associated with risk of COPD, thus pointing to a possible pathophysiological role for APN in this condition [104]. The results of animal studies linking APN to COPD-like disease are contradictory, with reports of a spontaneous emphysema-like phenotype, but also of protection from tobacco-induced emphysema, using different strains of APN KO mice [51–53]. Altered levels of APN are also present in other conditions with pulmonary involvement, such as tuberculosis and infection with non-tuberculous mycobacteria [105, 106], but again the meaning of this association remains unclear.

3.6 Organ and tissue transplant

Although several studies investigated modulation of APN levels in patients undergoing organ and tissue transplant in the context of insulin resistance and the metabolic syndrome [107], only a few reports evaluated the association of APN with transplant outcome. Serum APN levels increase with progression of chronic graft-versus-host disease (GVHD) after allogeneic stem cell transplantation and decrease as GVHD improves, indicating a positive

association between APN and GVHD severity [108]. In recipients of kidney transplants, low levels of APN predict allograft failure [109], although a different study demonstrates that elevated APN levels are not associated with protection from transplant failure [89]. As mentioned above, contradictory, possibly strain-dependent, results have also been reported for the role of APN in mouse models of heart and skin transplantation [55, 56, 72]. Thus, more evidence is necessary to understand the regulation of APN production and the role of this adipokine in transplantation.

3.7 Critical illness

As reviewed in [6, 7], evidence for modulation of APN levels in critically ill patients is somewhat controversial, with studies indicating both reduced and increased circulating levels of APN in this population. Although some studies demonstrate a positive correlation between APN, markers of inflammation and disease severity, the need for longitudinal data that include pre-morbid APN levels is underscored by the authors of the above-mentioned reviews. Similar to what reported for other conditions, strain-dependent findings have also been obtained using models of sepsis or endotoxemia in APN KO mice [14, 62–65].

4. Mechanisms potentially contributing to regulation of APN in inflammatory and autoimmune diseases

Multiple lines of evidence indicate that inflammation inhibits production of APN by adipocytes through several mechanisms, including cytokines, oxidative stress and hypoxia as well as direct activation of co-stimulatory molecules, such as CD40, on adipocytes [110–113]. These effects are mediated by modulation of transcriptional factors involved in inflammation, including NFκB and RP140 [114, 115]. Reduced levels of APN in obese and metabolically unhealthy subjects are thought to be, at least partly, a direct consequence of chronic inflammation [1–4]. However, circulating and local levels of APN tend to be positively, rather than negatively, correlated with markers of inflammation in the various inflammatory and immune-mediated pathologies mentioned above. Therefore, despite the strength of the evidence linking inflammation to reduced adipocyte-derived APN, other mechanisms must either overcome the suppressive effect of inflammation on APN production or modulate the association in non-metabolic diseases. These potential mechanisms are discussed below and summarized in Figure 1.

4.1 Fat mass and adipocyte size

The single most important contributing factor to the apparent paradoxical regulation of APN in inflammatory and immune-mediated diseases is probably adipose tissue physiology. Although the majority of studies evaluating regulation of APN in inflammatory/immune diseases control for body mass index (BMI) and sometimes for other surrogate markers of adiposity, this may not be sufficient due to the tight interconnection between APN and adipocyte morphology and function.

Even in healthy populations BMI does not distinguish fat mass from lean mass and certainly does not quantify the subcutaneous *versus* the visceral adipose depots that have different overall effects on health outcomes [1–4]. This is a very important issue when evaluating the association between a given disease and APN production. For example, in critical illness there is a relative loss of lean mass, with preservation or even increase in fat mass (discussed in [7]). Therefore, matching by BMI would lead to misleading results in this population. Moreover, when COPD patients are matched to controls by fat mass rather than BMI, no significant differences in APN levels are detected [116]. Therefore, rather than the commonly used BMI, a precise measure of fat mass, better if augmented by indication of adipose tissue distribution, is necessary to obtain meaningful results.

Weight loss, which is common in several of the conditions discussed in this review, enhances expression of APN [117]. A well-designed study in chronic heart failure demonstrates that patients with cachexia have higher APN compared to BMI-matched weight stable patients with heart failure but no cachexia, despite the presence of higher markers of inflammation in cachectic patients [118]. In another study, serum levels of APN and systemic inflammation are higher in non-cancer cachectic patients compared to a weight-stable control group [119]. Since even relatively minor weight loss in the absence of cachexia is sufficient for upregulation of APN production [117], controlling for weight loss prior to entry into the study is necessary to correctly interpret APN values even when the populations are matched by BMI or fat mass at the time of analysis.

Moreover, small adipocytes produce higher levels of APN compared to the hypertrophic adipocytes present in the visceral adipose compartment of obese subjects [1–4]. Thus, controlling for adipocyte size may be necessary in order to precisely evaluate the mechanisms contributing to production of APN in disease. Data obtained in critically ill patients demonstrate the presence of small adipocytes with enhanced ability to store fat and glucose, upregulation of PPARγ as well as the presence of macrophages polarized towards the anti-inflammatory M2 phenotype in both subcutaneous and omental adipose tissue [120, 121]. These characteristics are likely associated with enhanced ability to produce APN. On the other hand, no change in adipocyte size but higher inflammation was reported in subcutaneous adipose tissue of COPD patients [116], while reduced adipocyte size in the presence of low, rather than high, APN is present in rats with adjuvant-induced arthritis [122]. These data suggest that the association between disease, adipocyte size and APN production is likely complex and needs to be investigated on a case-by-case basis.

To further complicate matters, the connection between APN, fat mass and adipocyte size is bidirectional, since transgenic mice that overexpress APN have increased fat mass but reduced adipocyte size, whereas APN KO mice develop fat atrophy with aging [51, 123]. Thus, when studying regulation and role of APN in disease, careful evaluation of adipose tissue amount, location, morphology and function as well as weight history appears necessary in order to disentangle the relative contribution of alterations in adipose tissue *versus* other potential factors.

4.2 Tissue of origin

Expression of APN is differentially regulated in visceral *versus* subcutaneous adipocytes as well as in non-adipocyte cellular sources. Thus, for example, feeding a high-fat diet leads to significant donwregulation of APN expression in visceral adipose tissue but, on the contrary, to upregulation of APN in the subcutaneous depot and in skeletal muscle in mice [14, 124, 125]. Moreover, whereas activation of NFκB inhibits APN production in adipocytes, it does not affect APN synthesis by airway epithelial cells [15, 115]. Thus, differential regulation of APN production in different tissues and adipose depots may account for some of the apparently paradoxical findings discussed above. However, the relative contribution of the different adipose tissue depots and extra-adipocyte sources to the circulating pool of APN remains to be elucidated, particularly in the context of inflammatory/immune pathologies.

4.3 Hormonal milieu

Several hormones contribute to regulation of APN production. Insulin upregulates APN gene expression and release; reduced APN levels in insulin-resistant states can thus be partly a consequence of insensitivity of adipocytes to insulin's action [126]. In turn, low APN exacerbates insulin resistance, thus creating a vicious cycle. Aldosterone inhibits APN production, whereas natriuretic peptides increase it: these effects may be important in the context of hypertension and kidney disease [127–129]. Moreover, activation of beta-

adrenergic pathways and stimulation of the cannabinoid receptor CB1R lead to significant downregulation of APN production in adipocytes [130, 131]. Androgens inhibit APN production, which is one of the reasons for the lower levels of APN observed in men compared to women, and the relative amount of estrogen and androgens is likely to play an important role, as suggested by data obtained in women with polycystic ovary syndrome [132]. Thus, consideration of the hormonal milieu and sympathetic tone may help explain some of the apparently paradoxical findings reported above.

4.4 Microbiota

Interactions between APN and the microbiota may contribute to explain some of the results connecting APN to inflammatory and immune-mediated diseases in both human and animal studies. Alterations in the commensal flora have been described in patients with each of the conditions associated with elevated levels of APN, including liver disease, critical illness, COPD, chronic kidney disease and autoimmune diseases, including type 1 diabetes [133–138]. A two-way interaction between pattern recognition receptors on host cells, such as TLR4 and TLR5, and bacterial components of the microbiota modulates susceptibility to both inflammatory and metabolic diseases in experimental animals [139, 140]. Since APN binds LPS and inhibits its activity, both directly and through downregulation of TLR4 [37, 141, 142], it is conceivable this adipokine might interact with the commensal flora.

A role for the microbiota in modulation of APN production is supported by limited evidence indicating that alterations in the gut microbial composition induced by administration of bile acids or antibiotics are associated with increased circulating APN levels, although it is unclear whether this effect is secondary to modulation of adipose mass, adipocyte size or other factors [143, 144]. Furthermore, supplementation of maternal diets with probiotics increases APN levels in colostrum, further supporting a link between the microflora and production of APN [145]. In contrast, it is currently unknown whether changes in APN levels, including gene deficiency or overexpression, alter the composition of the microbiota. Divergence in the composition of the microbial flora has been described in mouse colonies raised apart [146], thus hinting at the possibility that some of the conflicting results obtained using APN KO mice may be the result not only of different experimental conditions, but also of variations in the composition of the microbiota.

4.5 Nutritional and lifestyle factors

Life style factors, such as diet, smoking, alcohol consumption and exercise are also important modulators of APN levels [1]. Nutritional regulators of APN include saturated fatty acids, which inhibit its production, and omega-3 polyunsaturated fatty acids that increase APN production [147, 148]. Exposure to niacin (vitamin B3) [17] or betaine (part of the methionine-homocysteine cycle and a component of many foods) increases APN production [149]. Exercise and perhaps alcohol increase APN, whereas smoking decreases it [1].

Among nutritional factors, iron plays a critical and direct role in production of APN. In fact, iron overload negatively regulates transcription of APN in adipocytes *via* FOXO1-mediated repression [150]. In mice, loss of the adipocyte iron export channel ferroportin results in adipocyte iron loading and decreased APN synthesis [150]. This is a potential indirect mechanism for inflammation to inhibit APN production in obesity, since obesity-associated inflammation leads to elevation of hepcidin, which downregulates ferroportin [151]. In fact, an association between increased iron stores and low APN has been reported in the obese [152]. In turn, low APN exacerbates iron-mediated injury of hepatocytes, thus creating a feed-forward pathological loop [153]. Several of the diseases discussed in this article are associated with alterations in iron metabolism, which can contribute to modulation of APN

production. However, whether any of these conditions leads to altered iron loading specifically in adipocytes remains to be investigated.

4.6 Pharmacological treatment

Several commonly used drugs regulate APN production. These include not only thiazolidinediones and fibrates, but also sulfonylureas, valproic acid, modulators of the renin-angiotensin system, calcium channel blockers, and possibly different immunosuppressive/anti-inflammatory therapies including methotrexate, cyclosporin and anti-TNFα treatment [6, 21, 77, 154]. Some of these drugs directly alter APN production and release while others modulate circulating APN levels indirectly. This mechanism clearly cannot account for some of the contradictory results between APN and inflammatory diseases obtained in animal models, but the above-mentioned evidence indicates the importance of controlling for pharmacological interactions when evaluating the association between APN and disease in human studies.

4.7 Alteration in clearance and tissue reservoirs

Lastly, though very importantly, elevated levels of APN in at least some of the conditions discussed in this review may result from reduced APN clearance, rather than increased production. This mechanism has been suggested mostly in the context of kidney disease, but may also apply to conditions that affect the liver, since this organ is very important in clearing APN from the circulation [90].

An additional potential mechanism for increased circulating levels of APN in the absence of increased output from adipocytes or other cellular sources is downregulation of T-cadherin, one of the receptors for APN [155]. Deficiency of this molecule in mice leads to major upregulation of circulating APN levels [58]. The proposed mechanism calls for T-cadherin to sequester APN in tissues, thus creating an APN reservoir that is released into the circulation in the absence of T-cadherin [156]. Genetic linkage studies associate mutations in the human *Cdh13* gene, which encodes for T-cadherin, with circulating APN levels [157], suggesting that modulation of this pathway is likely to be relevant. Epigenetic modulation leads to loss of T-cadherin expression in cancer, indicating active regulation of this protein in humans [158–160]. However, nothing is known about regulation of T-cadherin production and expression in the diseases discussed in this review and associated with elevated APN.

Evaluation of the relative contribution of increased APN production *versus* reduced clearance and/or regulation of T-cadherin-associated tissue reservoirs will require studies that include measurement of tissue levels of APN as well as its binding molecules.

5. Conclusion

As discussed in this review, in contrast with data obtained in patients with metabolic disease, most studies report elevated levels of APN in patients with inflammatory and immune-mediated pathologies. The exact mechanisms leading to this increase and the specific role of APN in the pathophysiology of these conditions remain to be elucidated. Carefully controlling for a variety of factors that may contribute to regulation of APN production, release and clearance is necessary to dissect the mechanisms behind this apparently paradoxical association.

Acknowledgments

The author is supported by NIH grant DK083328.

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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Highlights

- Adiponectin is elevated in inflammatory and immune-mediated diseases
- Positive association between adiponectin and inflammation in inflammatory diseases
- Adipose tissue physiology influences adiponectin levels in inflammatory diseases
- Many conflicting factors contribute to regulation of adiponectin levels
- Strain-dependent phenotypes of adiponectin KO mice

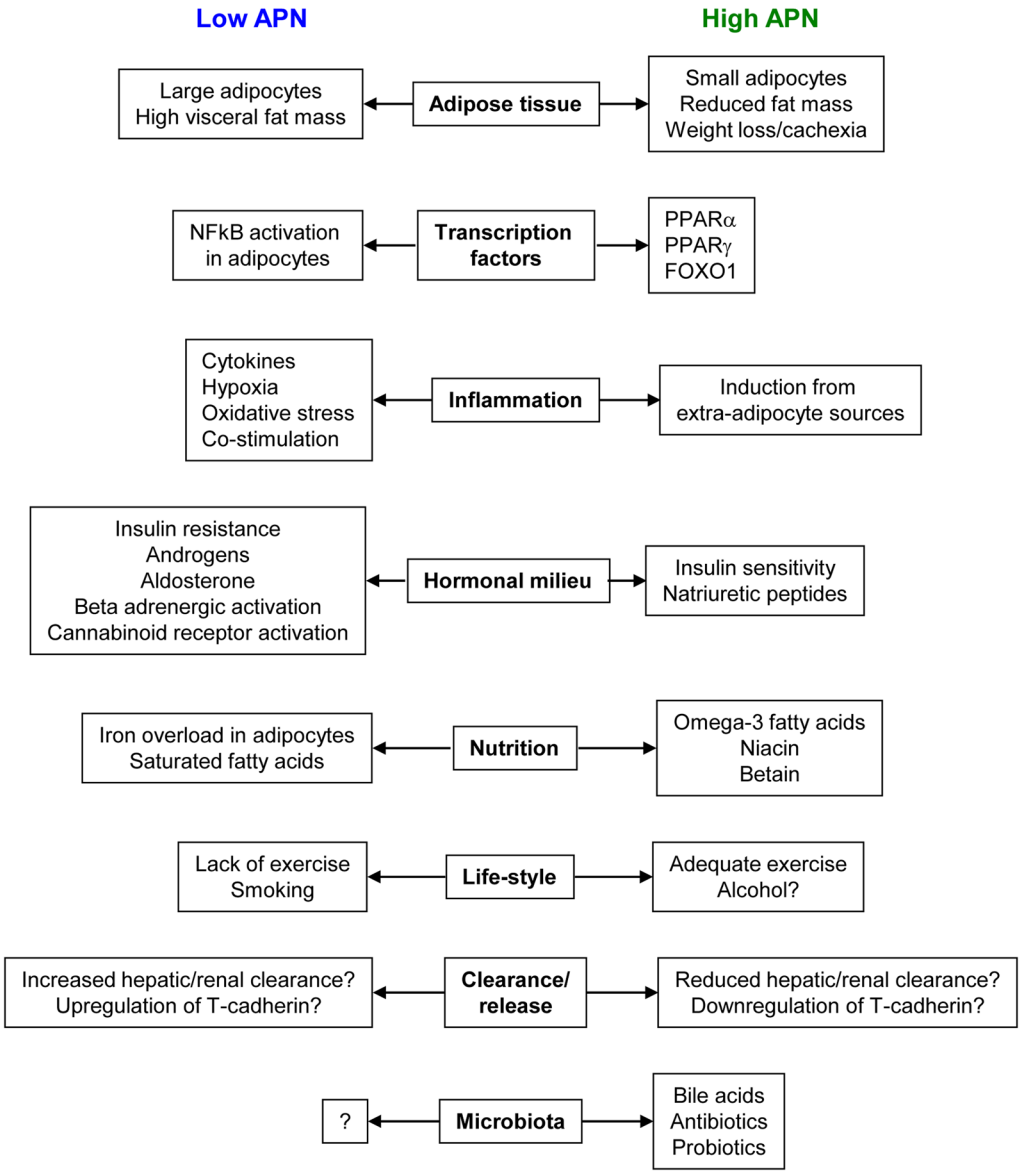

Figure 1. Potential mechanisms contributing to regulation of APN levels in inflammatory and immune-mediated diseases

The apparently paradoxical presence of elevated levels of APN in the presence of systemic inflammation, as well as the positive association between APN and markers of inflammation in different inflammatory and immune-mediated disease can possibly be explained by the balancing activity of several factors that concomitantly contribute to modulation of APN production, clearance and release with opposite outcomes. The figure lists the various potential categories of mechanisms discussed in the text.

Table 1

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

Cell type	Dose APN	Type APN	Effect on NFκB	Ref.
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) and source of APN used is reported together with the effect on NFκB activation.

Table 2

Phenotype of APN KO mice in models of immune/inflammatory disease

Disease model	Strain	Outcome of KO	Ref.
Colitis	[66]	Worse than WT	[49]
	[18]	Better/no difference from WT	[47, 48, 50]
Pulmonary disease	[66]	Worse than WT	[51–53, 57]
	[67]	Better than WT	[54]
Kidney disease	[67]	Worse than WT	[70]
	[18]	Better than WT	[69]
Transplant rejection	[66]	Worse than WT	[55]
	[18]	Better than WT	[56]
Endotoxemia/sepsis	[66]	Worse than WT	[14, 62, 63, 65]
	[18]	No difference from WT	[64]
SLE	[66]	Worse than WT	[59, 68]
Acute pancreatitis	[66]	Worse than WT	[60, 61]

Survey of manuscripts reporting use of APN KO mice in models of immune/inflammatory diseases. The experiments model, strain as well outcome of APN KO compared to mice is reported. SLE: systemic lupus erythematosus