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REVIEW ARTICLE

# Roles of Adiponectin in Acute Kidney Injury

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Adiponectin (APN) is an adipokine shown to have potent antiobesity, antiatherosclerotic, suppression of macrophage-to-foam cell transformation, and inhibition of proinflammatory cytokines. Studies have revealed that plasma concentration of APN is approximately three times higher in patients with end-stage kidney disease than in healthy people. However, low plasma levels of the hormone have been shown to elicit a protective effect against inflammation in animal models of ischemia/reperfusion-induced acute renal failure. This review summarizes the possible molecular signaling pathways involved in the effects of APN accumulation in the circulation on acute kidney injury in humans and in rodents.



## 1. Adiponectin and adiponectin receptors

Adiponectin (APN), which is also referred to as Acrp30, adipoQ, ApM1, and GBP28, contains 244 amino acids and was first discovered by several independent groups nearly at the same time in the late 1990s.[1] There are four structural domains based on its primary sequence: an N-terminal signal peptide, a short hypervariable region, a collagen domain, and a C-terminal globular domain homologous to C1q.[2]

Adipose tissue is the most abundant source of APN. Recent studies have demonstrated that other cells, namely colonic mucosa cells, liver cells, skeletal muscle cells, placental cells, salivary gland epithelial cells, bone-forming cells, myocytes, and myofibroblasts, also release APN, although in lower amounts.[1] Another interesting characteristic of APN is that it exists in five configurations and six forms: globular APN (gAPN), full-length APN (fAPN), low molecular weight APN, medium molecular weight APN, high molecular weight APN, and serum albumin-bounded low molecular weight APN.[1] The monomer fAPN is the basic unit of these configurations and forms. The gAPN form is the globular domain of fAPN, which might be generated by elastase digestion.[3] Other configurations include an oligomer and a multimer of fAPN, both of which are held together by disulfide bonds.

To date, there are three known receptors for APN: APN receptor 1 (AdipoR1), APN receptor 2 (AdipoR2), and T-cadherin. AdipoR1 and AdipoR2 are integral membrane proteins containing seven transmembrane domains; however, in both receptors, the N terminus is internal and the C terminus external, making them structurally and functionally distinct from G-protein-coupled receptors.[4] AdipoR1 is abundantly expressed in skeletal muscle, whereas AdipoR2 is predominantly expressed in liver. AdipoR1 is the high-affinity receptor for gAPN and AdipoR2 is the intermediate-affinity receptor for gAPN and fAPN.[4,5] Recent studies have revealed that AdipoR1 and AdipoR2 are also expressed in brain, placenta, colon, kidney and cancer tissue, and could be regulated by cytokines and insulin as well as by exercise.[6–13] T-cadherin, an atypical glycosyl phosphatidyl inositol-anchored cadherin, is expressed on endothelial and muscle cells. Hug et al demonstrated that T-cadherin was the receptor for the eukaryotically-expressed hexameric and high-molecular-weight forms but not for the trimeric or globular forms of APN in endothelial cells.[14] T-cadherin lacks a cytoplasmic domain and is, therefore, believed to act as a coreceptor.[15] Activation of AdipoRs is mediated by a novel adaptor protein containing a pleckstrin homology domain, a phosphotyrosine binding domain, and a leucine zipper motif (APPL1), AMP-activated protein kinase (AMPK), and peroxisome proliferator-activated receptor alpha (PPARα).[5,16] Other potential and downstream signaling molecules/pathways include the mitogen activated protein kinase-glucose transporter 4 pathway, IκB kinase (IKK)-nuclear factor kappaB (NFκB) signaling, caspase signaling, endothelial nitric oxide (NO) synthase (eNOS)-heat shock protein 90 (HSP90), and the TSC 1/2-TOR/p70 S6 kinase pathway.[4,5,16]

## 2. Acute kidney injury and inflammation

Acute kidney injury (AKI) occurs in 1% of hospital admissions and up to 7% of hospitalized patients develop AKI.[17] An increase in plasma

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proinflammatory cytokine levels predicts mortality in patients with AKI.[18] Potential tubular and vascular factors, as well as inflammatory processes, are involved in the pathogenesis of AKI.[19] Inflammation is now believed to play a major role in the pathophysiology of AKI.[20,21] Experimental studies in AKI have utilized I/R, sepsis–endotoxemia, and nephrotoxic models.[22] These models of AKI are associated with an increase in infiltrating neutrophils in the kidneyand induced inflammatory reactions which can be attenuated by anti-intercellular adhesion molecule-1 (ICAM-1) and/or anti-CD44 therapy.[23–29] Other leukocytes such as natural killer cells also play an important role in renal tubular cell apoptosis during ischemia/reperfusion (I/R) injury. Macrophage-mediated inflammation has been described in various kidney diseases including glomerulonephritis, diabetic nephropathy, and unilateral ureteric obstruction as well as ischemic AKI in rats and mice.[30–34]

## 3. Anti-inflammatory effect of APN

Consistent with the epidemiologic association of reduced APN levels in patients who are obese and in those who have type 2

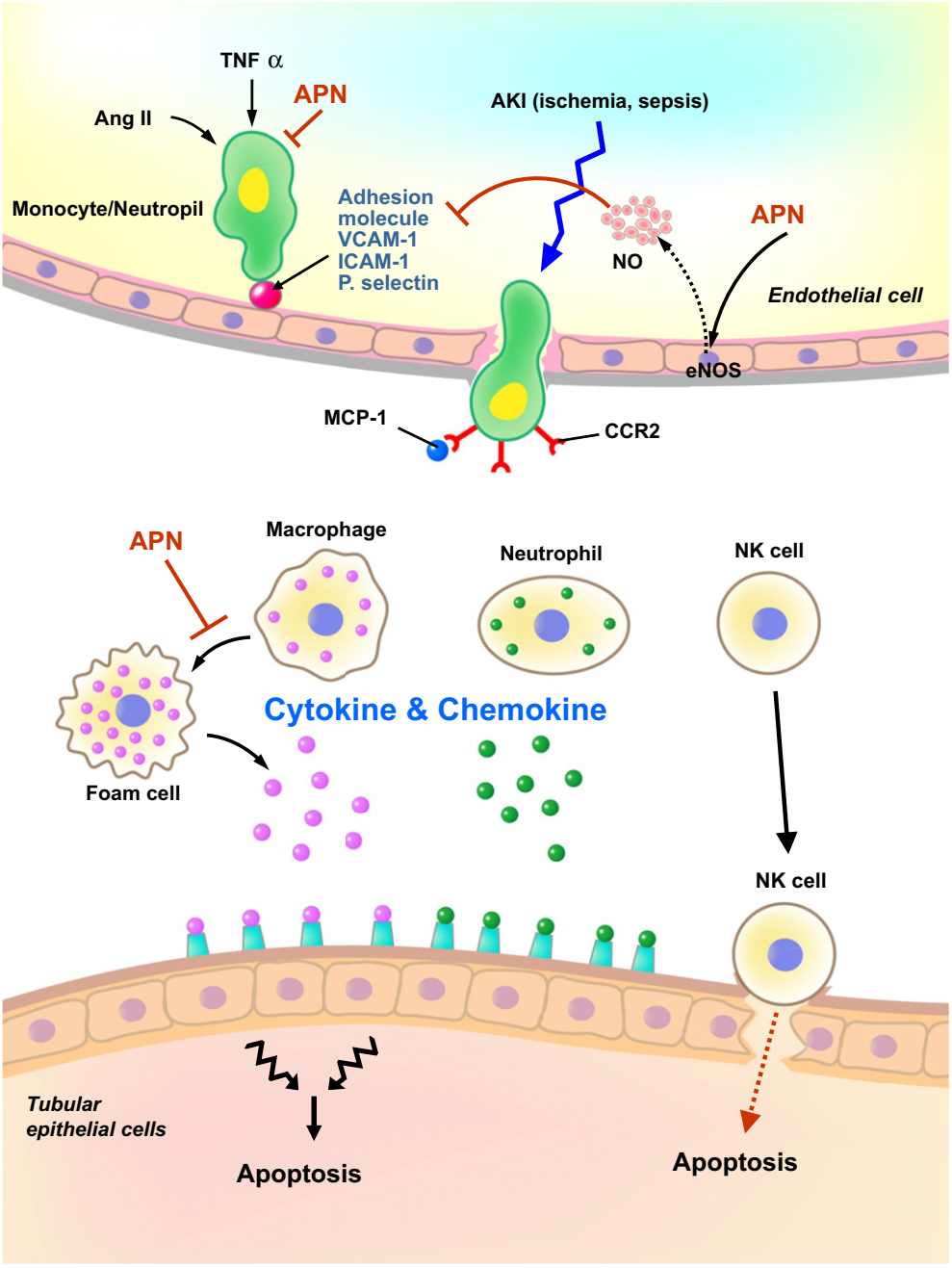


**Figure 1** Schematic diagram presenting the signaling pathways of adiponectin involved in the mechanisms of acute kidney injury. When a human kidney is under AKI (I/R or septic stress), vascular endothelial cells will induce adhesion molecule (ICAM, VCAM, P-selectin, E-selectin) overexpression. These molecules enhance recruitment of monocytes and neutrophils from endothelial cells into interstitium. Activation of foam cells from macrophages and neutrophils stimulate local cytokines and chemokines (Interleukin-6, -12, TNFα) secretion via the NFκB activating pathway, leading to renal epithelial cell apoptosis. In addition, infiltrated NK cells can induce apoptosis in tubular epithelial cells contributing kidney injury. Treatment of APN can induce the NO production by eNOS in endothelial cells and decrease the recruitment of monocytes/neutrophils to attenuate the expression of adhesion molecules. Furthermore, APN inhibit cytokines or chemokines production by foam cells to protect renal epithelial cell apoptosis.

diabetes, *in vitro* studies have shown that APN can reverse the deleterious effects of tumor necrosis factor-α (TNFα) and other cytokines that trigger an inflammatory signaling cascade, enhance leukocyte endothelial interactions and thereby lead to some of the early processes of atherosclerosis.[35,36] APN suppresses macrophage-to-foam cells transformation,[37] human aortic smooth muscle cell proliferation,[38] and the development of atherosclerosis by attenuating the expression of vascular cell adhesion molecule-1 (VCAM-1) and ICAM-1 in vessel walls.[39] APN also protects against endothelial monolayer hyperpermeability induced by angiotensin II or TNFα; this effect has been observed for both gAPN and fAPN and is associated with amelioration of actin stress fibers, intercellular gap formation, and β-tubulin disassembly.[40]

It has been shown that endothelial NO availability increases in response to APN through a mechanism that involves APN stimulated binding of regulatory Hsp90 to eNOS.[41,42] Consistent with these *in vitro* data, adiponectin inhibition of leukocyte adhesion in TNF-inflamed microvascular networks *in vivo* has been shown to be hindered by pharmacologic blockade of eNOS with N-nitro-L-arginine methyl ester.[43] Pathways that involve protein kinase A or cyclic adenosine monophosphate(cAMP)-dependent protein kinase signaling have also been implicated in the effects of adiponectin in the endothelium.[44]

Ouedraogo et al reported that gAPN mediated suppression of TNF-α-induced activation of NF-κB was accompanied by cAMP accumulation but was blocked by inhibitors of adenylate cyclase or PKA in endothelial cells.[43,44] These findings imply that multiple pathways are involved in the suppression of endothelial inflammatory signaling by APN to attenuate kidney injury.

## 4. Antiapoptotic effects of adiponectin

The antiapoptotic activity of adiponectin has been demonstrated in human cardiac microvascular endothelial cells. Pretreatment with adiponectin was shown to stimulate APPL1-dependent AMPK activation, reverse Akt inhibition in a phosphatidylinositol 3-kinase-dependent manner, block IKK-NFκB and phosphatase and tensin homolog signaling, reduce caspase-3 activity, block Bax translocation, and inhibit endothelial cell apoptosis.[45]

In a mouse I/R model, myocardial apoptosis and TNFαexpression were observed in APN knockout (KO) mice; however, the effects were inhibited in mice exposed to fAPN.[46] In addition, APN-KO mice exhibited enhanced formation of NO, superoxide, peroxynitrite, and inducible NO synthase (iNOS)/gp91-phox protein expression after I/R injury; however, the effects were significantly reduced in mice that had been exposed to gAPN before reperfusion.[47] Kataoka et al reported that gAPN treatment significantly inhibited angiotensin II induced apoptosis in human umbilical vein endothelial cells by promoting and stabilizing the association between eNOS and HSP90.[48]

In vascular smooth muscle cells, APN was shown to antagonize inorganic phosphate (Pi)-induced apoptosis and to ameliorate the accelerating effect of TNFαon Pi-induced apoptosis by restoring the Gas6-mediated survival pathway via AMPK.[49] In renal epithelium cells, we found that APN protective effects against I/R-induced apoptosis by inducing the expression of hemeoxygenase-1 and the PPARα dependent pathway, which itself was mediated through the enhancement of cyclooxygenase-2 and 6-keto prostaglandin $F_{1\alpha}$ expression.In addition, I/R-induced renal dysfunction (elevated serum creatinine and urea levels), inflammation (number of infiltrating neutrophils, myeloperoxidase activity), and apoptotic responses (apoptotic cell number and caspase-3 activation) were attenuated in APN-treated mice.[9] Those data suggest that APN protects the cell from apoptosis via an AMPK-dependent, PPARα-dependent antiapoptotic mechanism.[9]

## 5. Conclusion

Inflammation plays a major role in the pathophysiology of AKI. Tubular and endothelial cells recruit neutrophils, macrophages, natural killer cells, and lymphocytes into the kidneys, which induce the generation of inflammatory cytokines and chemokines in response to AKI. APN elicits its effects through multiple pathways (Figure 1), resulting in the suppression of endothelial inflammatory signaling and the inhibition of apoptosis in tubular epithelium cells. However, APN concentrations have been shown to be higher in patients with chronic renal disease than in healthy controls but lower in obese and type 2 diabetic patients as well as in mice with acute renal failure. These conflicting results between chronic and acute renal failure may be associated with the degradation rate of APN, or to some other APN-specific protease, or both. Further studies are warranted to investigate these discrepancies.

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