Adiponectin and endothelial cells

Adiponectin enhanced endothelial Nitric Oxide (NO) production, inhibited oxidative stress, ameliorated inflammation, apoptosis and endothelium-leukocytes interaction, and reduced lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) expression, as well as oxidized-low-density lipoprotein (ox-LDL) uptake.

Adiponectin plays a role in regulating endothelial function by mediating NO production and oxidative stress. Both full-length adiponectin and gAb induced endothelial NO synthase (eNOS) activation and NO production in Human Umbilical Vein Endothelial Cells (HUVEC) [14]. In HUVEC, gAb increased the activity of eNOS through activating AMP-activated protein kinase (AMPK) by stimulating its phosphorylation at r176 [18]. Severe endothelial dysfunction was observed in the aortic segments of high-fat diet fed rat. After gAb incubation, the endothelium-dependent relaxation was partly improved and total production of NO as a result of enhanced eNOS activity was also increased [18]. Both full-length adiponectin and gAd suppressed ROS induced by high glucose or by treatment of HUVEC with ox-LDL. gAb suppresses excess ROS production under high-glucose conditions via a cAMP/PKA-dependent pathway, an effect that has implications for vascular protection in diabetes [19]. gAd also induces the expression of superoxide dismutase 2 (SOD2), suggesting another mechanisms by gAd to antagonize oxidative stress [20]. Thus, adiponectin reverses endothelial dysfunction through increasing NO production by eNOS phosphorylation, and decreasing NO inactivation by blocking ROS production/enhancing ROS scavenging.

Adiponectin exerts anti-apoptotic effects on endothelial cells. gAb inhibited angiotensin II induced endothelial apoptosis through promotion and stabilization of the association between eNOS and heat shock protein 90 (HSP90) in HUVEC [21]. HMW form of adiponectin dose-dependently suppressed apoptosis and caspase-3 activity in HUVEC. Transduction with dominant-negative AMPK abolished the suppressive effect of adiponectin on HUVEC apoptosis [11].

Adiponectin exerts anti-inflammatory effects in endothelial cells. gAd suppressed tumor necrosis factor-alpha (TNF-)-induced intercellular adhesion molecule-1 (ICAM-1) expression in a dose-dependent manner in mouse aorta and HUVEC. Adenovirus-mediated overexpression of AdipoR1 and AdipoR2 in endothelial cells significantly enhanced the suppressive effects of a subeffective dose of adiponectin on TNF- -induced ICAM-1 expression and nuclear factor-kappaB (NF- B) activation. Promoter reporter assays and small interfering RNA revealed that peroxisome proliferator-activated receptor-alpha may function as an important pathway downstream of adiponectin and its receptors. Thus, upregulation of AdipoRs in endothelial cells potentiates the anti-inflammatory effect of adiponectin [22]. In HUVEC, lymphotoxin (LT)- receptor (LTBR) serves as an interacting partner of AdipoR1, AdipoR1 interacted with LTBR and regulated adiponectin-mediated inhibition of lymphotoxin-induced NF- B activation and the expression of adhesion molecules [23]. However, a PCR array study found that gAd induces the expression of MCP-1, VCAM-1, E-selectin, IL-6, and IL-8, as well as plasminogen activator inhibitor-1 (PAI-1), and colonie stimulating factor-2 (CSF-2), which implicated the possibility of gAd's proinflammatory effects [20].

Adiponectin has anti-atherosclerotic effects. LOX-1 is the major endothelial receptor for ox-LDL, and uptake of ox-LDL through LOX-1 induces endothelial dysfunction and atherosclerosis [24]. Adiponectin inhibited TNF- induced expression of LOX-1 in mouse coronary arterial endothelial cells, and reduced aortic ox-LDL uptake [25].

Adiponectin regulates the function of endothelial progenitor cells (EPC). EPC play an important role in neovascularization and re-endothelization. The phosphorylation of Akt and the activations of Cdc42 and Rac1 were significantly increased by adiponectin. Full-length adiponectin increased the migration activity of EPC, which was completely inhibited by a PI3K inhibitor, siRNA of Cdc42 or Rac1, although siRNA of Akt had no effects, indicating that adiponectin promotes the migration activities of EPC mainly through PI3K/Cdc42/Rac1 [26]. Administration of gAb at physiological concentrations promoted EPC migration and tube formation, and dose-dependently upregulated phosphorylation of eNOS, Akt and augmented NO production. Chronic incubation of EPC in high-glucose medium significantly impaired EPC function and induced cellular senescence, but these suppression effects were reversed by treatment with gAb. gAb reversed high glucose-impaired EPC functions through NO- and p38 MAPK-related mechanisms [27] .

Thus, adiponectin induces gene expression and activation of various signaling pathways, such as AMPK, PI3K/Akt, cAMP/PKA, and NF- B, as well as various MAPKs, including ERK1/2, JNK, and p38MAPK in vascular endothelial cells.

Adiponectin and vascular smooth muscle cells

Adiponectin has been proposed to show anti-atherogenic properties through the inhibitory effects against various growth factors. Adiponectin also suppresses VSMC proliferation and migration through direct binding with platelet-derived growth factor (PDGF)-BB and generally inhibited growth factor–stimulated ERK signal [28]. In cultured VSMC, adenovirus expressing full-length adiponectin attenuated DNA synthesis induced by growth factors including platelet-derived growth factor, heparin-binding epidermal growth factor (EGF)-like growth factor (HB-EGF), basic fibroblast growth factor, and EGF and cell proliferation and migration induced by HB-EGF [29]. Insulin-like Growth Factor-1 (IGF-1) is one of the potent mitogens, which has been considered to play important roles in both atherogenesis and plaque stabilization. Adiponectin inhibits IGF-1-induced VSMC migration by the suppression of ERK1/2, but not Akt activation [30]. HMW or trimeric forms, but not the globular forms induced VSMC differentiation by activating AMPK, leading to the inhibition of mammalian target of rapamycin complex 1 and S6K1, which in turn stabilized IRS-1, driving Akt2-mediated inhibition of FoxO4 and subsequent contractile protein induction. Although adiponectin and rapamycin have similarly beneficial effects on VSMC phenotype, in EC, rapamycin inhibited Akt phosphorylation, whereas adiponectin maintained it [31].

Adiponectin and macrophages

Excessive lipid accumulation in macrophages plays an important role in the development of atherosclerosis. A critical step in the development of atherosclerotic plaques is the infiltration of monocytes into the subendothelial space of arteries where they differentiate into macrophages [32]. Activated macrophages express scavenger receptors and internalize modified lipoproteins, thereby transforming themselves into foam cells. Adiponectin suppresses macrophage to foam cell transformation [33]. Adiponectin reduces lipid accumulation in macrophage foam cells [34] and prevents atherosclerosis by increasing cholesterol efflux from macrophages [35]. In addition, adiponectin selectively increases the tissue inhibitor of metalloproteinase-1

expression in human monocyte–derived macrophages through