Adiponectin and humans

Many studies have emerged highlighting the importance of adiponectin in human cardiac pathologies as well as metabolic diseases. These cardiac pathologies such as coronary artery disease, hypertension and myocardial infarction have been correlated to attenuated circulating adiponectin levels [1-3]. Furthermore, hypoadiponectemia is associated with obesity and diabetes [4-6], indicating it’s correlation with systemic insulin sensitivity and the ability to directly regulate whole body energy metabolism, including the heart. In healthy lean humans, circulating adiponectin levels range from 2-30 mg/L [7]. Adiponectin has attracted much attention lately because of its cardioprotective effects, which are attributed to its anti-inflammatory, insulin sensitizing and antiatherogenic properties [8-10].

Adiponectin is a protein hormone consisting 247 amino acids and is found in chromosome 3q27, which is considered to be a locus that is highly susceptible for the development of metabolic syndrome and coronary heart disease [11-13]. Interestingly, single nucleotide polymorphisms in the adiponectin gene have been reported in humans. Some of these polymorphisms markedly reduce plasma adiponectin levels and predispose the carriers to insulin resistance [14]. I164T polymorphism is one such mutation (isoleucine is substituted by threonine at the 164th position) that is reported to be a causative factor for hypoadiponectemia and the development of type 2 diabetes. Furthermore, individuals with this mutation are highly susceptible for the development of hypertension and coronary artery disease, suggesting the protective role of adiponectin against development of heart disease in humans [15, 16]. Various other polymorphisms in the adiponectin gene were reported in different ethnic groups that were strongly associated with the develop-
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Adiponectin structure

Adiponectin structurally is associated with the complement 1q family and consists of a carboxy terminal globular domain and an amino terminal collagenous domain. The full length adiponectin (fAd) consists of an N–terminal stalk made of 22 collagen repeats and a highly conserved globular domain at the C-terminal [20]. Proteolytic cleavage of fAd by leukocyte elastase produces smaller globular adiponectin (C-terminal) fragments (gAd) [21]. Both fAd and gAd are found to be biologically active and are present in human plasma [20]. Further, these forms of adiponectin (gAd and fAd) mediate distinct and time-dependent effects on cardiomyocyte energy metabolism via AdipoR1 and AdipoR2 [22]. In circulation it has been found that via its globular or collagen domains adiponectin forms various multimer complexes. The three major complexes in plasma are a low molecular-weight trimer (via globular domain interactions), a middle-molecular-weight hexamer, and a high-molecular weight 12- to 18-mer (via collagenous domain interactions) [23]. Highly conserved cysteine residues present at the N-terminal is crucial for the formation of these disulfide bonds [24]. All these adiponectin complexes are biologically active in humans and animal models. HMW forms have been shown to significantly improve circulating glucose in diabetic humans and animal models, suggesting that HMW is the most active form of adiponectin [25]. HMW form is found to be inversely correlated in patients with coronary artery disease while the circulating LMW form remains unchanged. Furthermore, significant weight reduction in patients elevates the circulating HMW form of adiponectin [26]. Therefore, the HMW form may play a more prominent role than the LMW form in exerting protection against development of cardiovascular diseases and obesity.

Adiponectin receptors and signaling in the heart

All forms of adiponectin complexes have been found to mediate their cellular effects by binding to adiponectin receptors, AdipoR1 and AdipoR2. These receptors have seven transmembrane domains and are functionally and structurally distinct from G-protein coupled receptors (GPCR) because of its inversed topology with the internal N-terminal and external C-terminal. AdipoR1 is ubiquitously expressed and is most abundant in skeletal muscles while AdipoR2 is abundantly expressed in liver [27]. Adiponectin receptors are expressed in human cardiomyocytes, cultured HL1 (murine derived atrial cardiomyocytes) cells, neonatal rat cardiomyocytes and abundant in isolated adult rat ventricular cardiomyocytes [28, 29]. In addition to AdipoR1 and AdipoR2, T-cadherin has also been identified as an important receptor to sequester adiponectin protective mechanisms in the heart [30]. T-cadherin is a cell surface glycoprotein and is abundant in the myocardium [31].

The downstream effectors of adiponectin include APPL1, which was identified to act as an adaptor protein by directly interacting with AdipoR1 and AdipoR2 in primary rat adult cardiomyocytes [32]. APPL1 has many functional domains and is highly expressed in the heart [33, 34]. The interaction of APPL1 and adiponectin receptors promotes LKB1 translocation from the nucleus to the cytoplasm and induces anchoring of LKB1 to AdipoR – APPL1 complex in cardiomyocytes. Under normal physiological conditions LKB1 is localized in the nucleus [32]. LKB1 interaction with APPL1-AdipoR complex leads to activation of AMP activated protein kinase (AMPK), which mediates many cardioprotective effects. AMPK is an important mediator of regulating cellular metabolism during stress conditions. However, the full formation of AdipoR-APPL1-LKB1 complex by adiponectin signaling remains unknown. The cardioprotective effects attributed by adiponectin-AMPK signaling are further described in this review.

Cardiac derived adiponectin

Adiponectin, once thought of being exclusively secreted by adipose tissue has now been found to be secreted by human and murine cardiomyocytes as well. The levels of adiponectin produced by cardiomyocytes are relatively low in comparison to amounts produced by adipose tissue; therefore its contribution towards the circulating levels of adiponectin is minimal. However, adiponectin produced by cardiomyocytes can directly regulate cardiac metabolism by AMPK activation. These effects are found to be sequestered via cardiac AdipoR1 and AdipoR2, indicating cardiac derived adiponectin to act via an autocrine/paracrine mechanism [28]. Further work by Amin et al has shown that
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Figure 1. Endogenous heart specific adiponectin isoforms. Isolated neonatal cardiomyocytes produce adiponectin isoforms, including the high molecular weight form (HMW = High molecular weight, MMW = Medium Molecular Weight and LMW = Low Molecular Weight). Adiponectin oligomers were resolved by western analysis under non-reducing and non-denaturing conditions as described previously [34].

the adiponectin produced by cardiomyocytes is multimeric in form and is functional [35] (Figure 1). Cardiac derived adiponectin and cardiac adiponectin receptor expression is significantly reduced in human hearts with moderate to severe dilated cardiomyopathy (DCM). This down regulation of cardiac derived adiponectin was found to be functionally significant and may play a significant role in the pathogenesis of heart failure in humans [36]. Furthermore, the exact molecular signaling pathway of adiponectin (systemic and cardiac derived) mediated cardioprotection in humans is not known. However, rodent models are extensively used to elucidate how adiponectin sequesters its cardioprotective effects against numerous cardiac pathologies, which are discussed below.

Cardioprotective mechanism of adiponectin against ischemia reperfusion (I/R) injury

Individuals with hypoadiponectemia were found to have higher incidences of myocardial infarction independent of other cardiovascular risk factors [3, 37]. Furthermore, adiponectin helps to maintain the integrity of the cardiomyocytes surrounding the infarcted region and plays a critical role in myocardial remodeling after ischemic injury in humans [38]. Many studies conducted on experimental animal models demonstrate that adiponectin can exert protection against ischemia/reperfusion (I/R) injury. Intracoronary administration of adiponectin immediately before reperfusion in Polish domestic pigs has significantly reduced the infarction and apoptosis due to I/R injury [39]. Furthermore, adiponectin was found to act against the adverse post I/R cardiac remodeling by increasing myocardial survival, maintaining capillary density and attenuating cardiac fibrosis in mice [40]. T-cadherin was found to be crucial to mediate adiponectin protective effects against I/R injury in the heart [30].

Additionally, cardiac derived adiponectin was also found to play a prominent role in exerting protection against hypoxia-reperfusion injury in cardiomyocytes. Interestingly, ablation of locally produced adiponectin had a higher adverse impact on cardiomyocytes subjected to hypoxia reperfusion than ablation of cardiac AdipoR1 and AdipoR2 under the same conditions [41]. It was also found that cardiac derived adiponectin was significantly reduced (by 74%) in db/db (type 2 diabetic animal model) hearts, suggesting that the autocrine and paracrine effect of adiponectin was impaired in the diabetic heart. Recently it was observed that HIF-1 (Hypoxia Inducible Factor), the master transcription factor of regulating hypoxia in the cells can transcriptionally activate cardiac derived adiponectin. This was further confirmed by identifying presence of HIF response elements (HRE) sites in the adiponectin promoter. The HIF-1 mediated activation of adiponectin in response to ischemia attenuate post-ischemic injury in the diabetic heart [42].

Administration of adiponectin at the onset of ischemia protected the heart from contractile dysfunction and limits the infarction size by increasing the activation of AMPK-Akt-eNOS signaling pathway in isolated rat hearts [43]. Cardioprotective effects of NO (nitric oxide) produced by eNOS is well established as demonstrated by enhanced vasodilation, anti-inflammatory effects, reduced platelet adhesion/ aggregation and attenuated reactive oxygen species (ROS) production [44]. Interestingly, adiponectin can differentially regulate NO (nitric
Adiponectin and cardiac pressure overload/hypertrophy

Hypertension is one of the major risk factors for development of cardiac hypertrophy leading to heart failure [52]. It was found that adiponectin levels are inversely correlated in individuals with hypertension and left ventricular mass, thus hypoadiponectemia is suggested to be a biological marker for future development of hypertension [53, 54]. This was further confirmed by utilizing transgenic animal models such as adiponectin k/o mice. These mice had greater hypertrophy after trans-aortic constriction (TAC – left ventricular pressure overload model) compared to wild type [55]. Furthermore, adiponectin k/o mice developed salt induced hypertension and adiponectin supplementation ameliorated this effect [2]. Interestingly, T-cadherin disruption also exacerbates cardiac hypertrophy under pressure overload to a level comparable to adiponectin k/o mice. Therefore, it can be concluded that T-cadherin plays a crucial role in sequestering the cardioprotective effect by adiponectin against pressure induced hypertrophy [30].

It is well established that AMPK activation is increased in response to cardiac stress as a compensatory effect in mice. Adiponectin was found to activate AMPK in cardiomyocytes and sequester protective signaling mechanisms against cardiac remodeling. Adiponectin k/o mice subjected to TAC had severely attenuated AMPK levels and underwent extensive cardiac remodeling. This confirms that adiponectin is required to activate AMPK response to hypertrophic stress [55]. Additionally, it was observed that adiponectin deficient mice subjected to TAC are susceptible to greater hypertrophy, systolic dysfunction and attenuated myocardial capillary formation in response to stress compared to wild type. The impaired angiogenesis associated with adiponectin deficiency was due to reduction of AMPK induced vascular endothelial growth factor (VEGF) production [56]. Furthermore, adiponectin-AMPK mediated inhibition of ERK phosphorylation is vital to mitigate the hypertrophic signals induced by pressure overload, adrenergic stimulation, angiotensin II
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Adiponectin plays a protective role against ROS and cardiac remodeling

Hypertension, IR injury, myocardial infarction and diabetes contribute to increase reactive oxygen species (ROS) production systemically and in the heart. ROS acts as second messengers and affects intracellular signaling pathways that results in cardiomyocytes death, myocardial remodeling and the eventual heart failure. ROS is also responsible for initiating cardiac hypertrophy by activating MAPK, p38, ERK, and NF-kB pathways [60-63].

Exogenous adiponectin (gAD) treatment significantly reduced ROS production and subsequent cytochrome C release and apoptosis in H9C2 (rat embryonic cardiac myoblasts) cells subjected to hypoxia and reperfusion. AdipoR1-APPL1 plays a vital role in sequestering these adiponectin mediated antioxidant effects [64]. Pre-treatment of adult rat ventricular myocytes with adiponectin ameliorated H2O2 mediated increase in ROS production. ROS is a known activator of metalloproteinase (MMP) which induce cardiac hypertrophy and remodeling. Adiponectin specifically attenuated H2O2 mediated MMP-2 and MMP-9 activity and confer protection against ROS induced cardiac remodeling [65]. ERK activation is also involved in the development of ROS mediated cardiac hypertrophy. Adiponectin was found to inhibit the ROS associated ERK activation in cardiomyocytes. This cardioprotective effect was mediated by an adiponectin – AMPK signaling pathway [65][77].

Beneficial effects of adiponectin upon myocardial metabolism

The preferred substrate for energy metabolism in the heart are fatty acids, which accounts for 70% of the total ATP generated and glucose oxidation generating the remainder of the total ATP. This substrate preference is altered during the development of chronic pathological conditions, such as hypertrophy, heart failure, obesity and diabetes. Furthermore, this dysregulation in myocardial energy utilization leads to the inability of the heart to respond to many stresses such as myocardial infarction and dilated cardiomyopathy [66]. Many reports claim the ability of adiponectin to have profound effects on fatty acid oxidation and glucose oxidation via activation of AMPK signaling pathway.

Ventricular hypertrophy associated with hypertension and pressure overload shifts the myocardial energy metabolism from fatty acid utilization towards glucose oxidation [67, 68]. Therefore, adiponectin – AMPK signaling induces phosphorylation of acetyl CoA carboxylase (ACC), an important mediator of fatty acid oxidation, thus shift the fatty acid metabolism from synthesis towards beta oxidation [32, 69]. Exogenous adiponectin administration increased the phosphorylation of ACC through AMPK and reduced ACC activity in cultured neonatal cardiomyocytes treated with Endothelin-1 (ET-1), and inhibits the hypertrophy [58]. Additionally, adiponectin-AMPK signaling increases the translocation and membrane insertion of CD36 in primary adult cardiomyocytes [32]. Translocation of CD36 from intracellular compartment to the sarcolemma mediates the uptake of long chain fatty acids and is the rate limiting step in FA utilization in the heart [70]. Adiponectin enhances the gene expression and activity of CPT-1 (carnitine palmitoyltransferase), which increase the beta oxidation of long chain fatty acids in neonatal cardiomyocytes as well. It is suggested that activation of AMPK subsequently activates P38 MAPK, resulting in PPARγ activation and increased CPT-1 mRNA expression [71]. Therefore, adiponectin increases cardiac FA utilization and contributes to inhibition of cardiomyocyte hypertrophy [57].

Recently it has been found that a positive correlation exists between plasma adiponectin and LPL in humans [72]. LPL is abundant in the heart and is the rate limiting enzyme for hydrolysis of triglycerides from chylomicrons and very low density lipoproteins (VLDL). Therefore, LPL increases the availability of free fatty acids and utilization in the myocardium [73]. Adiponectin treatment increases cell surface expression of LPL and activity in isolated rat cardiomyocytes through remodeling actin cytoskeleton [74]. Cytoskeleton remodeling which involves reversible polymerization of G to F actin mediated by
RhoA-ROCK (Rho coiled coil forming) signaling pathway, is important for the translocation and activation of LPL [75, 76]. Adiponectin changes the LPL distribution pattern by activation of RhoA-ROCK axis and consequently enhances the phosphorylation and inhibition of cofilin, which is an actin de-polymerization protein [74]. All these observations suggest that adiponectin promotes efficient utilization of fatty acids and thus improve the outcome of hypertrophied and the failing heart.

Detailed analysis on the effect of gAd and fAd demonstrate that both forms of adiponectin stimulate glucose uptake in cardiomyocytes and have similar effects on ACC activity in neonatal cardiomyocytes. Both gAd and fAd increase glucose uptake initially, but after 24 hours of the treatment, glucose oxidation is reduced and fatty acid oxidation is elevated resulting in the inhibition of pyruvate dehydrogenase. Most interestingly, it was observed that the acute effects of gAd are mediated through AdipoR1 while the acute effects of fAd are mediated via AdipoR2 [22].

Adiponectin and the diabetic heart

Cardiovascular complications are the leading cause for morbidity and mortality in diabetics [77]. Decreased adiponectin levels are observed in patients with type II diabetes [5] and many studies support the predictive nature of low plasma adiponectin for the future development of diabetes [78-80]. Furthermore, it was shown that increased plasma adiponectin levels significantly increases insulin sensitivity independent of percentage of body fat and obesity in human subjects [81] (Figure 2).

Cardiac sensitivity for adiponectin is altered during the progression of type I diabetes. At the initial stages of the disease both exogenous and endogenous adiponectin fails to protect the heart from cardiac damage sustained from I/R injury, which may be due to significant reduction in AdipoR1 expression in the heart at this stage. The levels of AdipoR1 are restored in the heart as type I diabetes progresses. However, during the late stages of type 1 diabetes, the systemic levels of adiponectin are attenuated and therefore, the cardiomyocytes are more susceptible to damage from I/R injury [82].

The significance of cardioprotection from adiponectin in the diabetic heart is illustrated in db/db mice that were subjected to TAC. The db/db mice developed greater left ventricular posterior wall thickness and increased intraventricular septum when compared to the sham mice. The maladaptive response to TAC observed in db/db mice was ameliorated by adenovirus mediated supplementation of adiponectin [57]. Furthermore, short term adiponectin treatment can significantly ameliorate the contractile dysfunction associated with elevated endoplasmic reticulum (ER) stress in db/db cardiomyocytes. Adiponectin treatment significantly improved calcium handling and cardiomyocyte contraction in db/db cardiomyocytes [83] (Table 1).

In contrast to hypertrophy and heart failure, myocardial energy substrate utilization shifts more towards fatty acid oxidation from glucose.
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Table 1. Cardioprotective mechanisms of adiponectin isoforms

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oxidation in obesity and diabetes [84]. In diabetic/obese heart, fatty acid uptake is elevated to a level that cannot be met by the rate of fatty acid oxidation, leading to lipid accumulation and lipotoxicity [85, 86]. One of the contributing factors for cardiac contractile dysfunction associ-
ated with diabetes and obesity is lipotoxicity [85]. Therefore, adiponectin can exert beneficial effects on the diabetic/obese heart by increasing the efficiency of fatty acid oxidation and utilization and attenuate lipotoxicity. It was observed that adiponectin-AMPK signaling was able to enhance the insulin mediated phosphorylation of Akt, thus stimulate the glucose uptake in primary adult cardiomyocytes [32]. Therefore, adiponectin can offer a profound protection against the adverse cardiac events associated with metabolic derangement in the diabetic/obese heart.

PPAR and adiponectin

Many studies support the cardioprotective effects conferred by adiponectin against development of various cardiac pathologies. Further, it has the potential of being utilized as a biological marker to predict future development of cardiovascular diseases and diabetes. Therefore, development of therapeutic agents which can increase the adiponectin levels (systemic and cardiac derived) will greatly benefit patients with diabetes and cardiovascular diseases.

PPARγ is the master regulator of adipocytes differentiation and is involved in regulating many adipocytes specific genes. Its synthetic agonists, thiazolidinediones (TZD) are used in the treatment of diabetes as insulin sensitizers. Troglitazone, rosiglitazone and pioglitazone are members of the TZD class of insulin sensitizing drugs. TZD derivatives are known to induce adiponectin secretion from human and rodent adipocytes by binding to peroxisome proliferator response element (PPRE) region in the adiponectin promoter [87]. TZD treatment also improves the ratio of HMW to total adiponectin ratio in human and mice plasma and contributes to the insulin sensitizing effect of the drug [25]. PPARγ activation can regulate adiponectin and adiponectin receptor expression in isolated cardiomyocytes [29, 35, 41]. PPARγ induced activation of adiponectin and subsequent AMPK activation, profoundly affect the energy metabolism in the heart by increasing fatty acid oxidation and glucose uptake [29]. Rosiglitazone can induce cardiac specific adiponectin production which acts in an autocrine/paracrine mechanism predominantly through AdipoR1 and offer protection against I/R injury. Interestingly, absence of both AdipoR1 and AdipoR2 significantly increased basal cardiac adiponectin levels and potentiate protection offered by rosiglitazone. Even though this observation is not fully understood, a possible explanation would be that cardiac adiponectin is capable of acting through T-cadherin receptors present in cardiomyocytes as well [41]. The studies carried out by Amin et al have shown that rosiglitazone can inhibit adrenergic induced cardiac hypertrophy [35]. Further, rosiglitazone treatment in cultured cardiomyocytes significantly increased the expression and secretion of all forms of adiponectin, most significantly the high molecular weight form of adiponectin. Lastly, this group demonstrated that adiponectin and it receptor, AdipoR1 are required for PPARγ mediated AMPK activation in cultured cardiomyocytes [35].

In respect towards other PPARγ agonists, pioglitazone was found to significantly reduce angiotensin II induced fibrosis and cardiac hypertrophy in wild type mice, but the cardio-protective effect was abrogated in adiponectin deficient mice [88]. This study found that Pioglitazone attenuated angiotensin II induced ERK phosphorylation, increased circulating adiponectin levels and subsequent increase in AMPK phosphorylation in the heart. However, these cardio-protective effects of pioglitazone were not observed in adiponectin deficient mice [88].

As previously mentioned, adiponectin offers protection against cardiac fibrosis associated with angiotensin II. This cardioprotective effect was found to be mediated through adiponectin-AMPK-PPARγ pathway, which can enhance the activity of antioxidant enzymes, thus suppressing ROS mediated propagation of cardiac fibrosis and heart failure. Adiponectin treatment significantly reduces cardiac fibrosis mediated by angiotensin II in adiponectin k/o mice [89].

Conclusion

In this review, we have discussed adiponectin mediated activation of several cardioprotective signaling pathways in the heart against the formation of several cardiac pathologies. Circulating and cardiac derived adiponectin levels are significantly attenuated in diabetes, obesity and in cardiovascular diseases. Adiponectin sequencers it’s downstream signaling through activation of AdipoR1 and AdipoR2 in cardiomyocytes. T-cadherin was also identified as a receptor for adiponectin. APPL1 and LKB1 are downstream molecules of adiponectin signaling pathways.
Cardioprotective signaling of adiponectin

Most of these cardioprotective signaling mechanisms of adiponectin are mediated through activation of AMPK. Adiponectin has anti-inflammatory, antioxidant and anti-apoptotic properties which exert protection against I/R injury. Adiponectin has also been shown to be protective against cardiac remodeling and hypertrophy. TZDs can induce circulating and heart specific adiponectin expression and subsequently activate AMPK (Figure 3). However, the downstream targets of the adiponectin signaling pathway have not been fully identified. For example, the signaling molecules between APPL1 and AMPK remain unknown. Furthermore, most of the current studies have demonstrated the cardio protective effects of exogenous or circulating adiponectin. As cardiac derived adiponectin is found to be functional, the need to better understand the biological significance of cardiac specific adiponectin is important because it can serve as a direct target for pharmacological therapeutics.

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