1. Oxidative stress and adipokines and their health implications

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Abstract. Various studies have shown that, oxidative stress is largely responsible for the production of adipokines such as adiponectin, plasminogen activator inhibitor (PAI)-1 and interleukin-6 (IL-6) in the adipose tissue. The adipose tissue is an active participant in regulating physiologic, biochemical and pathologic processes, including, inflammation, carbohydrate/lipid metabolism, cardiovascular diseases (CVD), diabetes, and obesity. The regulatory function of the adipose tissue is made possible by the secretion of biologically active adipokines, including leptin, adiponectin, resistin among others. These active molecules exert profound anti-diabetic, anti-atherogenic, and anti-inflammatory roles. Oxidative stress thus, directly or indirectly plays a critical role at the molecular level through various physiologic and biochemical interactions to influence cellular activities. In the diabetic condition for example, oxidative stress impairs glucose uptake in muscle and fat and decreases insulin secretion from pancreatic β cells. Increased oxidative stress also underlies the pathophysiology of hypertension and atherosclerosis by directly
affecting vascular wall cells. The evolving role of adipokines in endothelial dysfunction and its molecular interaction with oxidative species may thus, add a new dimension to our understanding of molecular processes and its concomitant influence in disease states.

Introduction

The adipose tissue is responsive to central and peripheral metabolic signals. The tissue secretes a wide-range of bioactive substances that are peptide in nature. These substances are collectively called "adipokines." The widely noted adipokines include leptin, resistin, adiponectin, plasminogen activator inhibitor 1 (PAI-1). The adipokines are involved in a variety of physiological and biochemical processes including; homeostasis, vascular toning, energy balance, fat metabolism among others. Oxidative stress has been shown to be largely responsible for the production of these adipokines (Chena et al. 2009).

Among adipokines, leptin mediates different effects on cells of vessel wall. It evokes oxidative stress on endothelial cells, increased production of adhesion molecules, chemokines and promotes cell proliferation (Cooke and Oka, 2002). Recent studies have suggested that adipokines may interact in regulating metabolic homeostasis (Yu and Ginsberg, 2005. Ahima and Flier, 2000). It has been shown that fat accumulation itself could induce systemic oxidative stress in the obsessed state independent of hyperglycemia and cause a deregulation of adipokine production (David et al., 2005). The evolving role of adipokines in endothelial dysfunction and its molecular interaction with oxidative species may thus, add a new dimension to our understanding of complex biological processes which may have a multi-facet application in science, medicine and the pharmaceutical industry.

Oxidative stress

Oxidative stress (OS) has been defined as a “disturbance in the prooxidant-antioxidant balance in favour of the former, leading to a potential damage” (Halliwell and Gutteridge, 2007). Such damage is often called oxidative damage. It can be deduced from this definition that, oxidative stress is the overall consequent effect of reactive oxidative species (ROS) in the absence or limited supply of anti-oxidants which can impact negatively on cells, tissues or organs. It should however, be emphasized that not all damage caused by oxidative stress is oxidative damage. Increased oxidative damage can result not only from more oxidative stress, but also from failure of repair or replacement systems. Various research evidence have shown the
occurrence of oxidative damage *in vivo*. Two major causes of oxidative stress at cellular level have been given (Halliwell and Gutteridge, 2007). The first is *diminished levels of anti-oxidant defences* such as glutathione (GSH) or superoxide dismutase (SOD). For example, studies have shown that children with the protein-energy malnutrition disorder *Kwashiorkor*, prevalent mostly in Sub-Saharan African, suffer oxidative stress due to low levels of GSH. Secondly, oxidative stress can result from *excessive production of free radicals* by exposure to high levels of oxygen or excessive activation of the so-called “natural systems” that produce free radicals. In conditions of chronic inflammation for example, phagocytic cells are activated to generate free radicals. It should however, be pointed out that whatever the cause, oxidative stress can have damaging consequences on a given cell, tissue or organ. *In vivo* consequences of oxidative stress will depend on the cell-type exposed to the oxidative stress and the severity of the exposure. Among the consequences of oxidative stress are; *cellular proliferation, cellular adaptation, cell injury and cell death* (Halliwell and Gutteridge, 2007). It should be stressed further that, exposure of cells to the effect of oxidative stress is not a simple phenomenon but a complex series of processes that can activate a wide range of cellular signaling pathways which may include the production of adipokines in the adipocytes. Indeed, there is a growing evidence to support that ligand-binding and activation of receptor protein kinases to elicit phosphorylation is aided by reactive oxidative species (Nathan, 2003).

### The adipokines

The adipokine, *Leptin* is a pro-inflammatory protein that is a member of the IL-6 super-family of the cytokines. It is produced mainly by white adipose tissues and function to regulate energy balance. Leptin levels have been shown to be associated with renal function and poor nutrition. Studies have shown that high levels of leptin may be an important cause of uremic cachexia (Mak *et al.*, 2006). A study in which experimental mice with the same genetic background (C57BL/6J) were used to test whether indeed, hyperleptinemia is a cause of uremic cachexia, showed that uremic cachexia was impaired in B6.Cg-m<sup>+/+</sup>Lepr<sup>db/db</sup> mice, a model of leptin receptor deficiency (Mak and Cheung, 2007). Surprisingly, no change in weight gain, body composition, resting metabolic rate (RMR) were observed among the animal model after they have undergone nephrectomy. Again, the study observed that, experimental uremic cachexia could be ameliorated by blocking leptin signaling through the hypothalamic MC-4R. The study
concluded that inhibition of leptin signaling may provide a novel therapeutic strategy for inflammation-associated cachexia in chronic kidney disease (CKD) (Mak et al., 2006).

Another important adipokine is Adiponectin; an adipocyte hormone, which has been shown to be involved in the metabolism of macromolecules particularly, carbohydrates (glucose) and lipids. Great interest has been shown by researchers in this molecule because of its atherogenic and cardioprotective properties. A study, showed a decrease in blood adiponectin levels in patients with coronary artery disease and with type II diabetes (Zoccali et al., 2002). Interestingly, the observed plasma adiponectin levels were inversely related to the severity of cardiovascular injury. Again, other studies have indicated a high risk of cardiovascular death among patients with end-stage renal disease (ESRD) and low plasma adiponectin (Heimbürger and Stenvinkel, 2005). Adiponectin also exhibits anti-inflammatory activities. It, for example, inhibits IL-6 production accompanied by the induction of the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist. The anti-inflammatory properties of adiponectin is buttressed by it inhibition of the nuclear factor kappaB by adiponectin (Gable et al., 2006). It has thus been suggested that replenishment of adiponectin might represent a novel therapeutic treatment for ESRD (Mak and Cheung, 2007).

Resistin is another class of adipokine synthesized and secreted by the adipose tissue. It is a peptide hormone. Studies have shown that abnormal expression of resistin is often associated with insulin resistance and, glucose intolerance. The glucogenic effect of resistin have been demonstrated in various studies (Steppan et al., 2001). For example, levels of resistin have been shown to rise in both diet-induced obesity and genetic models of combined obesity and diabetes. Again, when experimental animals fed with a normal or a high-fat diet, resistin-deficient mice showed significantly, a better glucose tolerance than did wild-type mice (Banerjee et al., 2004).

Physiologically, resistin is vaso-active and plays a role in early stages of atherosclerotic lesion formation. This property of resistin has been demonstrated in cultured endothelial cells where adhesion molecule 1 and monocyte chemoattractant protein 1 were expressed in presence of resistin. Like adiponectin, resistin also exhibits pro-inflammatory properties. It influences proinflammatory effects on smooth muscle cells and the kidneys (Verma et al., 2003). It has been suggested that, decreased glomerular filtration rate and inflammation associated with chronic kidney disease (CKD) patients may be due to elevated levels of resistin in the kidney which is an important site of resistin clearance (Axelsson et al., 2006).
Molecular linkage between oxidative stress and the adipokines in disease states

In obesity, oxidative stress is responsible for the aberrant production of adipokines such as adiponectin, plasminogen activator inhibitor (PAI)-1 and interleukin-6 (IL-6), which is causally associated with obesity-related inflammation, insulin resistance and cardiovascular disease. However, the signaling transduction pathways participating in adipokine dysregulation induced by oxidative stress are largely unknown. Adipokines appear to play a central role and conceivably may serve as the cellular link mediating both the metabolic syndrome of insulin resistance and the endothelial dysfunction present in the obese state (Fig. 1). It has been hypothesized that fat accumulation itself could increase systemic oxidative stress independent of hyperglycemia, and that, increased oxidative stress in obesity might relate to the dysregulated production of adipocytokines (David et al., 2005). Adipokine levels appear to correlate closely with adiposity, with increasing levels in subjects with higher body mass index (BMI) (Azuma et al. 2003). In a study to find the association between oxidative stress and obesity-related disorders, it was shown that oxidative stress, in different ways of exposure, regulates gene expression of various adipokines in 3T3-L1 adipocytes (Kamigaki et al 2006). It was also observed that secretion levels of adipokines changed by oxidative stress, in parallel with mRNA expression levels. The study suggested that oxidative stress, even of short duration, has a significant impact on the regulation of various adipokine gene expressions favoring atherosclerosis.

In the diabetic condition, oxidative stress impairs glucose uptake in muscle and fat and decreases insulin secretion from pancreatic β cells. Again, certain diabetogenic agents like alloxan act by imposing severe oxidative stress on the β cell. Studies have also shown that, by exposing human islet cells to a mixture of IL-1β and IFNγ, injured the cells but over-expression of antioxidant enzymes did not confer any protection (Chen et al., 2005). It is quite uncertain as to whether OS is a primary cause of diabetes. However, it is certain that diabetes does cause OS. This has been confirmed by the elevation of F2-IPs and lipid peroxides in diabetetics (Davi et al., 2004).

In a study to investigate associations of adiponectin, leptin, C-reactive protein (CRP), interleukin (IL)-6, and serum amyloid A (SAA), individually or in combinations, with risk of incident type 2 diabetes in an aboriginal Canadian population, it was observed that, low adiponectin, high leptin, and low adiponectin-to-leptin ratio at baseline were associated with increased risk of incident type 2 diabetes and metabolic syndrome variables including obesity (Ley et al. 2008). In an independent study to evaluate cardiovascular
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Figure 1. Interactions between the adipokines and the adipose tissue, skeletal muscle, liver and pancreas in obesity. The potential interactions between adipokines and tissues indicated above have both direct and indirect effects on adipose energy homeostasis. The adipokines induce insulin resistance and adaptive hyperinsulinaemia which are thought to cause endothelial dysfunction and promote proatherogenic effects.

disease risk a youth group (12-15 yr) with and without type 2 diabetes mellitus (T2DM) or obesity by comparing pro- and anti-inflammatory adipokines, markers of oxidative stress and the plasma phospholipid fatty acid profile, it was observed that plasma tumor necrosis factor-alpha (α-TNF), C-reactive protein, resistin, and total antioxidant status were not different among the three groups. However, plasma total leptin, soluble leptin receptor, and free leptin were significantly higher in the T2DM group than the control. Similarly, oxidized low-density lipoprotein was higher in the T2DM group compared with controls but not in the obese group. Again, interleukin-6 was significantly higher in the T2DM group compared with both the control and the obese groups, suggesting that T2DM, but not an...
increase in adiposity, was responsible for this elevation. It was concluded that changes in plasma adipokines and oxidative stress can be detected in patients with T2DM. However, many of the changes were mirrored in obese youth, suggesting that both populations are at an increased risk for future cardiovascular complications (Stringer et al., 2009). Recent studies have also shown that plasma adiponectin levels correlated inversely with the markers of systemic oxidative stress in non-diabetic human subjects (Shina et al., 2006).

Summary

The adipokines are involved in a variety of physiological and biochemical processes including homeostasis, vascular toning, energy balance, fat metabolism among others. Oxidative stress has been shown to be largely responsible for the production of these adipokines. It is thus likely, that oxidative stress, even of short duration may have a significant impact on the regulation of various adipokine gene expressions which at cellular level will regulate or de-regulate various physiological and biochemical pathways in health and disease conditions. This offers a novel opportunity for vigorous research to the understanding of the molecular linkages of oxidative stress and adipokines and their plausible concomitant effects.

References