Cellular & Molecular basis of metabolic syndrome

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The metabolic syndrome is a multi-facet condition characterised by visceral adiposity, insulin resistance, dyslipidaemia, and hypertension, all of which contributes to the development of low-grade inflammatory state, atherosclerosis and abnormal glucose intolerance. Various hypotheses had been put forward including thrifty genes, appetite control involving the limbic-hypothalamic system and altered homeostatic mechanisms to explain the interaction between genetic, intrauterine and environmental factors that lead to the syndrome. However, insulin resistance remains the unifying factor underlying all the clusters of the metabolic syndrome.

Even though existing clinical, epidemiological and experimental data support the role of insulin resistance as an important aetiologic component of this syndrome, current evidence suggest that neurohormonal mechanisms, including an endocrine function of adipocytes has a fundamental role to play. This is supported by the strong relationship between central adiposity and all the components of the syndrome, unlike the inconsistent association between the syndrome and the markers of insulin resistance.

Traditionally, adipocytes store excess calories as triglyceride in fat particles, thus acting as energy warehouses. Of late adipocytes have recently been found to regulate metabolic function by producing a whole range of cytokines, aptly named adipocytokines. While some adipocytokines, such as tumour necrosis factor-alpha and resistin induce insulin resistance, adiponectin on the other hand is an adipocytokine that has anti-diabetic and anti-atherogenic properties. Another visceral fat-derived adipocytokine, visfatin was identified recently with insulin-like activities. Thus, adipocytes play an important role in the regulation of energy metabolism and in the pathogenesis of metabolic syndrome. In addition to visceral adipocytes, increased free fatty acids and lipid accumulation in certain organs also contributes to insulin resistance.

At the cellular level, the peroxisome proliferator-activated receptors (PPARs) are a group of nuclear fatty acid receptors that are recognised to have important roles in metabolic syndrome. The three PPAR subtypes α, β and ɤ have distinct functional

activities. For example, heterozygous PPAR ɤ-deficient mice are found to be protected from the development of insulin resistance as a result of adipocyte hypertrophy triggered by a high-fat diet. Similarly, a Pro12Ala polymorphism in the human PPAR ɤ 2 gene, which has been reported to cause a reduction in PPAR ɤ activity, was associated with a decreased risk of type 2 diabetes in various ethnic groups including Japanese. It has been shown that moderate reduction of PPAR ɤ activity by RXR antagonist also decreased the triglyceride content of white adipose tissue (WAT) including the ones in muscle and liver, due to an increase in fatty-acid utilisation and a reduction in lipogenesis, thereby reducing high-fat diet-induced obesity and insulin resistance. In addition, studies have shown that the potent activation of PPARɤ by thiazolidinedione (TZD) which stimulates adipocyte differentiation and apoptosis prevents adipocyte hypertrophy. This in turn had the effect of alleviating insulin resistance due to the decreases in FFA and TNF α, and the up-regulation of adiponectin.

The activation of PPAR ɤ receptors induces the transcription of specific target genes, including adiponectin and LXR α, which regulates cholesterol metabolism. The liver X receptor α (LXR α), agonists induce glucose uptake and lipogenesis in adipocytes. Both PPAR ɤ and LXR α allow adipocytes to function effectively as sensors of lipid metabolism.

Another important consideration is the role of free fatty acids (FFA) in mediating insulin resistance thus metabolic syndrome especially in organs such as the liver, muscle and adipose tissue. It has been shown that the chronic influx of glucose and fatty acids into the cells of these organs resulted in an increased burden on the mitochondria, the only organelle that is capable of metabolising these two nutrients. The excessive fatty acid uncouples the action of the mitochondria and impairs its ability to metabolise glucose. In the pancreatic beta cells, this process also uncouples the serine phosphorylation of insulin receptor and insulin receptor substrate-1 resulting in impaired insulin secretion. Furthermore when fat gets into these cells, lipid intermediates are generated that leads to the formation of dangerous reactive oxygen species that cause abnormal signalling and dysfunction of the cells. In general, much of the effect of visceral fat on cardiovascular risk factors is mediated through the metabolic actions of free fatty acids (FFA) on insulin resistance, thus resolving

any lingering issue between obesity versus insulin resistance in mediating metabolic syndrome.

Pathways leading directly from central adiposity to the genesis of glucose intolerance, dyslipidemia, hypertension, low-grade inflammation and ultimately accelerated artherosclerosis have been elucidated which involved various fat-derived adipocytokines. Future therapies may accrue from the aggressive pursuit of newer molecular drug targets that have the potential to prevent or treat multiple aspects of the metabolic syndrome.