

ADIPOCYTE- AN ENDOCRINE ORGAN

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Abstract : The adipose tissue primarily consists of two functionally distinct types- brown and white adipose tissue. Brown adipose tissue is specialized for heat production by non-shivering thermo genesis and metabolism of this fat doesn't produce ATP. Whereas the white adipose tissue serves as a major energy reservoir and stores triacylglycerols in periods of energy excess and mobilizes the same during energy deprived states. White adipocytes are the major secretory cells of adipose tissue, making it a key endocrine organ. Adipocytes secrete a number of hormones and diverse range of protein factors termed as 'adipokines', which are collectively involved in metabolic regulation and are linked to pathogenesis of obesity. Adiponectin is the most abundant protein produced by adipose tissue, and it plays a negative feedback role in fat storage. Adiponectin is an endogenous anti-inflammatory and anti-atherogenic factor that is protective against insulin resistance and macroangiopathy. It has been seen that low circulating serum adiponectin levels correlate strongly with increasing BMI, obesity and insulin resistance. Leptin was one of the earliest adipokines to be identified as the product of ob gene in mice. Primary target of leptin is the hypothalamic arcuate nucleus and its systemic response is inhibition of food intake and an increase in overall energy expenditure. Apart from these hormones, adipocytes also secrete a number of cytokines and acute phase proteins, thus leading to increase in the circulating levels of inflammation related factors. This lead to emergence of the concept that obesity is a state of chronic mild inflammation and this inflammatory state plays a causal role in development of Type-2 Diabetes and metabolic syndrome in obese individuals.

INTRODUCTION

Obesity is a prevalent health hazard particularly in industrialized countries and is closely associated with a number of pathological disorders, including non-insulin-dependent diabetes, hypertension, cancer, gallbladder disease, and atherosclerosis.^{1, 2} Obesity is fundamentally a problem of energy balance; it develops when energy (food) intake is in excess of total energy expenditure (Basal Metabolic Rate, 'thermogenesis', physical activity, 'non-exercise activity thermogenesis'). Differences between intake and expenditure are primarily buffered by changes in the amount of lipid (triacylglycerols) deposited in the specialized fuel storage organ, white adipose tissue (or white fat).

The adipose tissue primarily consists of two functionally distinct types – brown and white adipose tissue. Brown adipose tissue is specialized for heat production by non-shivering thermogenesis, and in this tissue the stored lipid droplets serve primarily as a fuel for the production of heat. The mitochondria in these cells are unique; their membranes contain an uncoupler of oxidative phosphorylation (UCP -1 protein) and metabolism of this fat does not produce ATP. Whereas the white adipose tissue serves as a major energy reservoir and stores triacylglycerols in periods of energy excess and mobilizes the same during energy deprived states. In addition to fuel storage, white adipose tissue can act as a thermal insulator to heat loss and as a cushion to protect other organs.

ADIPOSE TISSUE AS AN ENDOCRINE ORGAN

The adipose tissue is made up of mature adipocytes, which store lipid; in addition it has a variety of other cells (e.g. fibroblasts, endothelial cells, macrophages) which constitute around 50% of the total cellular content. White adipocytes are

major secretory cells, making adipose tissue a key endocrine organ. Adipose tissue is now considered as the largest endocrine organ in most humans – and more so in the overweight and obese individuals.

Quantitatively, the most important secretion from adipocytes is fatty acids, which is released during the periods of negative energy balance (particularly fasting). In addition to fatty acids, several other lipid moieties are also released; these include prostanooids (which are synthesized by the tissue itself), and cholesterol and retinol, which are not synthesized but are rather stored and subsequently released.

Adipose tissue is now recognized as the source of key hormones which play an important role in the regulation of energy balance and adipocytes are also known to secrete a diverse range of protein factors and signals termed 'adipokines', which are involved in metabolic regulation and are increasingly considered to be directly linked to the pathogenesis of common obesity. These adipokines act both locally and distally through autocrine, paracrine and endocrine effects to regulate fat cell differentiation, and sense and adjust systemic energy balance.³ As energy surplus develops, adipocyte differentiation and lipid accumulation are inhibited through feedback loops of adipocyte-derived factors such as TNF- α , angiotensinogen (AGT), and resistin (for resistance to insulin). In states of energy deficit or excess, there is a corresponding change in the levels of adipocyte secreted proteins, (such as adiponectin, leptin), and trophic substances such as acylation stimulating protein (ASP) and angiotensin II (AngII). In states of energy excess, these signal a drive to adipocyte formation and renewed triglyceride accumulation. Insulin is central to this process, promoting lipogenesis and energy storage.

Increased activity of three of these adipokines namely tumor necrosis factor, interleukin 6, and resistin, play a role in the development of the insulin resistance present in obesity. In contrast, other adipokines, like adiponectin and leptin, are

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insulin sparing through stimulatory effects on the beta oxidation of fatty acids in skeletal muscle.

SECRETORY FUNCTIONS OF ADIPOSE TISSUE⁴

The following is a list of key substances known to be secreted by adipose tissue – table.

Table: Substances secreted by the adipose tissue:

Hormones	
·	Leptin
·	Adiponectin
·	Resistin
·	Glucocorticoids
·	Estrogens
Cytokines	
·	IL-6
·	TNF- α
·	VEGF
·	TGF β
·	HGF
Enzymes	
·	Aromatase
·	11- β HSD - 1
·	Complement factors
·	adipsin
Others	
·	PAI-1
·	Acylation-stimulating protein (ASP)
·	Angiotensinogen

Adipokines

The adipokines are highly diverse in terms of protein structure and physiological function. They include classical cytokines, growth factors and proteins of the alternative complement system; proteins involved in the regulation of blood pressure, vascular haemostasis, lipid metabolism, glucose homeostasis and angiogenesis.

Adiponectin

Adiponectin [Adipocyte complement-related protein (ACRP)], is expressed abundantly and exclusively in white adipose tissue.⁵ It is the most abundant protein produced by adipose tissue. Serum adiponectin is found to circulate as oligomers of four to six trimers each.⁶ Its serum concentrations are reduced in obese mice and humans and rise following weight loss. This suggests that adiponectin plays a negative feedback role in fat storage.⁷ It has also been observed in studies on human subjects that low circulating serum adiponectin levels correlates strongly with increasing BMI, obesity and insulin resistance.^{8, 9}

Adiponectin appears to be an endogenous anti-inflammatory and anti-atherogenic factor that is protective against insulin resistance and macroangiopathy.¹⁰ Its concentrations correlate with the insulin sensitivity state and rise in response to insulin. Further, evidence has emerged from studies which suggest that the insulin sensitizing action of thiazolidinediones (acting via

PPAR) may be mediated through increased adiponectin.¹¹

Adiponectin has a tendency to retard atherosclerosis. This effect is either mediated through a direct action of adiponectin on the endothelium or indirectly through reduction in the expression of leukocyte adhesion molecules and inflammatory cytokines (e.g. TNF α).^{8, 14, 15}

In view of such extensive favorable actions of adiponectin and the initial encouraging results seen in animal studies, this molecule and its associated receptors could be the target of future successful preventive strategies or therapies in obesity, atherosclerosis and type 2 diabetes mellitus.^{8, 15, 16}

Leptin

Leptin was one of the earliest adipokines to be identified as the product of the ob gene in mice. Non production of leptin by a mutant strain of mice (ob/ob) produced a state of obesity, elevated cortisol levels, insulin resistance, and reproductive dysfunction.¹⁷

Leptin's primary physiologic function is the defense of body fat. Declining levels in adipose tissue and serum signal the presence of energy deficit to the brain. It is an essential signal from adipocytes to the hypothalamus in the control of appetite and energy balance and is believed to keep the CNS informed about the body's energy reserves. Leptin acts through cell surface receptor, OB-R and signal transduction involves Janus kinases.¹⁸

The primary target of leptin is believed to be the neurons of the hypothalamic arcuate nucleus neurons. The systemic response is inhibition of food intake and an increase in overall energy expenditure by the organism.¹⁹ Leptin reduces the levels of intracellular lipid in skeletal muscle, liver and pancreatic beta cells, thereby improving insulin sensitivity. In muscle this insulin sensitizing effect is achieved through inhibition of malonyl CoA, permitting increased transport of fatty acids into mitochondria for beta oxidation. These changes are partially mediated by central sympathetic activation of adrenergic receptors.²⁰ Peripheral effects of leptin include modulation of reproduction, angiogenesis, immunity and regulation of triacylglycerol metabolism.¹⁸

Though studies have described a positive correlation between BMI and circulating leptin levels in humans²¹, the role of leptin in the pathogenesis of common obesity is still not well elucidated. Except in rare instances of genetic leptin deficiency syndromes, exogenous leptin has not proved to be effective in regulating appetite or raising body metabolism.^{22,23}

Resistin

This name for this hormone was coined after an association was observed between "resistin" and insulin resistance.²⁴ However, later work suggested that the likely effect of resistin was on hepatic glucose output rather than insulin sensitivity of peripheral tissues.²⁵ The hormone is believed to be expressed at much higher levels in visceral fat as compared to subcutaneous fat. Inflammatory cytokines and steroids are believed to increase expression of resistin while

thiazolidinediones inhibit it.

The physiological role of resistin is still unclear and under evaluation

INFLAMMATION AND OBESITY

A number of inflammation-related proteins are released by white adipocytes. One of the most important recent developments in obesity research is the emergence of the concept that obesity is characterized by chronic mild inflammation. The basis for this view is that the circulating level of several cytokines and acute phase proteins associated with inflammation is increased in obese individuals. As adipocytes secrete a number of cytokines and acute phase proteins, it is considered that the expanded adipose tissue mass contributes, either directly or indirectly, to the increased production and circulating levels of inflammation-related factors in obesity. In other words, the state of inflammation in adipose tissue in obesity leads to an increased production and release of inflammation-related factors.

ADIPOSE TISSUE AND THE DISEASES OF OBESITY

The central change to the body in obesity is the increase in the amount of adipose tissue – which may constitute more than half of total body mass in those with a BMI that is in excess of the threshold of obesity. It is not, however, only the total amount of fat that is important, but also its distribution. Thus, a more central fat deposition ('android' or 'apple' type, as compared to 'gynoid' or 'pear' shaped) is associated with a greater risk of the metabolic syndrome and several of the other diseases linked to obesity. The current view is that the inflammatory state of obesity plays a key causal role in the development of type 2 diabetes and the metabolic syndrome (which includes atherosclerosis, hypertension and dyslipidemia). A central hypothesis is that the increase in inflammation-related adipokine production that occurs in obesity lead to the associated diseases. In this context, the reduction in adiponectin in the obese is thought to be of particular significance in view of the anti-inflammatory effect of this adipokine.

CONCLUSION

The mechanisms by which obesity contributes to insulin resistance, hypertension, and endothelial disease are among the most important questions facing medical investigators today. Research into the function and regulation of adipocyte signaling proteins, adipocytes differentiation, and the control

of fat partitioning will likely result in further insight into these mechanisms and the discovery of therapies for treatment of obesity and obesity related diseases.

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