The increasing global burden of obesity has become a major public health problem. Prevalence of obesity has been increasing in the world and now, worldwide obesity has exceed 285 million. Obesity is defined as abnormal or excessive fat accumulation that results in health risk. A common measure of obesity is the body mass index (BMI). A person with a BMI of 30 or more is generally considered obese. In addition, this disease is a major risk factor for serious chronic diseases including diabetes, cardiovascular diseases and some types of cancer. However, the mechanisms whereby obesity leads to these metabolic complications are not fully understood.

Adipose Tissue

There are two types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT). It is easy to distinguish the adipocytes by their morphology:
- White adipocytes have a <90% comprised by a lipid droplet and a “squeezed” nucleus.
- Brown adipocytes have several lipid droplets, a roundish nucleus and many mitochondria.

The adipose tissue is highly vascularized and during obesity development, there is a fat mass expansion associated with angiogenesis. However, this enlargement of the vascular network is not sufficient to supply enough oxygen to all adipocytes and local hypoxia occurs.

This hypoxia may induce adipocyte death and macrophages recruitment, which in turn can secrete pro-inflammatory signals and trigger systemic insulin resistance.

Inflammation

The obese adipose tissue, and particularly visceral fat, is infiltrated with macrophages, which form Crown-like structures (CLSs) surrounding death and dying adipocytes. These macrophages produce pro-inflammatory cytokines that enter the systemic circulation and contribute to the development of insulin resistance. Some of this cytokines like TNFα, IL6 and IL1β have been reported to impair insulin signaling.

Adipose tissue macrophage (ATM) play an important role in the establishment of the chronic inflammatory state associated with obesity and its metabolic abnormalities. ATM from lean individuals are M2 macrophages (anti-inflammatory properties), whereas ATMs from obese individuals are predominantly M1 (pro-inflammatory).

Therapies for Type 2 Diabetes

Leptin
Leptin is an adipose secreted cytokine and plays an important role in satiety, food intake and energy expenditure. It's an important negative regulator of weight and it has been described as a potential molecule to target on obesity therapy. However, it has been reported a tiny loss-weight due to this therapy.

Adiponectin
Adiponectin exerts insulin sensitivity, is anti-inflammatory and anti-atherosclerotic. In obese adipose tissue its secretion and activity is decreased. This molecule acts in the brain, increasing the energy expenditure and causing weight loss. In some studies, the administration of recombinant adiponectin improved insulin sensitivity in the liver, increased insulin secretion and obtained beneficial effects on body weight and hyperglycemia. Recently, Oda-Kahe has produced a synthetic small molecule that is an agonist receptor of adiponectin (Adiponectin), with really good results, making adiponectin and its agonist receptors some promising candidates for therapy.

VEGFA
VEGFα, a vascular endothelial growth factor A, is a key molecule in vasculogenesis and angiogenesis. Recent evidence suggest a potential role of this growth factor in the control of energy metabolism. VEGF-A overexpression protects against diet-induced obesity and insulin resistance. The overexpression leads to an increase in BAT thermogenesis and also promotes a “BAT-like” phenotype in WAT depots. In addition, VEGF-A has anti-inflammatory properties with a chemotactic activity specific for M2 macrophages.