Hypoxia and Inflammation in Obesity

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Obesity

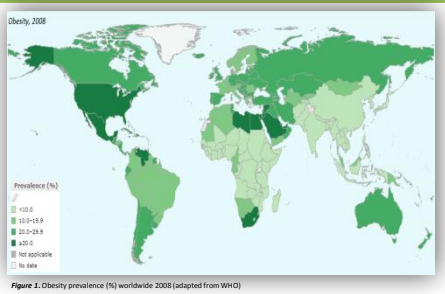

Figure 1. Obesity prevalence (%) worldwide 2008 (adapted from WHO)

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.

Diabetes

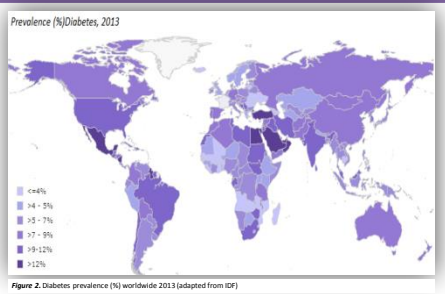

Figure 2. Diabetes prevalence (%) worldwide 2013 (adapted from IDF)

The association of obesity with type 2 diabetes has been recognized for decades, and the major basis for this link is the ability of obesity to engender insulin resistance. Although many details of the mechanisms by which the enlarged adipose tissue mass that defines obesity causes systemic insulin resistance remain unknown.

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 ≈90% comprised by a lipid droplet and a "squeezed" nucleus.
- Brown adipocytes have several lipid droplets, a roundish nucleus and many mitochondria. .

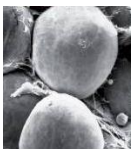

Figure 3. Scanning EM image from WAT (Cinti S, 2012)

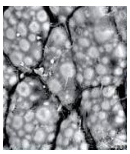

Figure 4. Scanning EM image from BAT (Cinti S, 2012)

WAT's function is to store excess energy in the form of TGs. In contrast, BAT oxidizes fuels and dissipates energy in the form of heat. Both secrete cytokines.

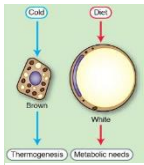

Figure 5. Functions of white and brown adipocytes (Cinti S, 2012)

WAT is distributed throughout the body and there are two types:

- vWAT or visceral
- sWAT or subcutaneous

Accumulation of vWAT (apple shape) has higher risk of weight-related health problems than sWAT (pear shape).

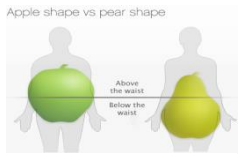

Figure 6. Different body fat distribution leads to "apple" and "pear" shape (adapted from fitneAss)

The three Hs

During obesity there is an expansion of adipose tissue mass due to:

- **Hypertrophy**: adipocyte enlargement
- **Hyperplasia**: increased number of adipocytes

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.

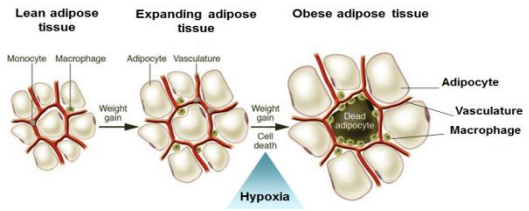

Figure 7. Inflammation and hypoxia in obese and normal tissue (adapted from Neels et al, 2006)

Adipose tissue hypoxia (ATH) represents a novel causative risk factor for the chronic inflammation in obesity. Hypoxia induces inflammation through activation of HIF-1α and NF-kB, each of which activates transcription of several angiogenic and/or pro-inflammatory cytokines.

This process also provides a mechanism for the pathological responses in adipose tissue, such as ER stress, oxidative stress, adipocyte death, adiponectin reduction and leptin induction.

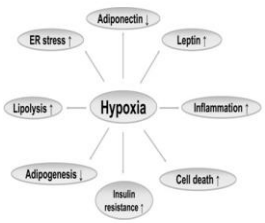

Figure 8. Hypoxia as a common root for various changes in adipose tissue in obesity (Ye J, 2013)

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.

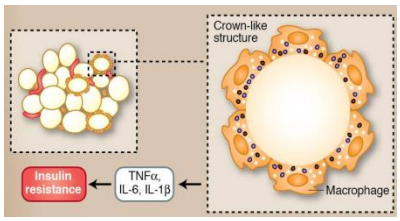

Figure 9. Infiltration of macrophages forming Crown-like structures. (Cinti S, 2013)

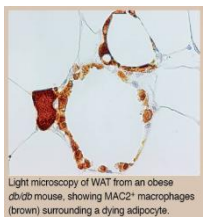

Figure 10. Macrophages surrounding a dying adipocyte (Cinti S, 2013)

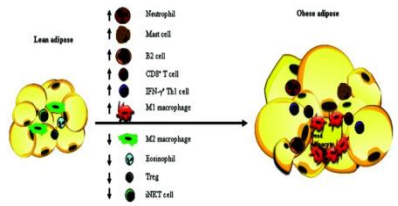

Figure 11. Changes of immune cells populations in adipose tissue in obesity (Feng B et al, 2013)

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

Conclusion

On the basis of the current data, the sequence of events linking obesity with insulin resistance could be:

- Adipocyte hypertrophy due to obesity
- Adipocyte stress, possibly involving hypoxia and the production of chemo attractants
- Chemo attraction and infiltration of macrophages
- Death of adipocytes
- Chronic reabsorption of adipocyte remnants by macrophages and massive production of cytokines
- Increased levels of circulations cytokines contributes to insulin resistance in peripheral tissues

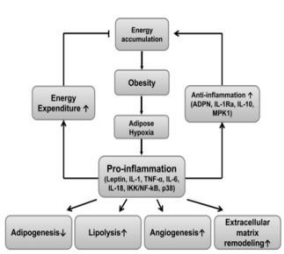

Figure 12. Impact of pro-inflammation and anti-inflammation events in adipose tissue on glucose homeostasis in peripheral tissues (Ye J, 2013)

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-apoptotic. 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 a recombinant adiponectin improved insulin sensitivity in the liver, increased insulin secretion and obtained beneficial effects on body weight and hyperglycemia.
Recently Okada-Iwabu have produced a synthetic small molecule that is an agonist receptor of adiponectin (AdipoRon), with really good results, making adiponectin and their agonist receptors some promising candidates for therapy.

VEGF-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.

Most cited references

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