Nicotinamide adenine dinucleotide biosynthesis and consumption in dysfunctional white adipocytes

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Abstract

In addition to its role in storage of dietary energy in a highly concentrated form, the white adipose tissue (WAT) is an active endocrine organ that regulates various physiological processes in the body. It plays a central role in insulin responsiveness and energy homeostasis, which is mediated by the action of a wide range of biologically active molecules - adipokines.

During its "remodeling", the obese WAT becomes inflamed and dysfunctional, which causes insulin resistance. Dysfunctional WAT in obesity exhibits increased production of reactive oxygen species (ROS) and decreased activity of some of the key antioxidant enzymes, which leads to oxidative stress. Indeed, protein carbonyls in the visceral adipose tissue are considered as a reliable biomarker of the level of oxidative stress in this tissue. Their negative correlation with serum adiponectin is indicative of systemic effects of oxidative stress in the visceral WAT.

Glutathione S-transferase isoform A4 (GSTA4) has an important role in protection of the white adipocytes from oxidative stress and protein carbonylation. However, GstA4 is downregulated in adipocytes treated with tumor necrosis factor α (TNFα), as well as in adipose tissue from obese mice, suggesting the link between oxidative stress, inflammation and insulin resistance.

GstA4 silenced 3T3L1s are a good experimental model to study the consequences of oxidative stress in dysfunctional adipocytes in obesity induced insulin resistance. Among other findings, it has been shown that the expression of Sirtuin 3 (Sirt3) is decreased in GstA4 silenced 3T3-L1 adipocytes (Bernlohr lab., unpublished results).

Sirtuins are enzymes that deacetylate lysine residues on both histone and nonhistone proteins. Mammals have seven sirtuins with different subcellular localization. SIRT3 is located in mitochondria. There is evidence that SIRT3 can delay the onset of a number of oxidative stress- and age-related pathologies. Sirtuin activity is nicotinamide adenine dinucleotide (NAD^+) dependent and is directly linked to the energetic and redox status of the cell.

We explored the expression of some of the key genes involved in NAD^+ biosynthesis and consumption in a model of inflamed white adipocytes. Our experiments demonstrated a significant disturbance of NAD^+ metabolism, and decreased Sirt3 expression. These findings indicate that Sirt3 and NAD^+ pathway can be considered as potential therapeutic targets in obesity induced insulin resistance.

Keywords
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