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Review

Feast and famine: Adipose tissue adaptations for healthy aging

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ABSTRACT

Proper adipose tissue function controls energy balance with favourable effects on metabolic health and longevity. The molecular and metabolic asset of adipose tissue quickly and dynamically readapts in response to nutrient fluctuations. Once delivered into cells, nutrients are managed by mitochondria that represent a key bioenergetics node. A persistent nutrient overload generates mitochondrial exhaustion and uncontrolled reactive oxygen species (^{mt}ROS) production. In adipocytes, metabolic/molecular reorganization is triggered culminating in the acquirement of a hypertrophic and hypersecretory phenotype that accelerates aging. Conversely, dietary regimens such as caloric restriction or time-controlled fasting endorse mitochondrial functionality and ^{mt}ROS-mediated signalling, thus promoting geroprotection. In this perspective view, we argued some important molecular and metabolic aspects related to adipocyte response to nutrient stress. Finally we delineated hypothetical routes by which molecularly and metabolically readapted adipose tissue promotes healthy aging.

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1. Introduction

White adipose tissue is one of the largest organs in the body and regulates energy and nutrient management in all organisms by highly coordinated metabolic adaptations (Sun et al., 2011). Much of the development and evolution of these adaptations have taken place in an environmental context including a repetition of scarcity (famine) and overload (feast) of food availability. In themodern society, the duration and magnitude of exposure to nutrient signals have increased due to excessive food/nutrient intake and augmented life expectancy. Actually, much of the daily time is in a postprandial state, thus a persistent flux of nutrient and growth factors is promoted.

Nutrient stress is generally considered from the standpoint of how cells detect and respond to an insufficient or excessive supply of nutrients to meet their bioenergetics needs (Wellen and Thompson, 2010). Excess of nutrients generally leads to a positive energy balance that results in weight gain, increased adiposity and accumulation of ectopic fat in key organs and tissues, partic-

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ularly in sedentary people with adverse effects on health and life span. Calorie restriction (CR) as well as fasting are efficient strategies able to remodel adipose tissue mitigating accumulation of fat and enhance life expectancy (Fontana and Hu, 2014; Fontana and Partridge, 2015). These dietary regimens have favorable effects on the body and even lead to improvement of cognitive functions and neuroprotection (Lettieri Barbato et al., 2012; Pani, 2015). CR is defined as a reduction in calorie intake below usual *ad libitum* intake without malnutrition. In rodents, 30% to 60% reduction in calorie intake early in life (from weaning to 6 months of age) leads to proportionate 30% to 60% increase in maximum life span. Moreover, about 40% reduction in calorie intake started in adulthood (about 12 months of age) limits the incidence of spontaneous lymphoma and extends maximum life span by only 10% to 20% (Weindruch and Walford, 1982).

Intermittent fasting also leads to reduced oxidative damage and increased stress resistance with a beneficial impact on maximum life span in rodents (Mattson, 2005). Generally fasting is viewed as a time-restricted period limited to the nocturnal period (about 8–14 h) during which there is a stop in the utilization of diet-derived energy. Increased health span and longevity in rodents has been linked since many years to intermittent fasting that is a protracted time without ingestion of calories and nutrients for at least 20 h on alternate days (Carlson and Hoelzel, 1946; Martin et al., 2006; Mattson and Wan, 2005). Studies carried out in humans demonstrated that several weeks of an alternate day fasting (ADF) reduce body weight and fat mass and improve clinical health markers thus restraining metabolic dysfunctions likely leading to prolonged life span (Johnstone, 2015; Seimon et al., 2015; Tinsley and La Bounty, 2015). However, only a few human studies have tested the effects of ADF on body weight and pro-longevity parameters in non-obese subjects. In a study by Heilbronn et al., it was demonstrated that normal-weight men and women with a regimen of ADF for 3 weeks, undergo minimal reduction of body weight (2%) and amelioration of blood triacylglycerol concentrations in men only (Heilbronn et al., 2005). Varady et al. showed that 12 weeks of ADF led to decrease of body mass (about 6%) with also a significant reduction of fat mass without changes in lean mass. Interestingly, also triacylglycerol concentrations decreased as well as C-reactive protein and leptin (Varady et al., 2013). These findings suggest that fat loss would result in decreased adipocyte size and this may lead to reduced secretion of certain pro-inflammatory mediators. However, the underlying mechanisms linking fat mass reduction and lifespan are not entirely elucidated and many aspects remain debated. Herein we have delineated hypothetical molecular signalling pathways driving metabolic reprogramming of adipose tissue to feeding/fasting transition and nutrient restriction regimens, and illustrated the beneficial impact of such metabolic flexibility on health and lifespan.

2. The light and the dark side of the white adipose tissue

White adipose tissue is a multi-depots organ anatomically divided in visceral and subcutaneous regions. White adipocytes represent the majority of cells in visceral and subcutaneous adipose depots. Differently from visceral depots that are mainly characterized by a homogenous population of white adipocytes, subcutaneous depots display both white and beige/brite adipocytes (Sanchez-Gurmaches and Guertin, 2014). White adipocytes show a large unilocular lipid droplet and a small amount of mitochondria. They store nutrients in the form of triglycerides and release fatty acids during times of negative energy balance to target tissues in need of energy. Beige adipocytes have several lipid droplets and a higher mitochondrial content and oxidative capacity than white adipocytes and sustain energy dissipation as heat through non-shivering thermogenesis (Kajimura et al., 2015).

The metabolic consequences of increased body fat and changes in its distribution have received extensive attention in the literature in recent years. Increased visceral adiposity leads to chronic inflammation and lipotoxicity and is often associated with a number of comorbidities (e.g. hyperinsulinemia, hypertension, insulin resistance, glucose intolerance) reducing life expectancy (Fontana and Hu, 2014; Guilherme et al., 2008). By contrast, subcutaneous adipose tissue is associated with improvement or maintenance of insulin sensitivity and reduced risk of developing metabolic disturbances. Mechanistically, such beneficial action has been attributed to its ability to function as storage and buffering system against the daily influx of nutrients, thus protecting against visceral and ectopic fat deposition. In doing so subcutaneous fat cells avoids the side effects exerted by excess glucose circulation and lipid and fatty acid deposition in other cells by enabling their safe storage in the form of triglycerides (Jankovic et al., 2015). Thus, also deterioration of the nutrient-buffering role of subcutaneous adipose tissue may have a negative impact on metabolic body homeostasis with adverse effects on life expectancy. Moreover, beige adipocytes residing in subcutaneous white adipose depots in some circumstances (e.g. cold exposure or physical exercise) can be induced to activate the thermogenic program setting a negative energy balance with favourable impact on overall body metabolism. For this reason, recruitment of energy-dissipating beige adipocytes has become appealing to treat metabolic disturbances as well as prevent obesity and its related diseases (for review see (Bartelt and Heeren, 2014; Kim and Plutzky, 2016; Peschechera and Eckel, 2013)).

Adipose tissue metabolism is regulated by many hormonal inputs (e.g. insulin, glucagon, catecholamine) in response to environmental stressor such as exercise, diet, or exposure to cold and is characterized by a great plasticity. However, recent papers shed light on some hormone-independent responses of adipose tissue to environmental stimuli. It has been recently demonstrated that white and beige fat cells display the adaptability to trigger a metabolic reprogramming and increase energy dissipation through cell autonomous mechanisms. Specifically cold exposure directly activates a thermogenic gene program in white and beige adipocytes independently of the canonical cAMP/Protein Kinase A/cAMP response element-binding protein pathway that is downstream of β-adrenergic receptors (Ye et al., 2013). Similarly, nutrient shortage as well as the nutrient restriction mimetic rapamycin, boost mitochondrial metabolism in white and beige adipocytes independently of cAMP/PKA signalling and are equally able to reduce adipocyte size (Barbato et al., 2015; Chakrabarti et al., 2010). Stimulation of β-adrenergic receptors is accompanied by a prominent change in intracellular redox homeostasis that shifts towards a pro-oxidant status (Lettieri Barbato et al., 2015a). Interestingly, it was found that the sole pharmacological inhibition of GSH synthesis is able to promote a favourable pro-oxidant milieu that is sufficient to induce thermogenic genes in white adipocytes without the intervention of an hormonal input (Lettieri Barbato et al., 2015a).

3. Insulin/IGF-1 signaling pathway orchestrates fat mass and longevity

One of the pathways that have been implicated in aging is the insulin/insulin-like growth factor (II/IGFs) signaling, an evolutionary conserved pathway linking nutrient levels to metabolism, fat mass and lifespan (Murphy et al., 2003). Mice with disruption of the insulin receptor gene specifically in the fat tissue (FIRKO mice) display reduced fat mass and are protected against insulin resistance