Experimental Gerontology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Review

Adipose tissue inflammation in aging

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A B S T R A C T

Adipose tissue has traditionally been viewed as an organ of interest within studies of obesity and diet-associated metabolic disorders. However, as studies reveal the role white adipose tissue plays as an energy storage, a lipid metabolism site, and an adipokine secretor, it has become recognized as an organ of importance for metabolic health in both the young obese and the old obese. Within the realms of aging research, the pursuit of senolytics has taken the field's spotlight, where the clearance of senescent cells has shown to attenuate aspects of age-related disorders. More interestingly, these senolytics have also revealed that these senescent cells, specifically $p16^{Ink4a}$ cells, accumulate within adipose tissue, skeletal muscles, and eye (Baker et al., 2011). These results implicate the importance of adipose tissue inflammation in aging and widen the discussion on how senescent cells among other immune and non-immune cells cross paths to influence an organism's lifespan and healthspan.

1. Introduction

The Centers for Disease Control and Prevention (CDC) estimates that by year 2030, 1 in 5 Americans will be 65 years or older (Prevention et al., 2013). This statistic would implicate two challenges. This proportion of older adults will be unprecedented in the United States, increasing both geriatric healthcare costs and the volume of age-associated diseases. Medical research is challenged with a shift from focusing on infectious diseases and acute illnesses towards chronic and degenerative diseases. Chronic and degenerative diseases cause a decrease in the quality of life of elderly, driving interest in research to investigate both healthspan and lifespan.

The past century has seen an impressive increase in human life expectancy and prevalence of obesity. Body weight and body mass index (BMI) in humans reach their peak at the 6th decade of life. The National Health and Nutrition Examination Survey (NHANES) estimated that 37% of 60 years and older adults are obese, with BMI ≥ 30 (Flegal et al., 2013). However, body fat percentage (the total mass of fat divided by total body mass) does not reach its maximum until the 7th and 8th decades (Jackson et al., 2002). Women generally have a higher percentage of body fat than men, in part as a response to the demand of pregnancies. There is also a change in fat distribution with aging, including a relative increase in intra-abdominal fat and ectopic fat deposition. Importantly, obesity in aging has been linked to many aging-associated chronic diseases. Excess weight in old age also contributes to the decline in physical function, loss of independence, and the development of frailty.

1.1. The seven pillars of aging

Targeting chronic diseases is a major challenge, as they are often intertwined. Nonetheless, clinicians and researchers alike have accepted that age-related diseases and dysfunction stems from similar pathways, mechanisms, and even biological bases—therefore, underlying processes can be targeted to impede aging or revert age defects. The 'Seven Pillars of Aging' serves as a visual model to depict the interconnectedness of aging processes and link them to chronic pathologies. The seven pillars consist of: metabolism, macromolecular damage, epigenetics, inflammation, adaptation to stress, proteostasis, stem cells and regeneration (Kennedy et al., 2014). Inflammation is of particular interest, as it is a ubiquitous trait of aging tissues and is present in most, if not all, age-associated chronic diseases.

1.2. Inflammaging

Human aging is in part, characterized by a chronic, low-grade inflammation that develops in various aging tissues. This phenomenon is termed 'inflammaging' (Franceschi et al., 2006; Franceschi & Campisi, 2014). The health detriments and benefits of inflammaging are inconclusive. While super centenarians boast a higher inflammatory cytokine profile (Arai et al., 2015), inflammatory mediators are critical to the pathogenesis of age-related diseases such as arthritis, diabetes, sarcopenia, cardiovascular disease (CVD), cancer, and dementia (Krabbe et al., 2004; Kevin Howcroft et al., 2013). While sources of inflammaging remain under investigation, some prominent conversations include

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http://dx.doi.org/10.1016/j.exger.2017.10.014
Received 4 October 2017; Accepted 16 October 2017

immunosenescence (Franceschi et al., 2006; Bauer & De la Fuente, 2013), self-debris (Furman et al., 2017), senescent cells (Tchkonia et al., 2013), mitochondria dysfunction (Wiley et al., 2016; De Felice & Ferreira, 2014), microbiome (Biagi et al., 2011), and adipose tissue (Stout et al., 2014a; Tchkonia et al., 2010; Salvioli et al., 2013; Wu et al., 2007).

This review aims to highlight and discuss adipose tissue inflammation in aging, not only as a component of inflammaging but also as an independent dialogue of how adipose tissue inflammation affects health in old age.

1.3. Adipose tissue inflammation in aging and obesity

Adipose, or fat tissue, is the largest endocrine organ in humans and in other cases, can be the largest organ in an obese individual. Adipose tissue plays a pivotal role in age-related metabolic dysfunction and longevity (Tchkonia et al., 2010; Palmer & Kirkland, 2016; Ahima, 2009). With old age, fat distribution shifts from subcutaneous to visceral fat depots, while triglycerides ectopically deposit on liver, muscle, bone marrow, and heart (Kuk et al., 2009). These changes are associated to the development and progression of a variety of age-associated diseases.

Obesity accelerates the onset of these age-associated diseases, further emphasizing the level of impact adipose tissue plays in aging (Stout et al., 2014a; Ahima, 2009). Similar to inflammaging, obesity is linked to a systemic, chronic, low-grade inflammation. Adipose tissue inflammation in obesity is also termed 'metaflammation' (Hotamisligil, 2017). While most recent studies focus on how adipose tissue dysfunction progresses in diet-induced obesity, much less efforts have been devoted to understanding the pathogenic mechanisms of old-age obesity. Whether inflammaging and metaflammation share common inflammatory pathways or have similar sources of inflammation, including the role of different fat depots, are important questions. It is likely there are fundamental differences between diet- versus age-dependent obesity, given the widespread immunological and physiological changes that are known to occur in old age.

The majority of interventions that extend lifespan function through nutrient sensing and processing pathways, and they have important effects on adipose tissue formation and function. Growth hormone deficient mice, in addition to improved lifespan, have less ectopic fat deposition, improved adipocyte progenitor cell function, and reduction in cellular senescence (Stout et al., 2014b). A number of single-gene mutations are known to extend lifespan in lower organisms, and similar lifespan extension is observed even if the mutations are restricted to adipose tissue (Giannakou et al., 2005; Bluher et al., 2003).

2. Obesity paradox and aging

The obesity paradox refers to a collection of unexpected findings, where several chronic diseases, including cardiovascular, have lower all-cause mortality rates in elevated BMI patients (Hainer & Aldhoon-Hainerová, 2013). The "obese healthy" implicates that having a higher BMI can be protective and that the "lean" BMI is in actuality, not the lowest mortality group. For example, obese (BMI $>$ 30) and severely obese (BMI $>$ 40) patients after coronary artery bypass grafting are at lower risk for postoperative complications than patients with a lower but "normal" (18.5 $<$ BMI $<$ 25) categorization (Hainer & Aldhoon-Hainerová, 2013). It has been controversial as to how this can occur—and many of these observations were thought to be particularly true in elderly patients. It is reasonable to postulate that, in some circumstances, adiposity may confer a degree of biological resiliency that enhances recovery after a stressful life event.

Studies described the mortality risks as a 'U-shaped curve' for the elderly while the younger individuals have a 'check-mark' or 'j' shape mortality curve. Where increased BMI in the overweight and even obesity ranges have exhibited protective effects on patients, although true in the datasets, also held many caveats in the design study. When body composition was measured using a different method, it seems BMI frequently misclassifies body fat status, and it was argued that BMI is a better predictor of lean body mass than of adiposity (Hainer & Aldhoon-Hainerová, 2013). Therefore, patients with higher BMI are protected by higher lean body mass and not body fat.

There are many other prominent theories summarized (Hainer & Aldhoon-Hainerová, 2013; Lavie et al., 2014)—with some arguing that lean individuals plagued with chronic conditions could also be suffering 'malnutrition-inflammation complex syndrome' which would be worse than carrying a high BMI. It was also hypothesized that young obese with abdominal obesity die earlier and those who survive towards higher age categories like those of the obesity paradox studies actually carry greater degree of lower-body obesity. Alternate theories suggest muscle quality determined by muscle mass and grip strength would also be important indicators of health (Hainer & Aldhoon-Hainerová, 2013; Lavie et al., 2014). Others suggest genetic predisposition contributes to the formation of these obese healthy (Lavie et al., 2014) or metabolically obese (Yaghootkar et al., 2014) phenotypes observed.

3. Diet-induced adipose tissue inflammation

3.1. Adipose tissue immunological profile during diet-induced obesity

In obesity, adipose tissue homeostasis is perturbed: the balance between energy intake and expenditure is pushed towards the former. In aging, there is also a reduction in resting metabolic rate and lower total daily energy expenditure, particularly in frail individuals (Abizanda et al., 2016). With excessive accumulation and expansion of adipose tissue in obesity, there is an increased likelihood of metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus (Bluher, 2016). Adipose tissue inflammation, specifically white visceral-gonadal adipose tissue, is a major contributor to metaflammation and insulin resistance. Compared to lean individuals, white adipose tissue (WAT) from obese adults secretes higher levels of tumor necrosis factor α (TNFα), an inflammatory cytokine capable of interfering insulin signaling. When TNFα is inhibited, glucose tolerance and insulin sensitivity is improved (Hotamisligil et al., 1993). Pro-inflammatory cytokines and chemokines such as interleukin 1b (IL-1b), monocyte chemoattractant protein (MCP-1), and interleukin 6 (IL-6) are also secreted at elevated levels from obese adipose tissue macrophages (Lumeng et al., 2011).

3.2. Adipose tissue macrophages, inflammation, and organelle stress

Aging is associated with important changes in the innate immune system. Macrophages perform important innate immune functions including phagocytic clearance of dying cells. Depending on the stimuli, macrophages can become polarized into "M1" or "M2" subsets. Classically-activated or M1 "killer" macrophages and alternatively activated M2 "healing" macrophages are convenient terms that describe the plasticity of macrophage subsets and function. However, it is important to note that macrophages may not form clear-cut activation subsets nor expand clonally (Martinez & Gordon, 2014). Studies aimed to elucidate the source of inflammation in obesity have found that macrophages accumulate in WAT (Weisberg et al., 2003) and exhibit a predominantly proinflammatory "M1" profile, as compared to the less or anti-inflammatory "M2" in lean healthy control adipose tissue (Lumeng et al., 2008; Lumeng et al., 2007). Hypertrophy and hypoxia also leads to the formation of crown-like structures where macrophages surround a dead or dying adipocyte (Murano et al., 2008). This very characteristic crown-like structure is used as one means of quantifying levels of inflammation in adipose tissue and has been shown to persist in the tissue even with weight loss in mice (Zamarron et al., 2017).

In obesity, adipose tissue macrophages are burdened with an