Journal of Cardiology 63 (2014) 250–259

Contents lists available at ScienceDirect

Journal of Cardiology

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

Review

Adipokines: A link between obesity and cardiovascular disease

Kazuto Nakamura (MD, PhD), José J. Fuster (PhD), Kenneth Walsh (PhD)*

Molecular Cardiology/Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, MA, USA

ARTICLE INFO

Article history:
Received 6 November 2013
Accepted 11 November 2013
Available online 16 December 2013

Keywords:
Cardiovascular disease
Adiponectin
Sfrp5
Leptin
TNFα

ABSTRACT

Obesity is a risk factor for various cardiovascular diseases including hypertension, atherosclerosis, and myocardial infarction. Recent studies aimed at understanding the microenvironment of adipose tissue and its impact on systemic metabolism have shed light on the pathogenesis of obesity-linked cardiovascular diseases. Adipose tissue functions as an endocrine organ by secreting multiple immune-modulatory proteins known as adipokines. Obesity leads to increased expression of pro-inflammatory adipokines and diminished expression of anti-inflammatory adipokines, resulting in the development of a chronic, low-grade inflammatory state. This adipokine imbalance is thought to be a key event in promoting both systemic metabolic dysfunction and cardiovascular disease. This review will focus on the adipose tissue microenvironment and the role of adipokines in modulating systemic inflammatory responses that contribute to cardiovascular disease.

Contents

Introduction

Obesity and associated metabolic disorders are becoming major health care concerns around the world. It is estimated that over 60% of adults and 30% of children are overweight in the USA, and if trends continue more than 50% of the world's adult population will be overweight in a few decades [1–3]. Obesity and its comorbidities have a devastating effect on vascular function and create conditions that favor cardiovascular disease. Obesity promotes cardiovascular disease via many mechanisms including ectopic lipid deposition, hyperglycemia, and the development of a procoagulant state, to name a few. This review will focus on how obesity influences the production in the adipose tissue of pro- and anti-inflammatory cytokines, referred to as adipokines, which contribute to the development of metabolic and cardiovascular diseases.

Obesity-induced changes in adipose tissue microenvironment

To understand how obesity has an impact on cardiovascular function, it is important to first focus on obesity-induced changes in the microenvironment of adipose tissue (Fig. 1). The excess of caloric intake leads to an expansion of the adipose tissue that is initially driven by an increase in the number of adipocytes (adipocyte hyperplasia) mediated by the recruitment and proliferation of adipogenic progenitors [4–7]. This hyperplastic response is severely blunted with age [8], so the sustained exposure to excessive energy intake ultimately leads to an increase in adipocyte size (adipocyte hypertrophy) that compromises the functionality of the

* Corresponding author at: Boston University Medical Campus, 715 Albany Street, W611, Boston, MA 02118, USA. Tel.: +1 617 414 2390; fax: +1 617 414 2391.
E-mail address: kxwalsh@bu.edu (K. Walsh).

0914-5087/$ – see front matter © 2013 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jjcc.2013.11.006

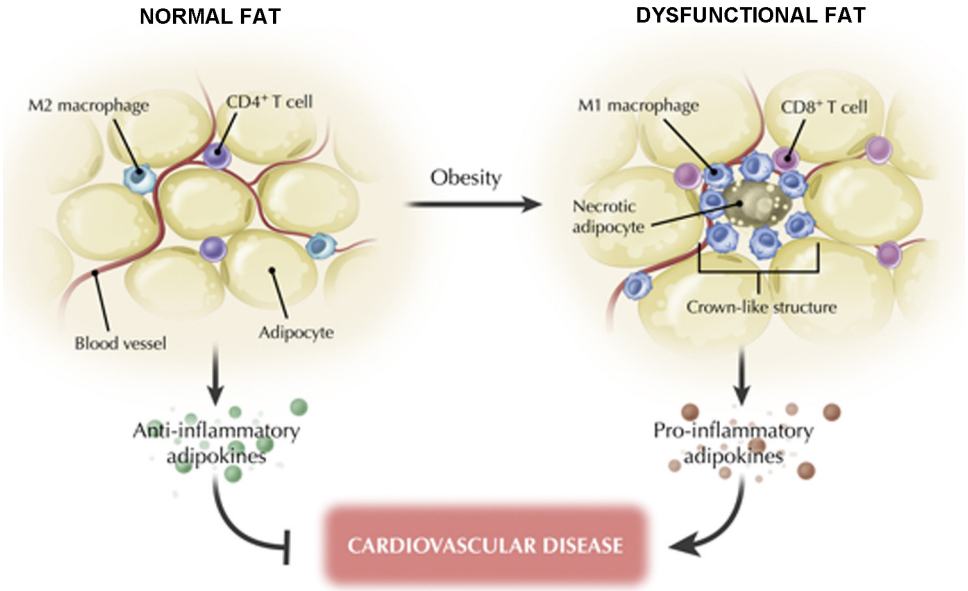

Fig. 1. Obesity-linked changes in adipose tissue composition. Obesity can promote changes in adipose tissue and promote the transition to a metabolically dysfunctional phenotype. As the body develops obesity, adipocytes undergo hypertrophy due to the increased storage of triglycerides. Macrophages in lean fat express markers of a M2 or "alternatively activated" state, whereas obesity leads to recruitment and accumulation of a M1 or "classically activated" state with macrophages and $CD8^+$ T cells in adipose tissue. Metabolically dysfunctional adipose tissue is indicated by the presence of crown-like histological structures that represent activated M1-like macrophages surrounding a necrotic adipocyte and $CD4^+$ T cells. Anti-inflammatory adipokines, such as adiponectin are preferentially produced by lean adipose tissue, whereas high levels of pro-inflammatory factors are produced in obese states.

adipose tissue [6,9]. In advanced obesity, lipid-laden hypertrophied adipocytes undergo necrotic and/or apoptotic cell death, contributing to the recruitment of inflammatory cells and to adipose tissue dysfunction [10–12].

Whereas adipose tissue is mainly composed of adipocytes, other cell types, including lymphocytes, macrophages, fibroblasts, and vascular cells, also appear to have important roles in controlling the functional status of this tissue. Obesity leads to major changes in the cellular composition of adipose tissue and also modulates the phenotype of individual cells within this tissue. For example, adipose tissue from obese organisms is infiltrated by a large number of macrophages, leading to increases in both absolute macrophage number and the relative level of macrophage-to-adipocyte ratio. Macrophage recruitment to adipose tissue is associated with systemic inflammation and insulin resistance [13,14]. In addition to this quantitative change, the macrophage phenotype is also altered by the obese state. The M1/M2 concept is a convenient means for classifying the inflammatory status of the macrophage. Macrophages that accumulate in adipose tissue of obese organisms tend to express genes associated with a M1-like or "classically activated" phenotype. In contrast, adipose tissue macrophages from lean organisms tend to express genes associated with a M2-like or "alternatively activated" phenotype [15]. Stimulation with T helper 1 (T_H1)-type cytokines, including interferon-γ, or bacterial products will promote the M1-like phenotype in macrophages. M1 macrophages produce pro-inflammatory cytokines, such as tumor necrosis factor (TNF)α, express inducible nitric oxide synthase (iNOS), and produce high levels of reactive oxygen and nitrogen intermediates [16]. This class of macrophages is typically associated with inflammation and tissue destruction. On the other hand, M2-like macrophages preferentially express anti-inflammatory cytokines, such as interleukin (IL)-10, and the enzyme arginase-1, which inhibits iNOS activity. These types of macrophages tend to be associated with wound healing, angiogenesis, and the resolution of inflammation [16]. It is believed that M1-like macrophages promote insulin resistance, whereas M2-like macrophages protect against obesity-induced insulin resistance [17]. Supporting this notion, ablation of CD11c-positive, M1-like macrophages normalizes insulin sensitivity in obese mice [18].

Another distinctive feature of adipose tissue from obese organisms is the presence of "crown-like" structures in histological sections. These features represent macrophages that surround dead or dying adipocytes [10,11]. Obese subjects lacking crown-like structures exhibit better metabolic control, diminished inflammatory gene expression, and reduced cardiovascular risk than body mass-matched individuals who display this histological feature [19]. On the other hand, the number of crown-like structures in adipose tissue is correlated with inflammation and insulin resistance in metabolic syndrome patients [10,19]. Typically macrophages function to rapidly remove dead cell debris prior to the disruption of their membranes. Thus, it is tempting to speculate that the presence of crown-like structures signifies a breakdown in the phagocytic process in adipose tissue, thereby exacerbating the pro-inflammatory state.

Obesity also influences the subsets of T cells that are present in adipose tissue, where they appear to function in the regulation of macrophage phenotype. $CD4^+$ regulatory T cells and T_H2-polarized cells are found in higher abundance in the adipose tissue of lean mice, and these cells contribute to the maintenance of adipose tissue function and insulin sensitivity, in part through promoting an anti-inflammatory alternative activation of macrophages [20,21]. On the other hand, under conditions of obesity, the accumulation of $CD8^+$ effector T cells and $CD4^+$ T_H1 cells in the adipose tissue will generate T_H1 signals and initiate the recruitment and activation of macrophages, perpetuating the pro-inflammatory cascade that is associated with insulin resistance [21,22]. Thus, obesity-induced alterations in the balance of T_H1- and T_H2-type signals are likely to influence macrophage recruitment and phenotype in adipose tissue, thereby generating either a pathogenic or a protective environment. B cells also appear to have a pivotal role in obesity-induced adipose tissue inflammation, promoting T cell and macrophage activation and contributing to insulin resistance