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Diabetes & Metabolism 40 (2014) 16–28

Review

Adipose tissue and adipocyte dysregulation

M. Lafontan [a,b,*]

[a] INSERM/UPS UMR 1048-I2MR, Institut des Maladies Métaboliques et Cardiovasculaires, Hôpital Rangueil, BP 84225, 31432 Toulouse cedex, France
[b] Université Paul-Sabatier, 118, route de Narbonne, 31062 Toulouse cedex 9, France

Received 19 August 2013; accepted 25 August 2013

Abstract

Obesity-associated insulin resistance is a complex disorder involving a number of candidate molecules, pathways and transduction systems possessing potential causal actions. Inflammation in adipose tissue (AT) is one mechanism proposed to explain the development of insulin resistance, while identification of factors that lead to or cause AT dysfunction when it reaches its limit of expansion represents an important challenge. Pathological expansion of AT is characterized by changes in its blood flow, and the presence of enlarged and dysfunctional adipocytes that begin an inflammatory campaign of altered adipokine and cytokine secretions. Adipocyte senescence, necrosis and death are associated with increased immune cell and macrophage infiltration of AT in obesity. This can boost inflammation and reinforce fat cell dysfunction and death. In addition, pathological fat mass expansion is also related to limited recruitment of fat cell progenitors able to proliferate and differentiate into healthy small fat cells to compensate for cell death and preserve adipocyte numbers. Limiting vascular development and enhancing fibrotic processes worsen inflammation towards chronic irreversibility. The AT expandability hypothesis states that failure of AT expansion is one of the key factors linking positive energy balance and cardiometabolic risks, not obesity *per se*. Besides the usual treatment of obesity based on behavioral approaches (specific dietary/nutritional approaches together with increased physical activity), a number of questions remain concerning the possible recovery of metabolic health after inflammation-preventing interventions.

Keywords: Fat cells; Blood flow; Inflammation; Lipogenesis; Lipolysis; Adipogenesis; Macrophages; Insulin resistance; Adipocyte hypertrophy

1. Introduction

Numerous studies have revealed various aspects of adipose tissue (AT) and adipocyte dysfunction in the pathophysiology of insulin resistance and other obesity-related diseases. It is currently accepted that excess body fat is associated with dysfunctional metabolism, systemic inflammation characterized by elevated circulating concentrations of proinflammatory markers, and increased risks of type 2 diabetes (T2D) and cardiovascular problems. The inflammatory state, which interferes with normal metabolism and disrupts insulin signaling, does not accord with the classical inflammatory paradigm, as it is associated with a reduced metabolic rate, as discussed in a recent review [1] (Fig. 1). AT is a heterogeneous tissue composed of adipocytes, and various microvascular and immune cells in its stromal vascular fraction (SVF). When considering the impact of AT on metabolism, its anatomical distribution plays an important role. Basically, AT is divided into two compartments: central (the subcutaneous upper abdominal and visceral fat masses); and peripheral (hip and gluteal–femoral fat). Excess central fat contributes to dyslipidaemia, hypertension and insulin resistance [2], whereas excess femoral fat has protective metabolic effects [3] and is associated with a reduced cardiovascular risk [4]. Considerable research has been devoted to unravelling the functional specificity of the various fat deposits in normal-weight, overweight and obese patients (see reviews [2,5]). Neural mechanisms are crucial for circadian rhythms and are also implicated in an important dialogue with AT in the control of homoeostasis of energy stores and fuel metabolism. Circulating hormones such as insulin and other signals originating in AT, including metabolites such as fatty acids (FAs) and adipokines such as leptin, adiponectin, retinol-binding protein 4 (RBP4) and apelin, circulate in proportion to body fat extent and send messages to the brain which, in response, sends signals to regulate food intake and to fuel metabolism (Figs. 1–3).

AT is now recognized as the predominant contributor to systemic inflammation, which characterizes the obese

* INSERM/UPS UMR 1048-I2MR, Institut des Maladies Métaboliques et Cardiovasculaires, Hôpital Rangueil, BP 84225, 31432 Toulouse cedex, France. Tel.: +33 5 61 32 56 41.
E-mail address: max.lafontan@inserm.fr

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http://dx.doi.org/10.1016/j.diabet.2013.08.002

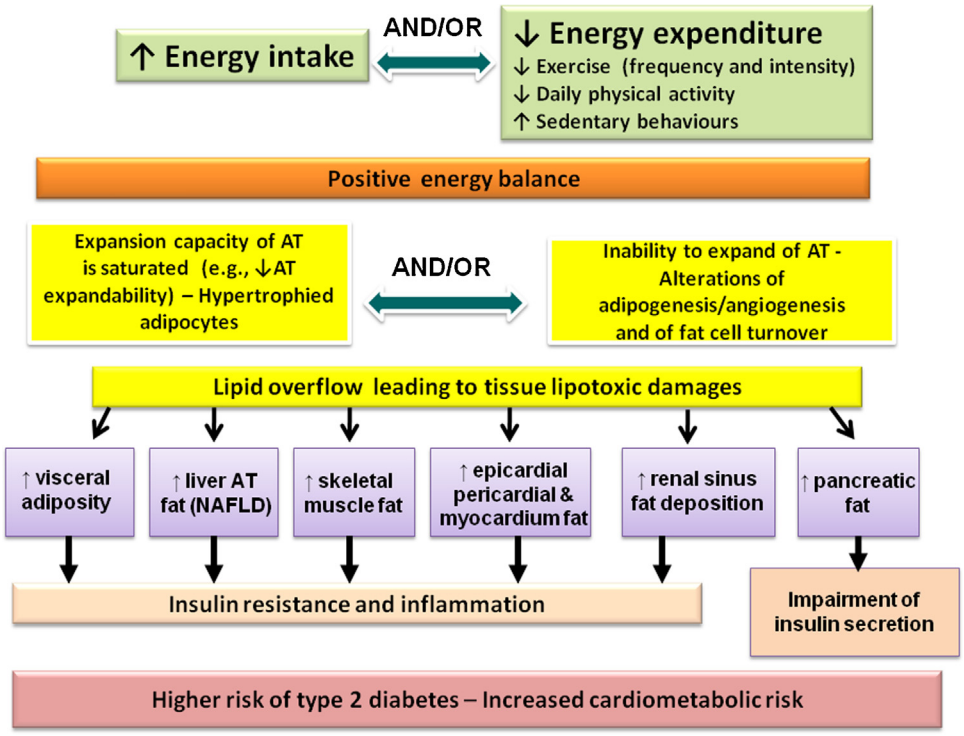

Fig. 1. Consequences of chronic positive energy balance leading to obesity and adipose tissue (AT) dysfunction. Deposition of non-esterified fatty acids (NEFAs) as triacylglycerols in the liver, skeletal muscle, epi-/pericardium and pancreas create a lipotoxic setting (with ectopic fat deposition and lipid-driven toxicity). In addition to NEFA release, adipocytes produce pro- and anti-inflammatory molecules at levels that deteriorate in obesity.
Adapted from Tchernof and Despres [2].

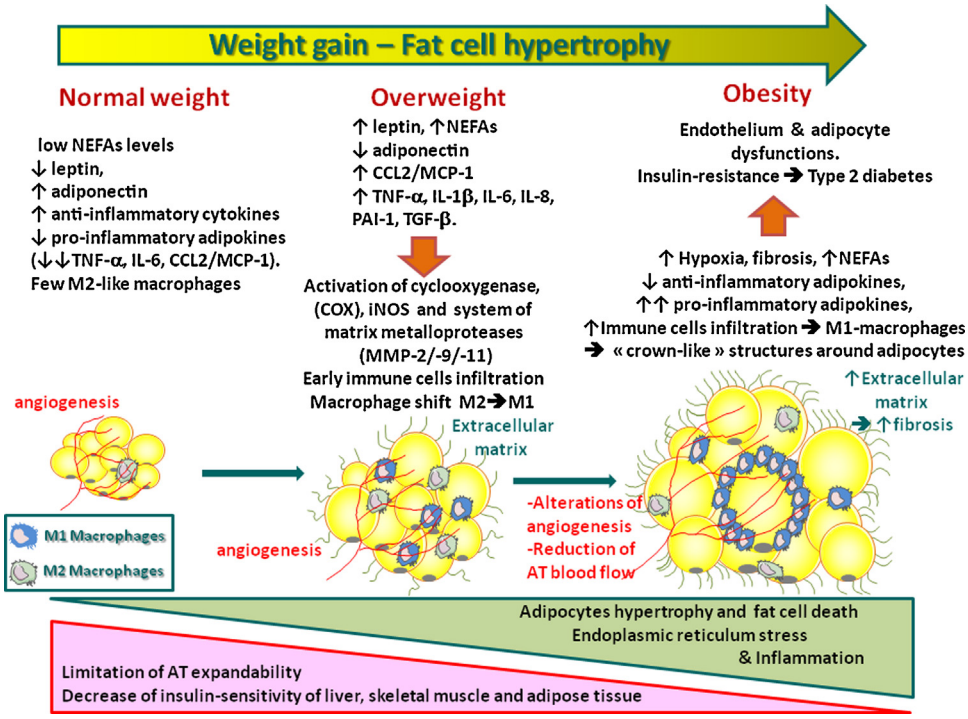

Fig. 2. Pathological changes over time in adipose tissue (AT) from expansion to obesity. Changes in extracellular matrix composition and angiogenesis aggravate the deleterious conditions caused by AT expansion. The vicious circle progresses towards aggravated insulin resistance, and increases the risk of type 2 diabetes and cardiometabolic disorders. NEFAs: non-esterified fatty acids; CCL2/MCP-1: C-C motif chemokine ligand 2/monocyte chemoattractant protein-1; TNF: tumour necrosis factor; IL: interleukin; PAI-1: plasminogen activator inhibitor 1; TGF: transforming growth factor; COX: cyclooxygenase; iNOS: inducible nitric oxide synthase; MMP: matrix metalloproteinase.