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Review

Role of adipose specific lipid droplet proteins in maintaining whole body energy homeostasis ☆

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ABSTRACT

Excess or insufficient lipid storage in white adipose tissue lipid droplets is associated with dyslipidemia, insulin resistance and increased risk for diabetes type 2. Thus, maintenance of adipose lipid droplet growth and function is critical to preserve whole body insulin sensitivity and energy homeostasis. Progress in understanding biology of lipid droplets has underscored the role of proteins that interact with lipid droplets. Here, we review the current knowledge of adipose specific lipid droplet proteins, which share unique functions controlling adipocyte lipid storage, limiting lipid spill-over and lipotoxic effects thought to contribute to disease. This article is part of a Special Issue entitled: Modulation of Adipose Tissue in Health and Disease.

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1. Introduction

Lipid droplets (LDs) are the lipid storage organelles of all organisms. Adipose tissue is the body's largest energy reservoir in mammalians and birds. Energy is stored in fat cell LDs as triacylglycerols (TGs). In the past fifty years, drastic life style and environmental changes have contributed to a worldwide pandemic of obesity and co-morbidities that demands a better understanding of adipose LDs, their role in maintaining energy homeostasis and impact on development of metabolic diseases. In recent years, our general knowledge of the biology of LDs has increased, reviewed extensively elsewhere [1–6]. This review is focused on specific aspects of adipose LD biology as it relates to metabolic diseases.

2. Critical role of adipose LDs in mammalian physiology and diseases

2.1. White adipose energy storing LDs

LDs in mammalian adipocytes in white adipose tissue (WAT) serve as the main long-term energy store and play a crucial role maintaining energy homeostasis [7,8]. The remarkable lipid storage capacity of white adipocyte LDs can be readily visualized by microscopic observation [5]. Most mature adipocytes have a single LD, whose size can range from 25 to 150 μm diameter, occupying most of the cell volume and thereby determining the cell size. Adipose depots grow by either increasing fat cell/LD size (hypertrophy) or increasing the number of fat cells (hyperplasia) (Fig. 1). Importantly, both mechanisms require coordinated and extensive cellular structural changes that accommodate the emergence and growth of the LD. In the fed state, adipose LDs store excess energy as TG. During fasting, when glucose becomes limiting, TGs in adipose LDs are rapidly hydrolyzed into non-esterified fatty acids (NEFAs) and glycerol. NEFA and glycerol leave the adipose and are transported via the bloodstream to other tissues (for glycerol mainly to the liver and for NEFA mainly to skeletal muscle and heart). During fasting plasma NEFA is almost entirely from hydrolysis of TG stored in the adipose LDs (Fig. 1) [9].

When energy and macronutrient levels are saturated by chronic overfeeding, surplus energy is stored in adipose LDs and leads to obesity, generally defined as excessive accumulation of TG in WAT. Concomitant with increased adipocyte LD size, pathological overgrowth of adipose tissue is associated with a cluster of changes including hypoxia, inadequate angiogenesis, increase in adipocyte cell death, macrophage infiltration, fibrosis and adipose tissue insulin resistance (Fig. 2). The adipocyte's micro-environment is severely impacted and limits adipose tissue expandability by inhibiting recruitment of new lipid storage units (preadipocytes) and/or preventing their maturation (Fig. 2) [10,11]. This scenario is supported by recent murine and human studies. Overexpressing adiponectin in murine adipose tissue, an adipokine with known anti-inflammatory and anti-insulin resistance properties [12], or down-regulating collagen VI, a highly

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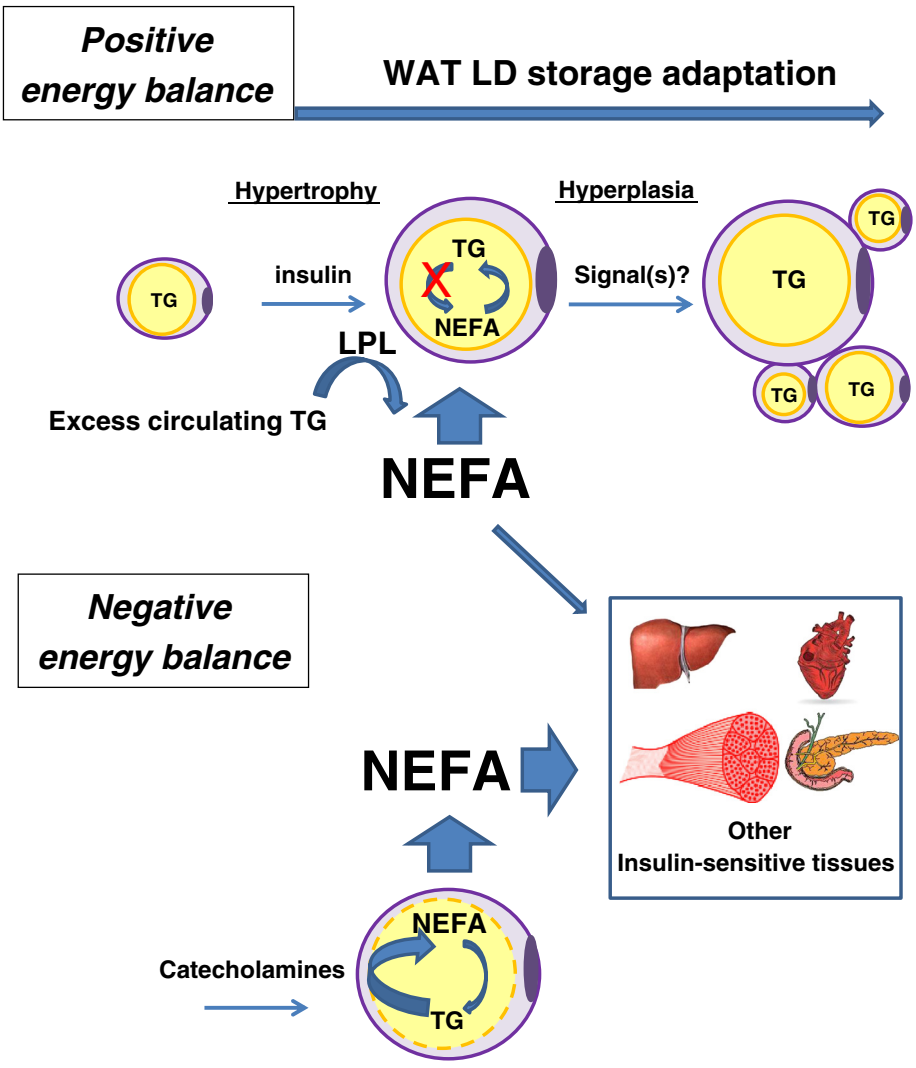

Fig. 1. Healthy adipocyte lipid storage expansion and lipid release. In the fed state with positive energy balance, excess circulating lipids are hydrolyzed by lipoprotein lipase (LPL) synthesized in adipose tissue parenchymal cells and spread along the vascular mesh. LPL-released non-esterified fatty acids (NEFAs) are then re-esterified into triacylglycerols (TG) and stored in adipocyte LDs. It is accepted that once LD growth has reached its capacity (hypertrophic growth), new preadipocytes are either recruited or undergo maturation (hyperplasia). This requires effective tissue remodeling including, adequate implementation of the adipogenic program, angiogenesis and extracellular matrix remodeling supported by endocrine paracrine and neuronal factors. Signaling from adipocytes filled to their LD storage capacity helping recruit preadipocytes are possible, but have yet to be identified.

enriched extracellular matrix component of adipose tissue [13], leads to expansion of adipocytes but paradoxically is associated with substantial improvements in whole-body energy homeostasis, both with high-fat diet exposure and in leptin deficient background [12,13]. The main difference found between fat cell/LD size from insulin-sensitive and insulin-resistant obese patient adipocytes is a propensity for a small fat cell/LD size in obese insulin resistant patients, suggesting a defect in LD growth and maturation [14]. Alternatively, treatment with pharmacological agents that promotes adipose tissue expandability such as thiazolidinediones (TZDs) reverses it [15].

More importantly, obesity is thought to be the most common cause of systemic insulin resistance and it is a key factor in the etiology of a number of diseases, including type 2 diabetes (T2D) [16]. Insulin resistance is defined as an inadequate response to insulin in target tissues, such as skeletal muscle, liver, and adipose tissue, reducing physiologic effects of circulating insulin. The hallmark of impaired insulin sensitivity in WAT is a reduced ability of insulin to inhibit LD lipolysis, resulting in elevated circulating NEFAs. An evidence based consensus is that high NEFA release from WAT causes insulin resistance in skeletal muscle, liver and other tissues [17,18]. It is inferred that these tissues are unable to store or oxidize the lipid influx. The lipid then floods cellular pathways and compartments, causing dysfunction labeled lipotoxicity (Fig. 2) [19]. It is purposed that the link between obesity and systemic insulin resistance is the result of ineffective lipid partitioning to adipocyte LDs and these lipids disrupt adipokine and cytokine secretion [20].

The proposed basis for the relationship between obesity and systemic insulin resistance relies on WAT LDs acting as a lipid sink for excess nutritional lipids, storing them in the form of neutral lipids. This LD centric view argues that as long as nutrient excess can be efficiently sequestered in insulin sensitive white adipose LDs, non-adipose tissues are protected from lipotoxicity. This concept was further shaped from observations that animals and humans with lipodystrophy, in which adipose tissue fails to develop properly or is ill-distributed, also have ectopic LD deposition, contributing to insulin resistance and eventually to decreased insulin secretion [21,22]. Supporting the importance of WAT LD function is the fact that monogenic mutations responsible for 95% of lipodystrophies were found to effect either adipogenesis or LD growth and function. These adipogenesis gene mutations include peroxisome proliferator-activated receptor-γ (PPARγ), Akt2, or lamin A/C. LD growth gene mutations found include perilipin 1 (PLIN1), cell

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