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Invited Review

PPARγ and GLUT-4 expression as developmental regulators/markers for preadipocyte differentiation into an adipocyte

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Abstract

In this document, we have integrated knowledge about two major cellular markers found in cells of the adipocyte lineage (an adipogenic marker and a metabolic marker). This review provides information as to how differentiation of a cell (such as an adipofibroblast, fibroblast or preadipocyte) to become a viable (and new) adipocyte is under different regulation than that experienced by an immature adipocyte that is just beginning to accumulate lipid. The differentiation, prior to lipid-filling, involves PPARγ. Subsequently, lipid-filling of the adipocyte relies on a late subset of genes and, depending on depot specificity, involves GLUT-4 or any number of other metabolic markers.

Keywords: PPAR; GLUT-4; Adipofibroblast; Preadipocyte; Differentiation; Signaling

Contents

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1. Introduction

Small, monogastric animals such as rats, and even larger domestic animals (pigs and cattle), have generated substantial knowledge about adipocyte development and regulation [1–3]. However, due to the presence of the rumen and rumen bacterial conversion of feedstuffs [4–9], mechanisms involving individual adipocyte development or regulation in ruminant animals is not as clear cut. To complicate matters, adipose tissue and its constituent adipocytes are under dynamic physiological regulation [10–12] that appears to be both animal-specific and depot-specific [1,2,4–7,9,13–20]. This complicated (animal and depot) regulation raises the complexity of our overall understanding of both adipose tissue development and metabolism.

In order for any adipocyte to assimilate lipid, however, a mesodermal cell such as a fibroblast, preadipocyte, or adipofibroblast stops proliferating and begins to express genes indicative of the differentiated adipocyte phenotype [1]. Cellular proliferation and the subsequent differentiation "switch" are components of adipogenesis [1]. Alternatively, adipogenesis is stopped and lipid metabolism begins when the differentiated cell (now called an adipocyte) begins to accumulate visible lipid in its cytoplasm [1]. Little is currently known about the appropriate extrinsic and intrinsic regulation of adipogenesis of meat animal-derived cells destined to become adipocytes [1]. For lipid synthesis, there is a requirement of a source of a three-carbon unit (needed to form the α-glycerol phosphate for final triglyceride storage), and intracellular free fatty acids to form the storage triglyceride [4,6–9,15,19–21]. Numerous articles have been published with regards to the regulation of carbohydrate and lipid metabolism in animals [4,6–9,15,20,22,23].

In general, while fatty acid synthesis/storage occurs in adipose tissue of all meat animals, fatty acid storage from dietary triglycerides is primarily driven by what is biologically available to the cell in a depot-specific manner. This appears particularly evident in ruminants when evaluating the bioavailability of carbon sources, since the subcutaneous adipose depot is quite differentially sensitive to acetate, rather than glucose [4,15,20]. While there is not much of glucose or insulin available to adipocytes in ruminants, the insulin/glucose mechanism is operable in some adipose depots [16] and some bovine adipocytes appear to remain responsive to both insulin and glucose [13,19]. Few papers looking at the cellular/molecular regulation of adipogenesis (or lipid metabolism) are available for ruminants and much of the work that has been done is with fetal (or very young) animals, or with other species.

2. Adipogenesis versus lipid metabolism: an overview of the involvement of PPARγ and GLUT-4

Although they may be expressed under different cellular mechanisms and pathways, these two adipogenic and metabolic regulators, respectively, are jointly linked in the differentiation of most adipose-type cells. PPARγ has been identified as an important adipogenic regulator/switch. PPARγ plays an important role in converting adipofibroblasts, fibroblasts, or preadipocytes into differentiated adipocytes. Remarkably, expression and activation of PPARγ induces adipose conversion of porcine [24], bovine [25] and human [26] satellite cells as well. Once a cell is transformed into a lipid-assimilating adipocyte, in most adipose depots GLUT-4 plays a major role in the energetic/metabolic functions of the adipocyte by allowing glucose transportation into the cell, after it has been signaled by insulin. PPARγ may regulate some (early) aspects of GLUT-4, which also links adipogenesis to subsequent events of lipid metabolism. In this review we have summarized literature in this area to highlight the recent significance of PPARγ versus GLUT-4 in adipocyte development, building on several excellent papers published previously [10–12,27–44].

3. Peroxisome proliferator activated receptors (PPARs)

Peroxisome proliferator activated receptors (PPARs) are a class of ligand-dependant nuclear receptor