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Review Article

Lipid droplet dynamics in skeletal muscle

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ABSTRACT

The skeletal muscle is subjected to high mechanical and energetic demands. Lipid droplets are an important source of energy substrates for the working muscle. Muscle cells contain a variety of lipid droplets, which are fundamentally smaller than those found in adipocytes. This translates into a greater lipid droplet surface area serving as the interface for intracellular lipid metabolism. The skeletal muscle has a high plasticity, it is subjected to major remodeling following training and detraining. This coincides with adaptations in lipid droplet characteristics and dynamics. The majority of lipid droplets in skeletal muscle are located in the subsarcolemmal region or in-between the myofibrils, in close vicinity to mitochondria. The vastly organized nature of skeletal muscle fibers limits organelle mobility. The high metabolic rate and substrate turnover in skeletal muscle demands a strict coordination of intramyocellular lipid metabolism and LD dynamics, in which lipid droplet coat proteins play an important role. This review provides insights into the characteristics, diversity and dynamics of skeletal muscle lipid droplets.

Contents

1. Introduction

The skeletal muscle is subjected to high mechanical and energetic demands, especially during high intensity and long duration exercise training. This requires plasticity of the tissue and a high supply and turnover of energy sources for ATP production. Lipid droplets (LDs) in skeletal muscle serve as energy depots, which, in addition to glycogen stores and supply of energy sources via the circulation, play an essential role in energy provision during exercise. The intramyocellular pool of LDs shows a high degree of heterogeneity. Cellular diversity in LDs is attributable to variations in size, intracellular localization, lipid content and composition of LD coat proteins. Furthermore, training and detraining result in remodeling of the muscle and impact on LD dynamics. Herein, I will discuss the characteristics, diversity and dynamics of skeletal muscle LDs.

Abbreviations: DAG, diacylglycerol; DGAT, DAG-O-acyltransferase; FA, fatty acid; IMCL, intramyocellular lipid; LD, lipid droplet; MAG, monoacylglycerol; MGAT, monoacylglycerol acyltransferase; PLIN, perilipin; TAG, triacylglycerol

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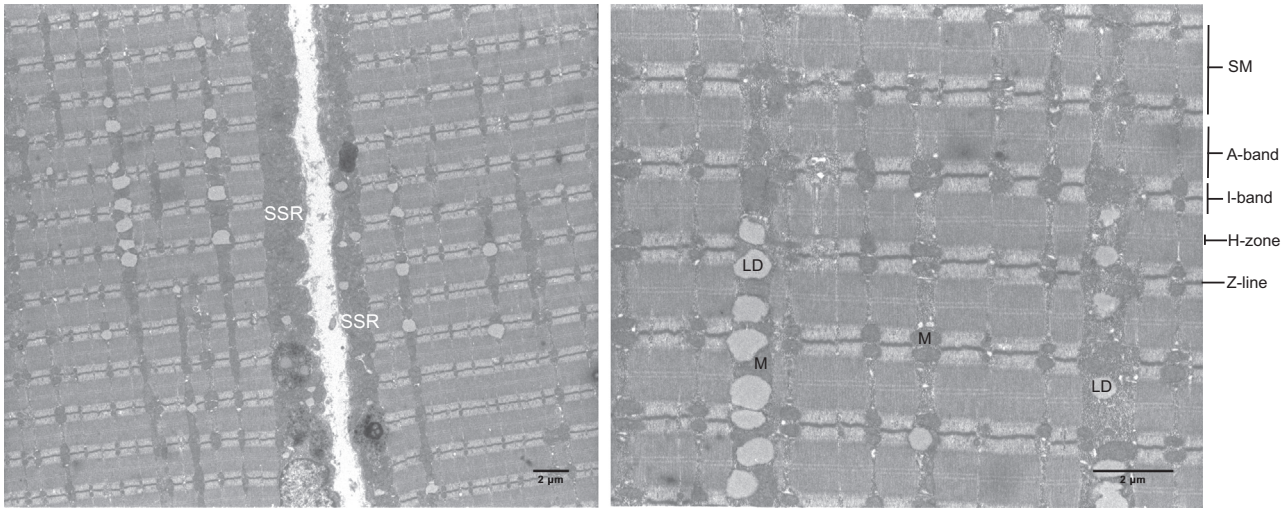

Fig. 1. Electron micrographs of human skeletal muscle (vastus lateralis). LD: lipid droplet, M: mitochondrion, SM: sarcomere, SSR: subsarcolemmal region. Myofibrils are a series of sarcomeres. Image courtesy of Prof. Dr. Matthijs Hesselink (Maastricht University, the Netherlands).

2. Organization and mobility of lipid droplets in skeletal muscle fibers

The contractile elements of the cytoskeleton in skeletal muscle are present in a highly organized fashion, resulting in the characteristic pattern of cross-striations. Muscle fibers contain multiple myofibrils consisting of bundles of actin and myosin filaments organized into sarcomeres. Intramyocellular LDs are localized either in the subsarcolemmal region near the plasma membrane or, more prominently, in-between the myofibrils (Fig. 1). In both cases, they are adjacent to mitochondria. In type 1 (oxidative) muscle fibers, which contain the largest number of intracellular LDs, mitochondria are localized in pairs at the I-bands, on both sides of the Z-bands. LDs are located in the near vicinity ([1] and Fig. 1).

During contraction of the muscle, fibers undergo gross alterations in cellular shape facilitated by binding of myosin to actin filaments resulting in movement relative to each other and shortening of the sarcomeres. Because LDs are localized in-between the sarcomeres, muscle contraction is associated with passive spatial translocation of LDs. In addition to passive contraction-related organelle translocation, observations in other cell types suggest a high intracellular mobility potential of LDs [2] and involvement of primarily microtubules, but also actin and intermediary filaments in facilitating LD movement [2,3]. Thus, LDs are capable of rapid, coordinated movement by being pulled along cytoskeletal elements by molecular motors. These movements are typically fast (hundreds of nanometers per second) [2]. Very little is known about LD motion in muscle. The highly organized character of the skeletal muscle fiber with narrow intermyofilamental spaces and limited subsarcolemmal spaces is likely to limit the mobility of LDs. Yet, the high metabolic rate of skeletal muscle suggests a requirement for a certain degree of mobility, in particular to facilitate turnover of LDs and interactions of LDs with other organelles like mitochondria and sarcoplasmic reticulum for lipid and protein exchange. Similarly, mitochondria were shown to be mobile in adult skeletal muscle fibers [4]. However, mobility was much higher in myoblasts, indicating that mitochondrial mobility is indeed limited due to spatial restrictions in skeletal muscle fibers [4,5]. This suggests similar limited mobility opportunities for LDs in skeletal muscle. Given the absence of any experimental evidence, further research is needed to characterize LD turnover and mobility in skeletal muscle.

3. LD size in skeletal muscle cells

LD size in skeletal muscle is reported to range between 0.3 and 1.5 µm in diameter in normal, healthy skeletal muscle with capacities to increase the size up to at least 3 µm with fat-storage enhancing (genetic) interventions [6–8]. Type 1 fibers tend to contain larger LDs than type 2 fibers [8]. LD size and number in muscle differs fundamentally from that in adipocytes, where LD size is in the 100 µm range [9] and where a single or a few LDs occupy almost the complete cell. This also implies a major difference in LD surface area, composition and intracellular dynamics. Compared to other nonadipocytes, skeletal muscle LDs are similar in size compared to cardiomyocellular LDs [10] and slightly smaller than hepatocellular LDs [11]. The relatively greater surface area of smaller LDs translates into a greater interface for lipid metabolic enzymes and potentially a greater capacity to mobilize lipids. Upon exercise, there is an initial reduction in LD size during the first minutes, followed by a reduction in both LD size and number [12].

4. Lipid storage

The vast majority of intramyocellular lipids (IMCL) are stored in LDs. Esterified lipids constitute the majority of the lipid content of skeletal muscle LDs, mostly in the form of triacylglycerol (TAG), followed by cholesterol and diacylglycerol (DAG) [6,13]. The high energy demand of the muscle requires a continuous turnover of lipid stores. In line with this, regulatory pathways for fat catabolism and anabolism in muscle cells are highly interrelated (reviewed in [14]). For example, activation of PGC1α – the major exercise-activated regulator of muscle oxidative capacity – is also associated with increased IMCL storage [15]. Furthermore, interventions associated with increased lipid supply are characterized by increases in both lipid storage and FA oxidation [16,17]. IMCL levels are increased already after 3 days of a high fat diet [18,19], which further demonstrates that IMCL storage quickly adapts to changes in lipid supply.

Fatty acids (FAs) transported into the muscle fiber or released by lipolysis of IMCL are first bound to acyl-CoA by acetyl-CoA synthetases, which localize to the plasma membrane but also to endoplasmic reticulum (ER), mitochondria and LDs [20,21]. Subsequently, FA-CoAs are either targeted to oxidation or are channeled to lipid storage pathways. TAG is the major neutral lipid

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