Chapter 5

Importance of Plasma Membrane Nanodomains in Skeletal Muscle Regeneration

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Additional information is available at the end of the chapter

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Abstract

Numerous studies showed the importance of skeletal muscle plasma membrane (sarcolemma) in the control of skeletal muscle biology. The emphasis in this review is on the sarcolemmal bioactive lipids decisive for survival, proliferation, differentiation, and function of skeletal muscle cells with the particular concern on muscle stem cells (resident satellite cells, RSC) responsible for muscle regeneration. Nowadays, it is obvious that cholesterol (CHOL), basic component of the lipid rafts (LR) through the control of assembled dystrophin–glycoprotein complexes (DGC), directs muscle fiber contractile properties. Another phospholipid, phosphatidylserine (PS), is a component of the inner plasma membrane leaflet, even though it allows the fusion of myoblasts when exteriorized. Sphingolipids, such as ceramide, sphingosine, sphingosine-1-phosphate, and ganglioside GM3, are important signaling molecules in the charge of RSC activation, their motility, and commitment to particular lineage (myoblasts and myofibroblasts). Phosphoinositides and phosphatidylinositol-4,5-biphosphate (PIP2) specifically establish protoplasmic platforms for protein interactions essential for cell viability and mitochondrial activity. Additionally, both prenylation and palmitoylation of certain proteins (i.e., heterotrimeric G proteins) determine their biological activity in signal transduction from G-protein coupled receptors (GPCR). Isoprenoids are therefore crucial for the recruitment and metabolic responses of RSC to physiological and pathological stimuli. Finally, iatrogenic modifications of sarcolemma with hydroxylamines and their derivatives lead to increased resistance of muscle cells to apoptotic stimuli and slow progression of some skeletal muscle dystrophies.

Keywords: sarcolemma, lipids, satellite cells, nanodomains, skeletal muscle regeneration

1. Introduction

Skeletal muscle growth and regeneration is dependent on the activation of mitotically quiescent resident cells known as skeletal muscle satellite cells (SC) located beneath the basal lamina (integral part of basement membrane) on the plasma membrane (sarcolemma) of adult skeletal muscle fibers. Activated by muscle injury including work overload (i.e., weight lifting), satellite cells proliferate making myogenic precursor cells (myoblasts) that migrate to the site of injury and after withdrawal from the cell cycle fuse collectively or with damaged fibers. The fusion process is mediated by plasma membrane proteins, some of which are the receptors for intermediate of lipid metabolism such as sphingosine 1-phosphate (sphingolipid, S1P). A great deal of plasma membrane surface and integral proteins at the extracellular site is glycosylated and prenylated, the processes indispensable for intracellular protein transport (from endoplasmic reticulum to Golgi apparatus, and from trans-Golgi network to the plasma membrane) as well as for lateral and vertical protein translocation within sarcolemma. In adult skeletal muscle, the self-renewing capacity of satellite cells contributes to muscle growth, and regeneration-associated hypertrophy as skeletal muscle-specific adaptation to workload. Hypertrophy also occurs in satellite cell-depleted skeletal muscle, although in this case neither increase in myonuclei in satellite cell-depleted fibers nor the muscle regenerates after $BaCl_2$-induced severe muscle damage [1]. Accordingly, the biochemistry and structural modifications of plasma membrane are seemingly indispensable for the commitment of satellite cells and their progeny of myoblasts to skeletal muscle renewal. In this review, we hypothesized that changes in the sarcolemmal composition of proteome, glycoproteome, and/or lipidome are the major determinants of satellite cells and muscle fibers to regenerate skeletal muscle. From the experiments and clinical observations related to statin-induced myopathy [2–4] as well as the successful efforts aiming to correct plasma membrane integrity by the modification of skeletal muscle plasma membrane fluidity, we conclude that closer examination of the plasma membrane composition and structural organization might shed more light on the molecular mechanisms of satellite cell commitment to muscle rejuvenation.

2. Skeletal muscle growth and regeneration

Nowadays, it is obvious that skeletal muscle growth and regeneration is firmly linked to the activity of satellite cells adjacent to extrafusal and intrafusal muscle fibers. Intact skeletal muscle encloses satellite cells in the quiescent state, with a dense nuclear chromatin (heterochromatin), fine rim of the cytoplasm, and little organelles. Covered by a thin layer of basement membrane, the satellite cell rests closely applied to the sarcolemma of the muscle fiber (Figure 1). The notion that satellite cells donate nuclei to a growing or regenerating fiber, one at a time, is widely known from a half of the century [5]. Although quiescent in normal skeletal muscle, satellite cells (named by Mauro, [6]) become activated and recruited to the cell cycle when there is a requirement to increase myonuclear number [7]. In response to signals accompanying skeletal muscle injury, denervation, exercise, or work overload, the activation reverses the morphology of satellite cells to lower chromatin density (euchromatin), expanded cytoplasm,

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and additional organelles [8–9]. Several lines of evidence suggest numerous molecules including hormones, growth factors, cytokines, and reactive species as potent incentives in the activation of satellite cells, yet it is still not clear how these muscle progenitors become receptive to the stimuli. Rearrangement of plasma membrane lipids, proteins, and their glycosyl and lipid conjugates might be considered as possible beginning of satellite cell commencement to sense some of the signals. Despite great biological and clinical interest, our knowledge of *in vivo* N-glycosylation sites – a prerequisite for detailed functional understanding – is still very limited [10]. Similarly, the conception of plasma membrane lipidome input to sense and transduce the signals for the activation of satellite cells is limited [11]. Thus, any endeavor intended to decipher the details and mechanisms hidden behind the dynamic changes of plasma membrane organization is an attractive approach with promising perspective for future clinical application in the treatment of skeletal muscle myopathies.

3. Sarcolemma

Plasma membrane in skeletal muscle has several exclusive features related to the structure and composition as well as unique characteristics of membranoskeleton. Nonetheless, some properties are fairly common for any membrane as phospholipids spontaneously form lipid bilayers in aqueous environments due to the amphipathic nature of the molecules with a highly hydrophobic "tail" (acyl chains) and hydrophilic "head" (glycosyl or phosphatidyl) moieties. Lipids in membranes are distributed disproportionately accounting for substantial differences in the extracellular vs. intracellular face of plasma membrane (PM). Anyway, a given membrane has a stable and specific membrane composition dependent on cell type and organelle, and any changes are observed only in certain physiological situation or pathological anomaly. The asymmetry of the external leaflet of PM (exoplasmic) is featured by highly enriched in choline-containing lipids such as phosphatidylcholine (PC) and sphingomyelin (SM), whereas the cytoplasmic leaflet (protoplasmic) is rich in phosphatidylethanolamine (PE), phosphatidylserine (PS), and other phospholipids [phosphatidic acid (PA), phosphatidylinositol (PI), phosphatidylinositol-4-monophosphate (PIP), and phosphatidylinositol-4,5-biphosphate (PIP2)]. The latter participates in cell signaling. Despite cross-sectional diversity, membranes posses lateral asymmetry in basal, lateral, and apical regions [12–13]. Lipids are also capable of displaying different phases under different conditions (mesomorphism). Some lipids, however, as cone-shaped lysophosphatidylcholine (LPC) or PE can form nonlamellar finite structures such as spherical micelles or tubular structures in membranes [14]. Nonlamellar prone lipids are involved in membrane fission and fusion processes with the aim of enzymes such as scramblases, flippases, and floppases. Finally, intact PM is extremely elastic as it reseals after mechanical rupture allowing for the separation of cell fragments (i.e., synaptosomes).

As thin (5–10 nm) lipid bilayer in eukaryotes, PM plays several tasks emerging beyond defining simple cellular boundary. It can organize complex tools for transportation (ion channels, transport proteins, pumps, and invaginations for macromolecules) or molecular sensing (receptors, Figure 2). PM is also essential to control intercellular communication (flow of information) through highly dynamic microdomains acting as platforms for molecule inter-

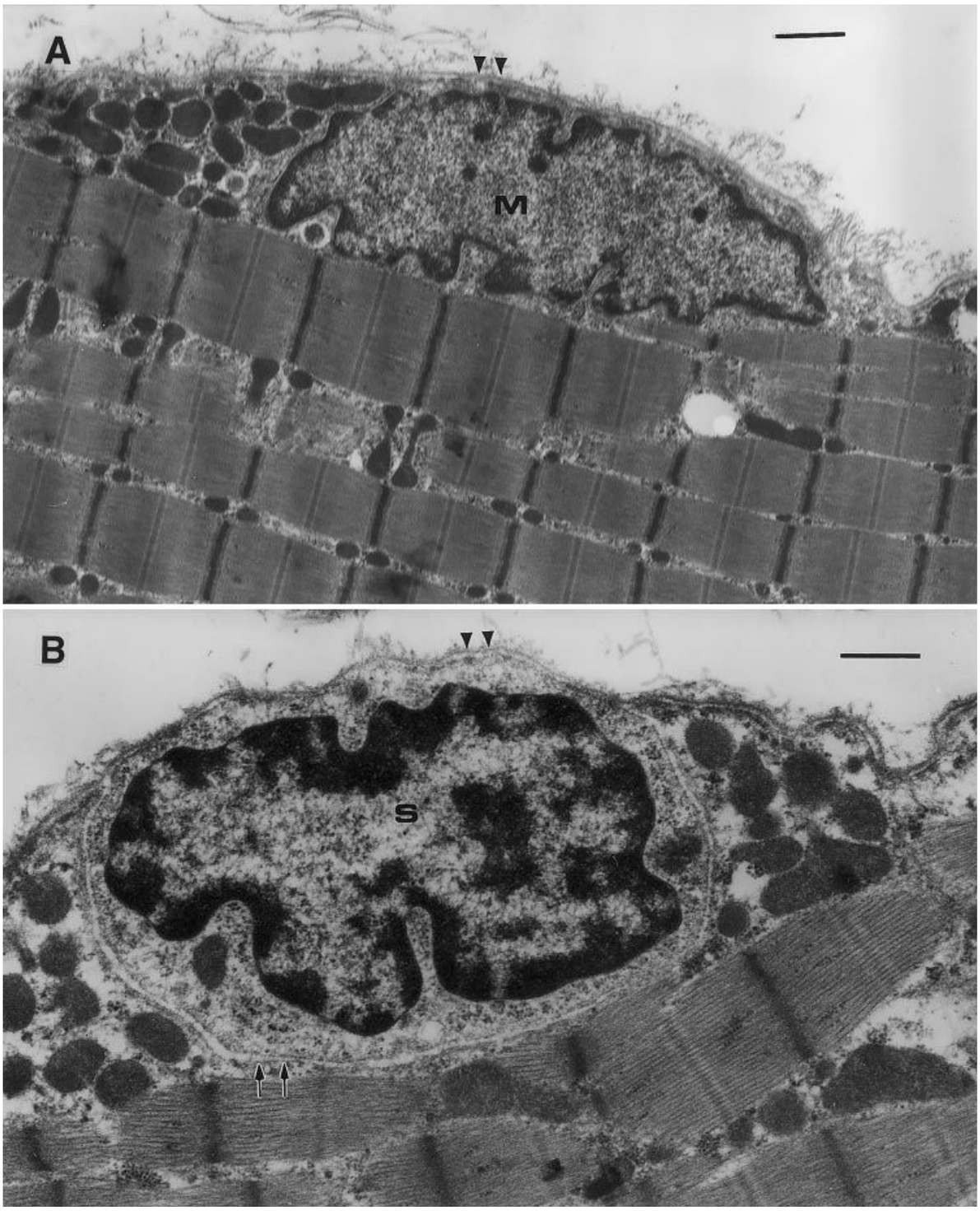

Figure 1. Electron micrograph of a typical myonucleus (*A*) and a muscle satellite cell (*B*). Muscle satellite cells (S) were identified by their location inside the basal lamina (arrowheads) and outside the sarcolemma (arrows) and an independent cytoplasm. In contrast, a myonucleus (M) is located inside the sarcolemma of the muscle fiber and does not contain an independent cytoplasm. Bar, 1 mm., reprinted from Sinha-Hikim et al. 2003 [133].

actions. Skeletal muscle cell plasma membrane is specifically adapted to resist consequences of muscle fiber shortening during contraction. Additionally, sarcolemma periodically invagi-

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nates, giving rise to the transverse tubule (TT) network liable for sensing depolarization by dihydropyridine receptor (DHP) essential to trigger of calcium flux evoked by activation of ryanodine receptor (RY). Dystrophin–glycoprotein complex (DGC), also known as dystrophin-associated protein complex (DAC), is embedded in sarcolemma (found in other cell types such as astrocytes) and plays paramount role in the aforementioned actions (Figure 3). It is composed of several proteins including, dystrophin (DP), dystrobrevin (DB), syntrophin (SP), dystroglycans (α- and β-DG), and sarcoglycans (α-, β-, δ-, and γ-SG). These proteins are assembled in order to transmit lateral force during isotonic twitch. Subsarcolemmal protein assemblies circumferentially aligned in schedule with the Z-disk or peripheral myofibrils are also known as costameres (assemblies of costameric proteins, Figure 4). They physically couple force-generating sarcomeres with the sarcolemma in striated muscle fibers and are thus considered a pitfall of skeletal muscle, a critical component of striated muscle morphology which, when compromised, is thought to directly contribute to the development of several distinct myopathies also termed sarcolemmopathies (Figure 5). Costameric proteins are found in a cholesterol (CHOL) rich membrane fraction pointing to lipid rafts (LR) as spatial localization of DGC [15]. Actually, LR are clustered at the level of DP complex through laminin-mediated interaction with dystroglycans [16]. Furthermore, CHOL depletion uncouples β-DG from sarcolemmal domains with related impairment of mechanical activity of skeletal muscle [17] (Figure 6), whereas DP repeats which interact with membrane lipids strengthen the sarcolemma providing flexible support to muscle fiber membranes (Figure 7) [18]. Additionally, DGC spatial organization is vital for physical interface between SP and sodium channels or neuronal nitric oxide synthase (nNOS), although not at the same time. DGC is regularly distributed along sarcomeres and aligned mainly with Z-disks to connect actin cytoskeleton with extracellular matrix (ECM) protein laminin (Figure 8). Laminin together with collagen IV, fibronectin, perlecan, entactins, agrin, and glycosaminoglycans is a component of basement membrane. Extrinsic protein β-dystroglycan is the laminin receptor and binds membrane-spanning (integral) α-dystroglycan that mediates interactions with DP and DB [19]. At the focal adhesions facing Z-lines, the integrin receptors ($\alpha 7\beta 1$) connect fibronectin/laminin with actin filaments of sarcomeres (Figure 9). Tallin, vinculin, and paxillin are intermediate filaments forming a lever that hooks up integrins with thin filaments [20, 21]. Caveolin-3 is the muscle-specific form of caveolin found mainly as intrinsic (inner leaflet) membrane protein at the sarcolemma and TT [22]. The functions of caveolin-3, β-DG, DP, and SG are controlled by cholesterol and sphingolipid concentrations in the lipid rafts and caveolae [17–18, 23]. In striated muscle, signal transduction through cellular membranes can be regulated by the interaction of the cytoskeleton with caveolae (C) – caveolin-enriched membrane domains [24]. Mounting evidence demonstrates that lipids themselves regulate the location and activity of many membrane proteins, as well as defining membrane microdomains (lipid rafts, caveolae, and coated pits) that serve as spatiotemporal platforms for interacting signaling proteins [11]. Lipid rafts (single lipid raft is approximately 50 nm in diameter) are defined as detergent insoluble glycolipid (GL)-enriched planar domains (detergent resistant membranes, DRM) highly enriched in cholesterol (CHOL), SM, glycosphingolipids (GSL), and glycosylphosphatidylinositol (GPI)-anchored proteins. To sum up, membrane lipids are classified into three major groups: glycerol-based lipids (glycosyl-glycerides and phospholipids), sphingolipids (SL) with sphingoid-base backbone (SM and GSL), and cholesterol. Similar LR may differ in

their size (fusion and fission), as well as in the proportions of lipids and proteins, somewhat modified by pathophysiological processes or nutritional and/or pharmacological interventions. Caveolae are dissimilar to LR as they are deficient in (GPI)-anchored proteins and poor in CHOL but rich in caveolins, the structural proteins assembled to stabilize membrane invaginations [25]. In extreme situations, PM may be subjected to disintegration, protein misfolding, and aggregation, and finally profound dysfunction causes cell death by necrosis. How these nanodomains are segregated within plasma membrane is a matter of debate, although cholesterol molecules establish closeness of PL, GL, GSL, SM, and proteins. Cholesterol (alcohol) acts as "glue" with hydroxyl group that combines with the phosphate head of phospholipids, whereas the hydrophobic steroid section works together with phospholipids acyl chains. Growing body of evidence points to physicochemical forces (intermolecular forces including electrostatic interactions, hydrogen bonds, Van der Waals forces, and hydration forces) which determine asymmetric geometry of membranes both laterally and in cross-section. Moreover, integral proteins also influence lipid structure in the membrane. One might bear in mind that according to lipidomics, more than 1000 different lipid forms are to be found in plasma membrane. To meet the requirements of fluidity, membrane components are also subject to considerable qualitative and quantitative seasonal changes adjusted by the cell [26]. It is determined by the environmental conditions (i.e., cold vs. heat) but also by needs of adaptation such as hyperplasia/hypertrophy or resistance to different types of stress (shear stress, oxidative stress including irradiation). In either case, physicochemical properties of membranes have to facilitate cell signaling and motility. In turn, cell signaling and motility are influenced by the glycosylation status of PM proteins, both integral represented by receptors and peripheral because they are heavily modified on the external leaflet.

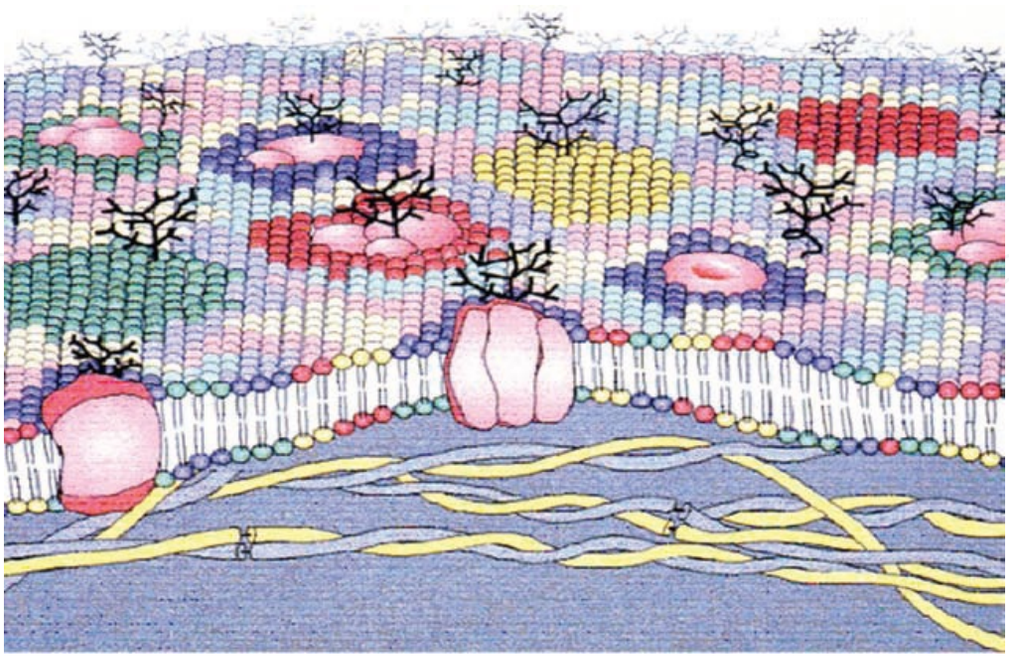

Figure 2. Schematic illustration of a biomembrane, depicting membrane lipid asymmetry as well as microdomains enriched in particular lipids and those induced by membrane proteins, reprinted from Escriba et al. [12].

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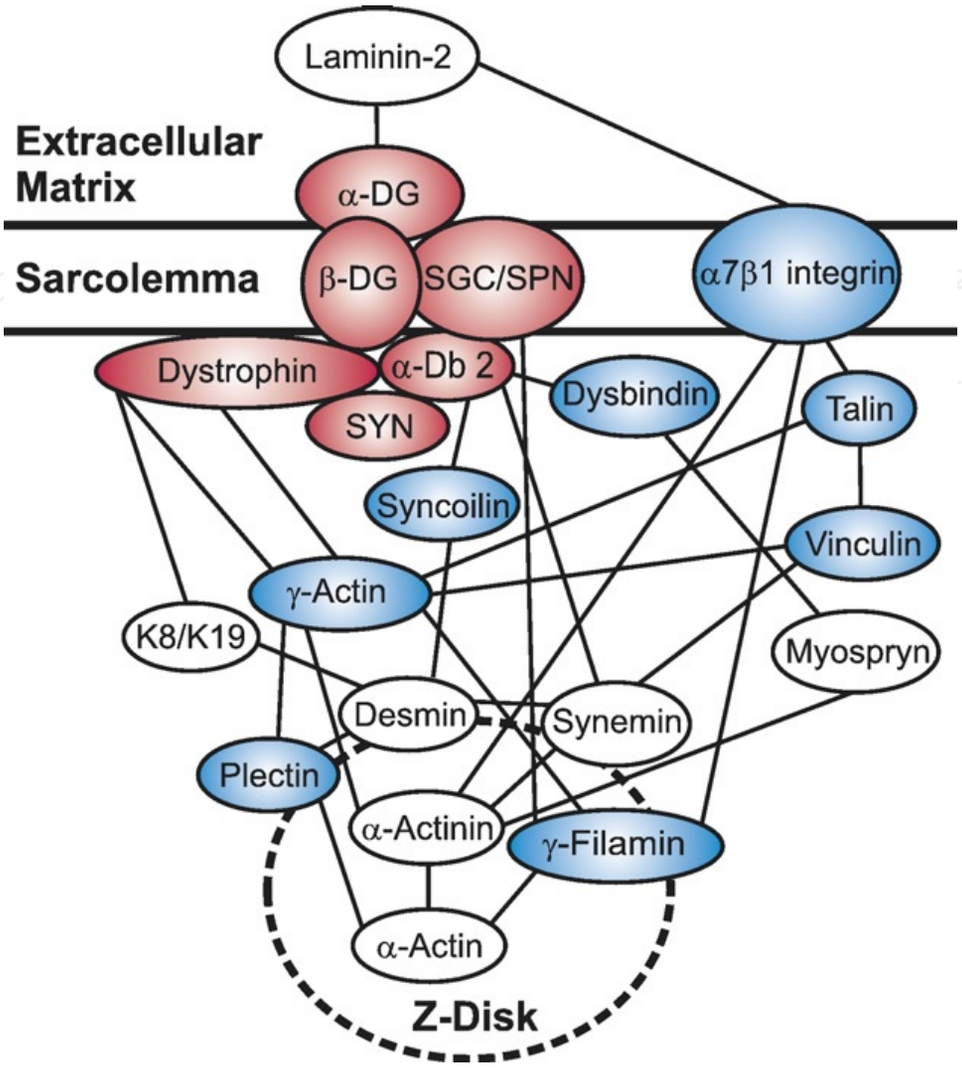

Figure 3. The dystrophin–glycoprotein complex network. Shown in red are the constituents of the core dystrophin–glycoprotein complex, which copurify as a highly stable complex from skeletal muscle and which show greatly decreased abundance in dystrophin-deficient muscle. α-Dystroglycan and β-dystroglycan (α-DG, β-DG); the sarcoglycan complex (SGC); sarcospan (SPN); α-dystrobrevin-2 (α-Db 2); syntrophin (SYN). Also shown are structural proteins that interact directly with components of the dystrophin–glycoprotein complex, their direct binding partners, and their location within striated muscle cells. Cytokeratins 8 and 19 (K8/K19). Proteins highlighted in blue are present at increased levels when dystrophin is absent, reprinted from Ervasti 2007 [23].

4. Statins and statin-induced myopathy

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase reversible inhibitors, became the most frequently prescribed drugs in modern societies used clinically to improve the lipid profile of hyperlipidemic patients, thereby decreasing the incidence of primary or secondary ischemic cardiac events [27–28]. The primary mechanism of action of statins is to lower CHOL levels by the inhibition of mevalonate formation, the rate limiting step in the cholesterol biosynthesis [29]. Pleiotropic effects of statins which seem to be independent of the

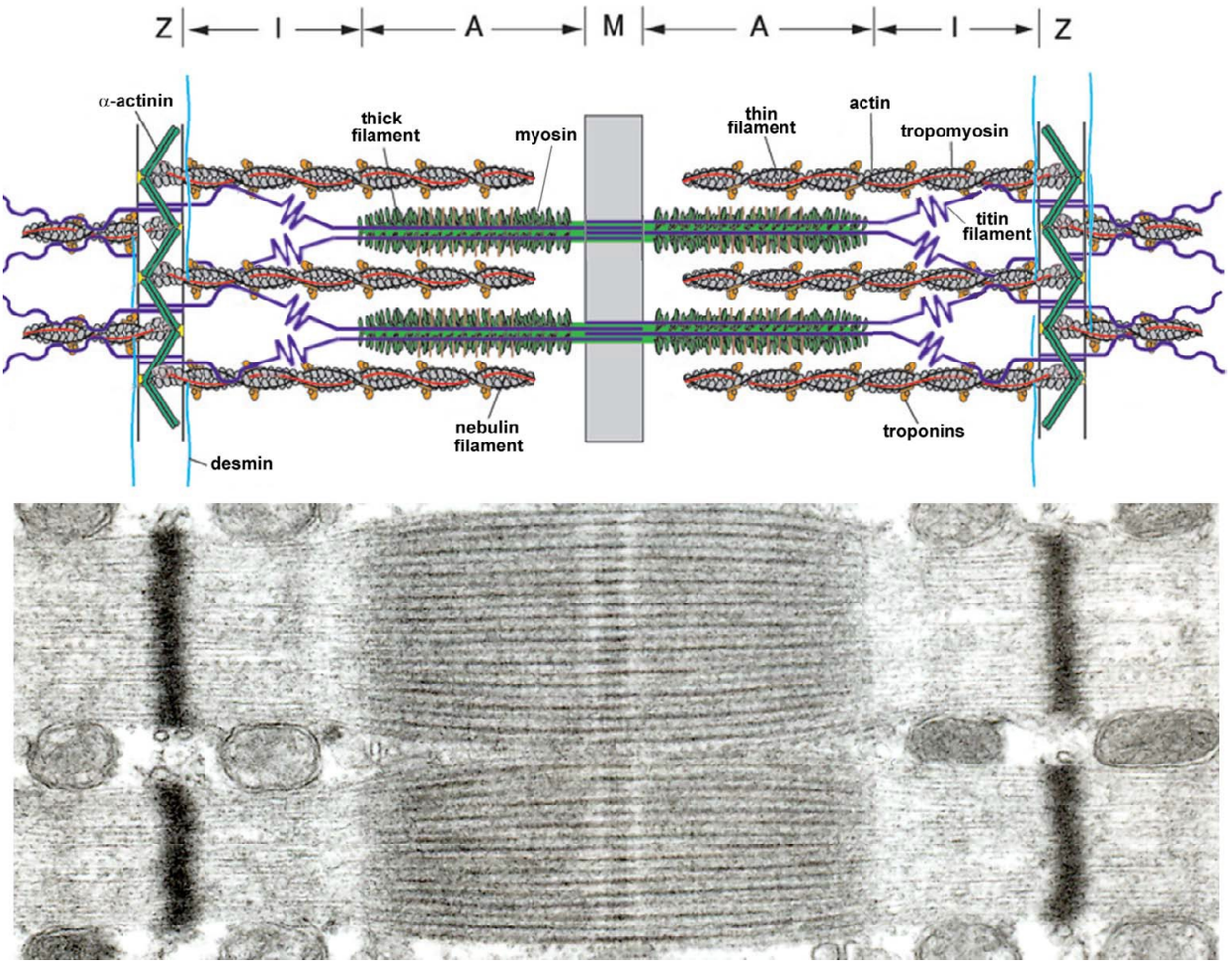

Figure 4. *Top*: Simplified model of two muscle sarcomeres in parallel. The sarcomere is composed of the thin (mostly actin) filaments, the thick (mostly myosin) filaments, and the giant filamentous molecule titin. The thin filaments are anchored in the Z-line, where they are cross-linked by α-actinin. The thick filament is centrally located in the sarcomere and constitute the sarcomeric A-band. The myosin heads, or cross-bridges, on the thick filament interact with actin during activation. Titin spans the half-sarcomeric distance from the Z-line to the M-line, thus forming a third sarcomeric filament. In the I-band region, titin is extensible and functions as a molecular spring that develops passive tension upon stretch. In the A-band, titin is inextensible due to its strong interaction with the thick filament. *Bottom*: Electron microscopy photograph of the ultrastructural organization of sarcomeres in parallel, reprinted from Ottenheijm et al. 2008 [134].

inhibiting effect on CHOL formation have also been reported [30–31], although statin-induced release of nitric oxide (NO) and prostaglandins (PGI2) does not explain side effects of statins on skeletal muscle cells (NO stimulates myogenesis, while PGI2 inhibits platelet activation). Even if statins are in general well tolerated and are safe for almost all patients, they were reported to induce different grades of myopathy in a significant part of the population, ranging from mild myalgia to morbid rhabdomyolysis [32–33]. There are risk factors for developing statin-induced myopathy (SIM), the significant component of statin intolerance during statin treatment, such as advanced age, excessive exercise, and multisystem disease as renal or hepatic insufficiencies, diabetes, or hypothyroidism [34]. Impaired metabolism of statins, pharmacokinetic interactions, and genetic effects are all probable causes of statin-induced

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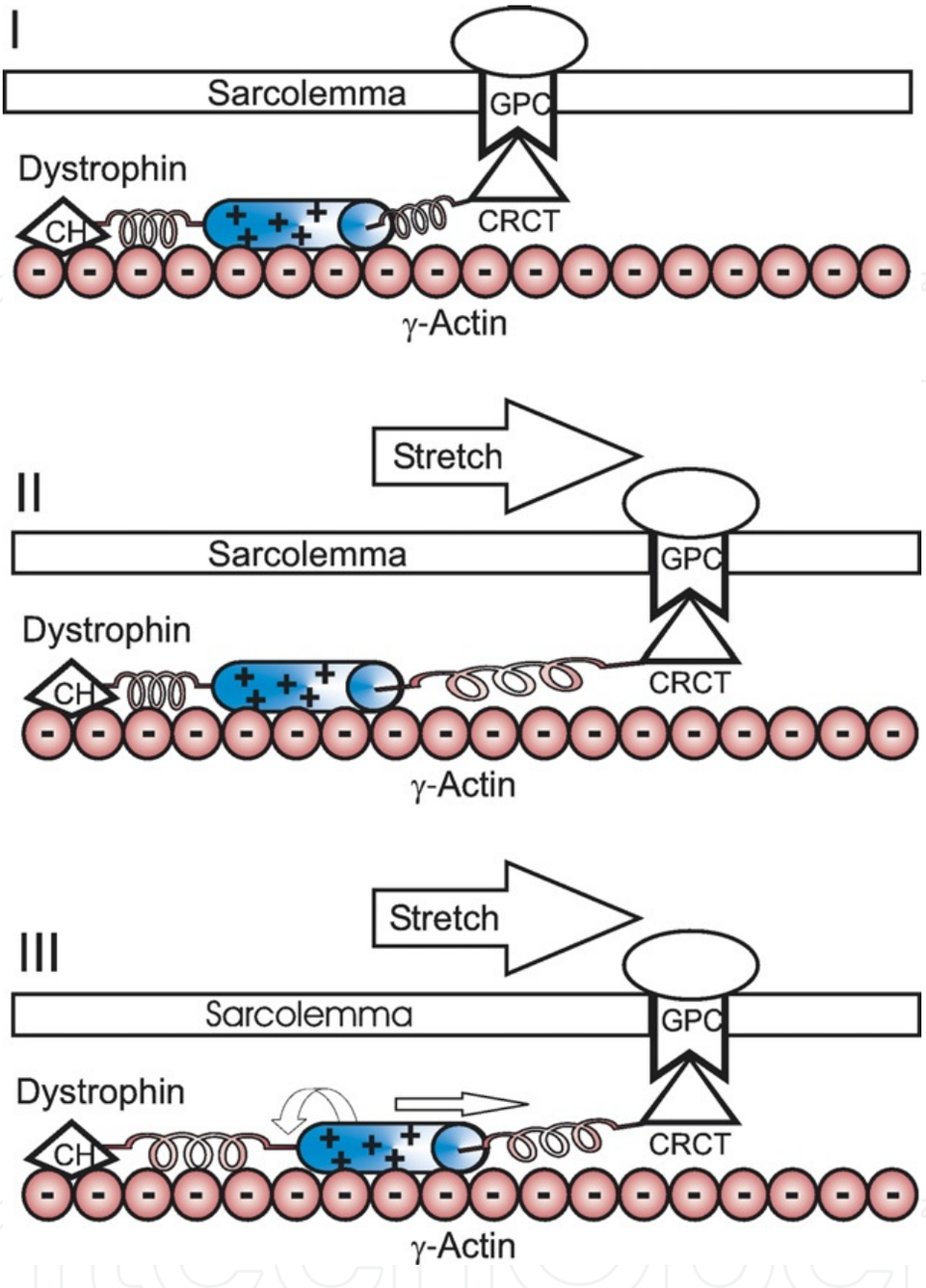

Figure 5. Dystrophin as a molecular shock absorber. Shown is a hypothetical model for how dystrophin may function to dampen elastic extension during muscle stretch. (I) Relaxed muscle. (II) Muscle stretch imposes forces that uncoil spring-like elements within repeats 1–10 and 18–24. (III) Electrostatic interaction of basic actin-binding repeats 11–17 with acidic actin filaments dampens extension of the spring-like elements. The "nonspecific" electrostatic interaction between the basic spectrin repeats and actin filaments is optimal because it does not require a specific orientation for interaction and would allow sliding between dystrophin and actin. As muscle rapidly shortens during contraction, the electrostatic interaction of the basic actin-binding repeats with acidic actin filaments would also serve to dampen elastic recoil, reprinted from Ervasti 2007 [23].

myotoxicity (muscle toxicity), although the molecular mechanism has not yet been elucidated in full. The most frightening clinical adverse effect is drug-induced rhabdomyolysis (0.1–0.5% in patients treated with pravastatin) the frequency of which is further increased by coadmi-

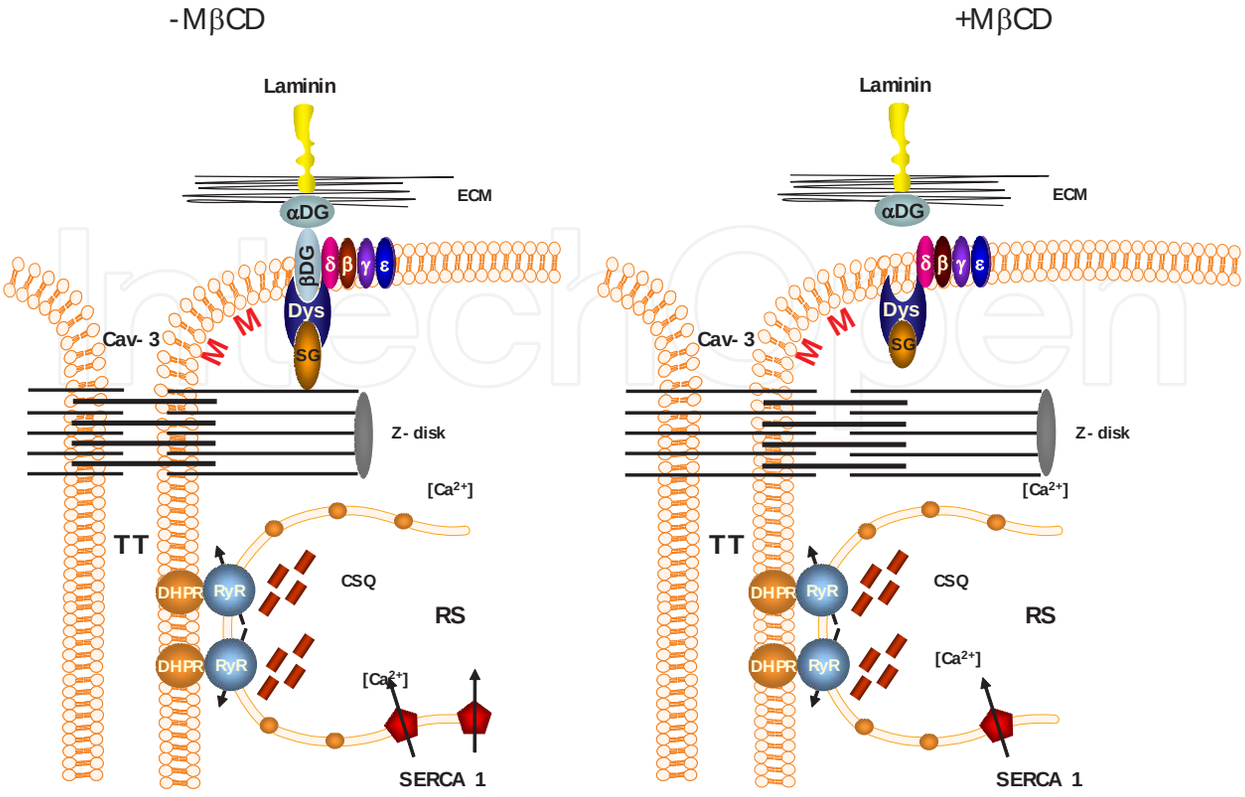

Figure 6. A model of the effect of membrane cholesterol depletion on the sarcolemmal distribution of β-DG. The sarcolemmal lipid rafts close to the clear opening of the TT-membrane are enriched in cholesterol, GM1 (ganglioside M1), Cav-3 (caveolin-3), and β-DG (dystroglycan). The schematic diagram illustrates the diminished contact between β-DG and Dys (dystrophin) in the presence of MβCD (methyl β-cyclodextrin); the β-DG/Dys interaction is essential for lateral force transmission. SERCA1 (sarcoplasmic reticulum calcium ATPase) and RyR (ryanodine receptor (SR Ca^{2+} channel)) function normally. SL, sarcolemma; SR, sarcoplasmic reticulum; EM, extracellular matrix; LR, lipid raft; Dys, dystrophin; SG, sarcoglycan; CSQ, calsequestrin, adapted from Vega-Moreno et al. 2012 [17].

nistration of fibrates [35]. Reductions in skeletal muscle membrane CHOL were initially thought to account for the range of myopathic reactions. Additionally, the lowering the isoprenoid levels has been suggested to contribute to these pathologies as protein prenylation, and the potential consequences of a generalized insufficiency of this form of protein modification [36] are important for the activity and anchorage of plasma and other membrane proteins (nuclear envelope, dystrophin–glycoprotein complex, cytoskeletal G-proteins, etc.).

There is growing interest to decipher the molecular mechanism of the statin-induced myopathy, both by scientific community and pharmaceutical companies. One in three people over the age of 45 is taking a statin to reduce heart attack risk, the HMG-CoA antagonist with three orders of magnitude greater affinity to bind and subsequently to inhibit HMG-CoA reductase activity than that of natural substrate (HMG-CoA). Two in five women taking the statin are weaker than before, with one in ten reporting they felt "much worse". As statins became the most frequently prescribed drugs to prevent cardiovascular crisis alongside with the effort to pace physical activity, the issue how to protect from statin-induced myalgia, myositis, and rare cases of rhabdomyolysis is of great concern. In fact, due to muscle toxicity, an estimated 5–

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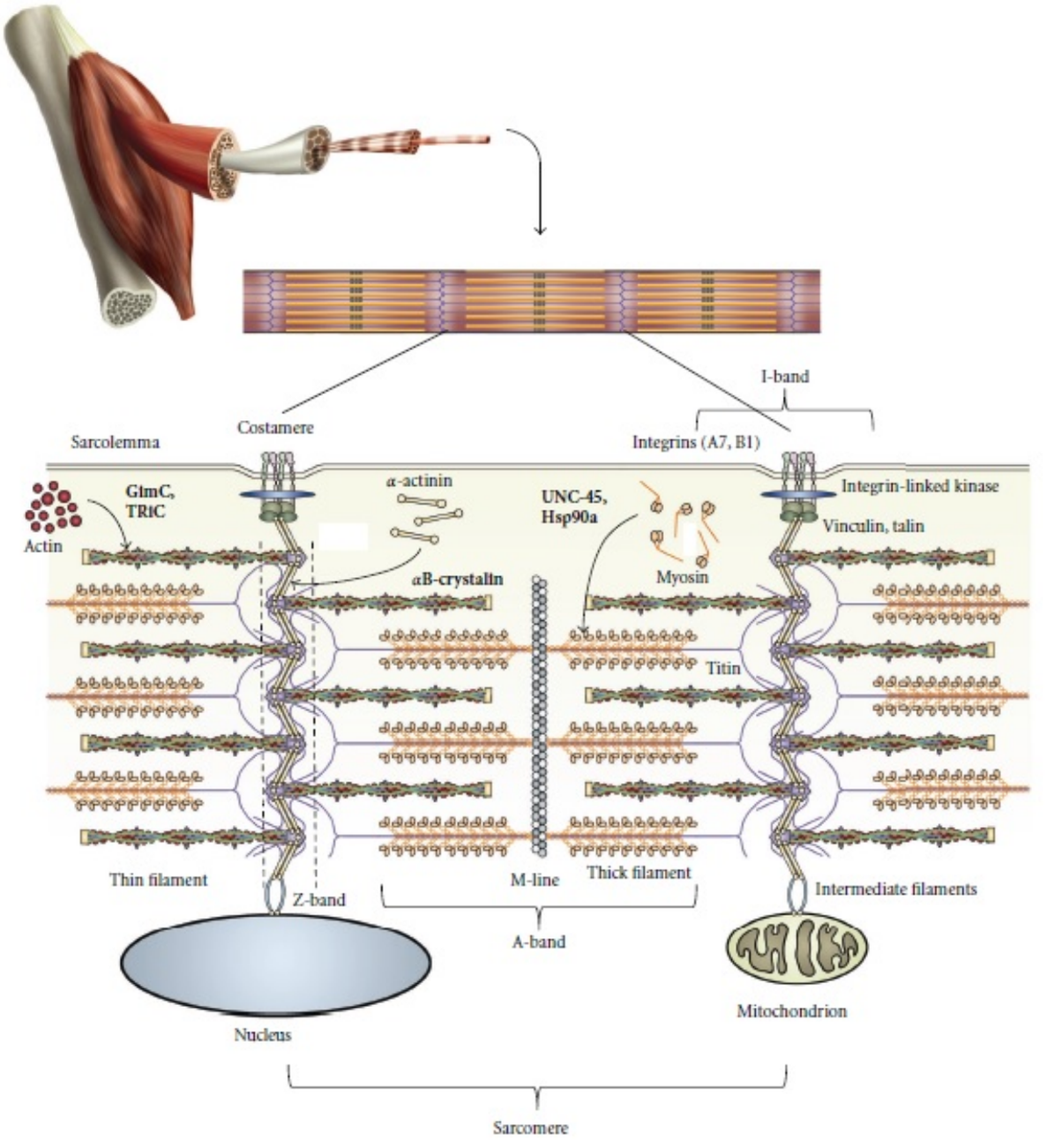

Figure 7. Schematic diagram of the sarcomere and costamere protein complexes of striated muscle cells. Major components of the mature sarcomere and costamere are shown, along with the cytoskeletal and motor filament systems, in context with the sarcolemma and organelles of syncytial myocytes. Known chaperone or cochaperone molecules are shown in bold, along with their substrates. Arrows indicate regions where chaperone-mediated protein folding is essential to incorporate polymeric filament proteins, adapted from Sparrow and Schock 2009 [135], reprinted from Myhre and Pilgrim 2012 [136].

10% of patients discontinue statin use due to myopathic symptoms. Reports of myositis and myopathic symptoms increase with increased statin dose [37], with different classes of statins, or when statins are coupled with other drugs [38], and with exercise [33]. The mechanistic underpinning of statin myopathy are believed to be multifactorial and partially attributed to

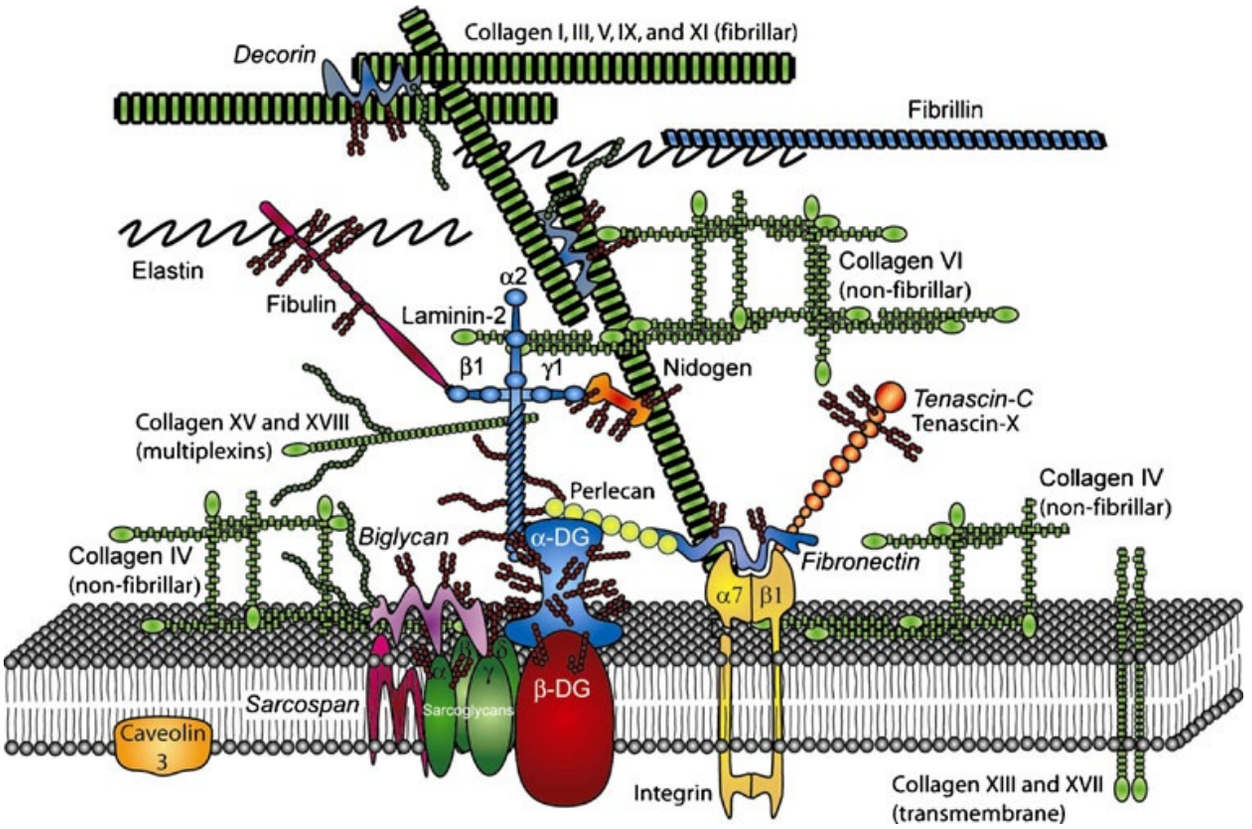

Figure 8. This figure shows the structure of the costamere and known molecular interactions. Below the membrane bilayer shown is the intracellular space and above it is the extracellular space. In the intracellular space, the costamere is attached to the contractile proteins through dystrophins (for the dystrophin glycoprotein complex, DGC), vinculin, talin, and paxilin (for the integrin complexes; not shown). In the extracellular space, both DGCs and integrin complexes bind to the components of the basal lamina that is attached to the rest of the extracellular matrix that consists mostly of fibrillar collagens, reprinted from Voermans et al. 2008 [137].

the regulatory effects of statins on apoptosis of muscle cells [39] and proliferation [3]. As skeletal muscle resident satellite cells (RSC) represent physiological reserve of undifferentiated muscle progenitors, it is obvious that activation followed by proliferation and migration are crucial in muscle adaptation to mechanical overload and regeneration from injury [40]. Thus, if statins impair RSC activation these processes could not be initiated. To tackle the problem of reduced CHOL concentration in plasma membrane and associated changes in the function of LR in muscle cells seems to be fundamental. The focal point is LR, where changes (biochemical and morphological) are presumably attributed to the consequences of disturbed cell signaling. As HMG-CoA reductase activity is ubiquitous, while the side effects of statins are confined to skeletal muscle, it is suggested that muscle tissue is featured by unique response to lower CHOL. RSC are targeted by CHOL depletion and the consequences are cumulative as muscle growth is stopped at the initiation phase (signal transduction). This assumption is supported by the data obtained from sarcolemma examination (single molecule microscopy and molecular studies), which demonstrate the isolation and downregulation of LR and the recruitment of mitochondrial oxidative phosphorylation system during myogenesis [41–42]. CHOL and GSL/SL are also present in the membranes of cellular organelles such as ER and

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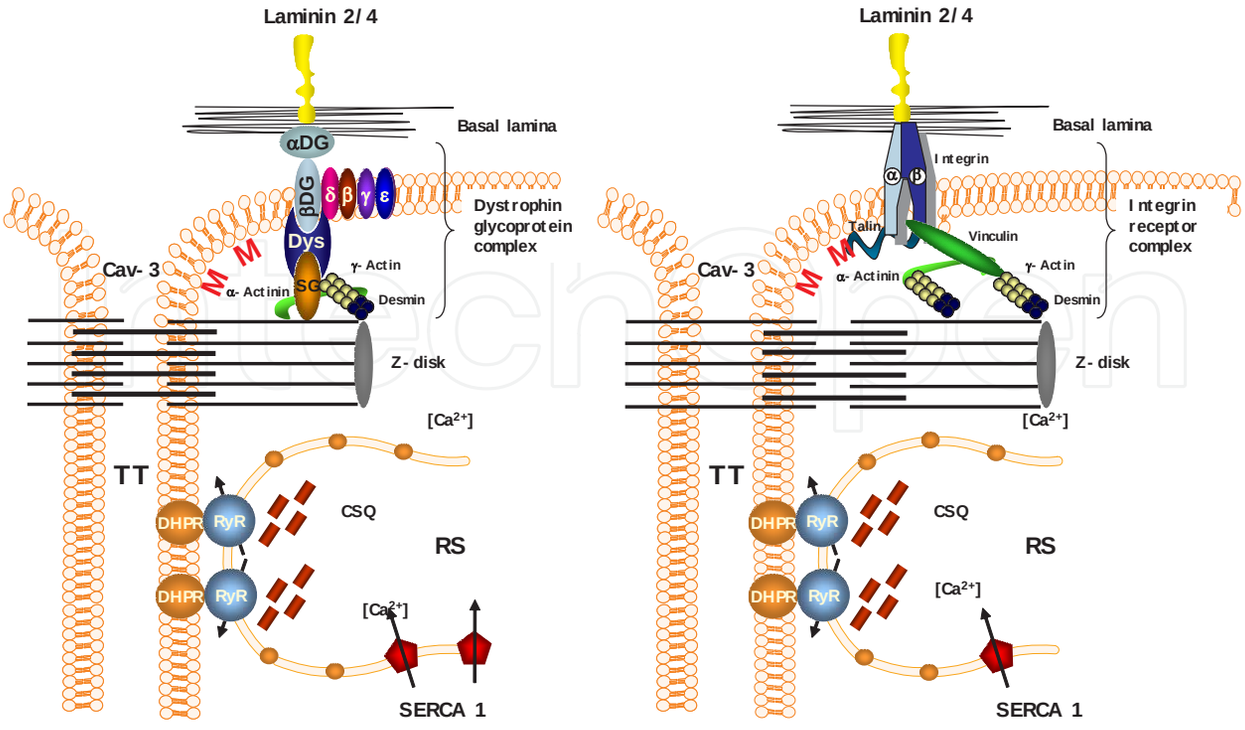

Figure 9. Schematic representation of a costamere and the focal adhesion complex (FAC). Two laminin receptors, a dystrophin/glycoprotein complex and an integrin receptor complex, are among the sarcolemmal structures that link the contractile apparatus of muscle fibers with the surrounding basal lamina. Components of both receptors, i.e., both dystrophin and the integrin-associated cytoskeletal proteins (talin, vinculin, α-actinin), colocalize in subsarcolemmal complexes which connect through γ-actin and the intermediate-filament proteins desmin and vimentin to the Z-disk of skeletal muscle fibers, adapted from Patel and Lieber 1997; Rybakova et al., 2000 [138–139], adapted from Fluck et al. 2002 [20].

Golgi complex (GC). Their role, however, remains obscure as methods to study effects of CHOL depletion in organelles are limited. The main concern should be placed on the sarcolemma and mitochondria, since these organelles control both muscle growth and development [43, 44].

5. Statin-induced myopathy and mitochondria

The development of statin-induced rhabdomyolysis is a morbid side effect of HMG-CoA reductase inhibition, occurring in less than 1 in 1000 statin-treated patients [45]. Even though occurrence of myopathy in statin-treated individuals has been estimated to range from 1 to 10%. Studies performed on rats confirmed that atorvastatin treatment reduces exercise capacity manifested by higher fatigability [46]. It is more common in statin users regularly exercised or statin-treated athletes pointing to the high correlation between the muscle contractive activity and muscle-associated complications of statin administration. Among several hypotheses raised to explain the aforementioned causal relationship between statins and physical exercise, growing body of evidence indicate both reactive oxygen species (ROS) and abnormal mitochondrial activity as probable inciting factors implicated in the deleterious effects of statins [47–48]. Actually, the inhibition of HMG-CoA reductase that hampers the

mevalonate pathway in addition to impaired cholesterol synthesis also reduces the synthesis of isoprenoids such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), intermediates affecting number of nonsteroid isoprenoids including coenzyme Q10/ubiquinone [49], and finally it adversely affects selenoprotein synthesis as well as the biosynthesis of dolichols, which are involved in the process of protein glycosylation (Figure 10). The latter mechanism is rate limiting by dolichyl phosphate, which acts as a donor of oligosaccharides in glycoprotein synthesis [50]. The importance of glycoproteins in skeletal muscle growth and regeneration is further emphasized by the examination of N-linked glycoproteome of C2C12 mouse myoblasts and myotubes [51]. It is clear from this study that approximately 128 (117 transmembrane, 4 glycosylphospatidylinositol-anchored, 5 ECM, and 2 membrane-associated) proteins were identified, while a few N-linked glycoproteins (including aquaporin-1 and β-sarcoglycan) were apparently of paramount value when myoblasts differentiate to myotubes. There was an evident decrease of aquaporin-1 and cadherin-2, whereas β-sarcoglycan expression level increased as the myoblasts fused and formed multinucleated syncytium. Ubiquinone is an important electron carrier between the complex I and complex III of respiratory chain in mitochondria. Thus, decrease in nonsteroid isoprenoids such as CoQ10 leads to the inhibition of complex I, incomplete reduction of oxygen at the level of cytochrome *c* oxidase (complex IV), and induces oxidative stress (augmentation of superoxide anion radical, hydrogen peroxide, and finally hydroxyl radical) postulated to cause myotoxicity of statins [48]. Myotoxicity is therefore at least in part the consequence of damage to lipids, proteins, and DNA, although lipids in cellular membranes are most likely targets of ROS (extensive lipid peroxidation). Additionally, limited access of proteins to prenylation impairs important lipid anchorages essential for PM attachment and function of a variety of proteins involved in cell signaling (i.e., heterotrimeric guanine nucleotide-binding protein-coupled receptors – GPCRs, GTP-binding small/G-proteins Rap1, Ras, Rac, and Rho).

6. LR partners control skeletal muscle regeneration

GPCRs, the most abundant PM receptors, regulate wide range of cellular processes through intracellular heterotrimeric G protein (GTP-binding protein). The latter acts as a signal transducer to control the activity of several catalytic proteins central to the message amplification and its intracellular broadening to effector proteins. Heterotrimeric proteins are composed of three subunits (Gαβγ). Agonist-mediated activation of GPCRs brings about conformational changes which lead to the exchange of guanosine diphosphate (GDP) for GTP on the Gα-subunit which then dissociates from Gβγ dimer. Now, Gα may translocate to the target protein(s), whereas Gβγ dimer inactivates the receptor through phosphorylation (it recruits G protein–coupled receptor kinase – GRK to inactivate the receptor). As GPCRs constitute the largest family of membrane receptors, there are at least 16 types of Gα subunits, 5 of Gβ subunits, and 12 types of Gγ subunits [52]. Gα signaling is stopped when GTP is converted to GDP by the intrinsic GTPase activity of the protein itself. In consequence, Gα-GDP is reassembled with Gβγ dimer and G-protein complex is reestablished. Importantly, target proteins for heterotrimeric G-proteins are membrane bound suggesting that lipid–

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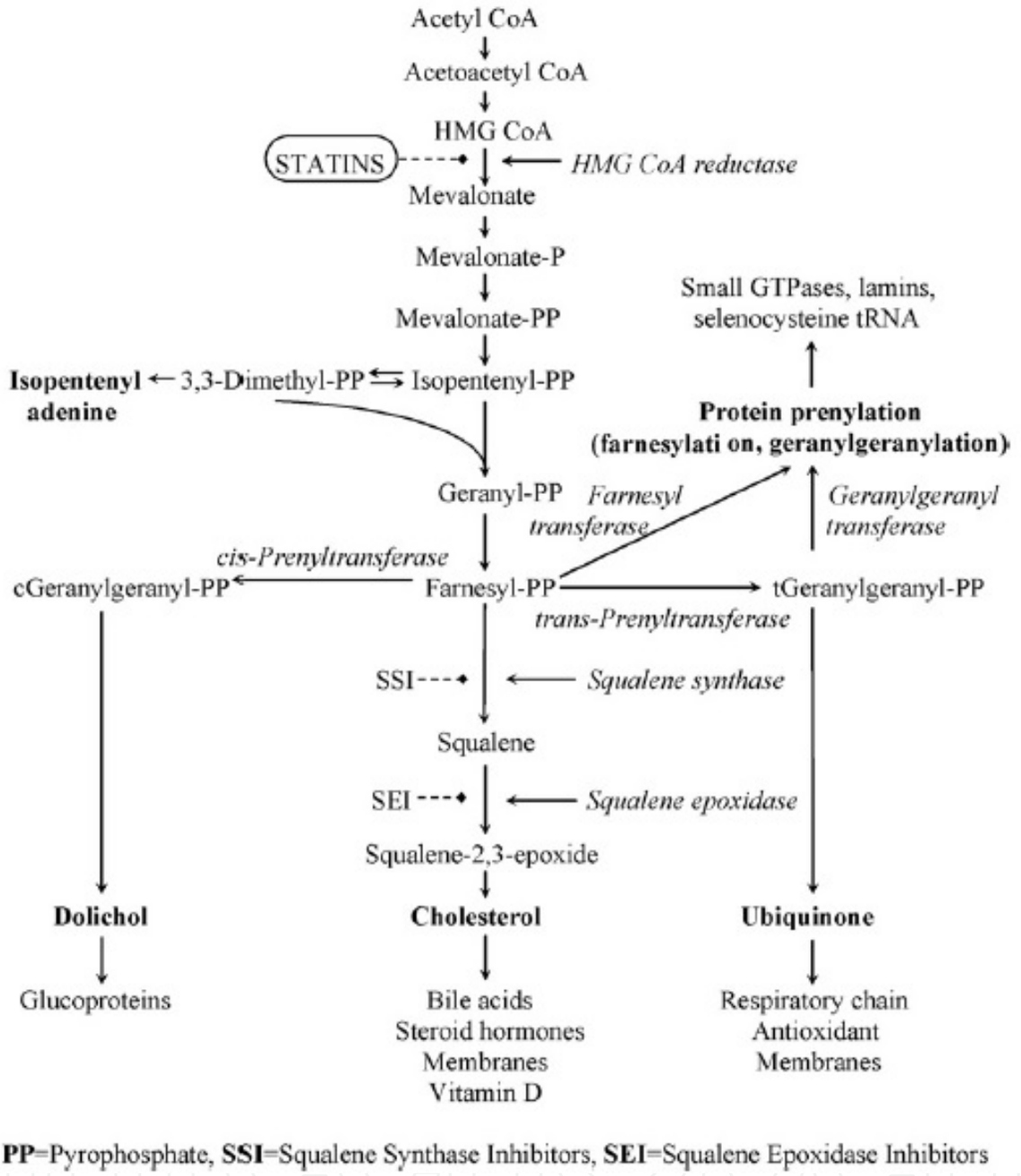

Figure 10. The biosynthetic pathway of cholesterol and other cometabolites, reprinted from Vaklavas et al. 2009 [58].

protein and/or lipid–lipid interactions are fundamental for G-protein-mediated signaling. Actually, all known Gγ proteins undergo isoprenylation on cysteine residues (either geranylgeranyl or farnesyl moieties) pointing to increased affinity to hexagonal nonraft phase (e.g., PE) of PM [53–54]. In contrast, Gα subunits are modified by myristoylation (Gα_i) and/or reversible palmitoylation (Gα) allowing them to get access to lamellar regions of PM (e.g., lipid rafts). It also explains how Gα subunits migrate to their cognate targets in LR after dissociation form G$\beta\gamma$ assembled to GPCRs. Minetti et al. [55] have showed in elegant study that skeletal muscle hypertrophy and differentiation are greatly influenced by signaling induced by

lysophosphatidic acid (LPA) acting on GPCRs which in turn activate a $G\alpha_i$ protein. Besides, $G\alpha_i$ enhanced muscle regeneration and caused switch to oxidative fibers and can act as a counterbalance to MuRF1 and MAFbx/atrogin-1. To sum up, lipid structures play active role in signal propagation with resulting localization of $G\alpha$ and $G\beta\gamma$ proteins.

Uncommon myopathic changes resultant from statin therapy offer the opportunity to gain new insight for the function of biochemical pathways downstream to HMG-CoA reductase in skeletal muscles. Irrespective of the type of statin treatment (hydrophilic or hydrophobic), the viability of skeletal muscle cells is considerably reduced, though the effect depends largely on the pharmacokinetic and pharmacodynamic properties of statins [56–57], while the signaling pathway(s) and molecular mechanisms are still not fully understood. Sometimes, signal transduction is dependent on small GTPase proteins that cycle between an inactive guanosine diphosphate (GDP)-bound and active guanosine triphosphate (GTP)-bound state. The posttranslational prenylation of these proteins occurs by the covalent addition of only two types of isoprenoids, FPP and GGPP, to cysteine residues at or near the C-terminus. Upon tyrosine kinase receptor activation, the prenylated (PM protoplasmic/inner leaflet attached) small GTPase protein Ras (MAPK kinase kinase kinase) binds GTP and becomes activated to initiate MAPK cascade ending with the stimulation of muscle cell growth (hyperplasia). In addition, small GTPase protein Rab1 (more than 60 Rab small GTPase isoforms have been identified) is involved in organelle biogenesis and intracellular vesicular trafficking [58]. Overall growth and survival signals depend on the activation of both protein receptor and nonreceptor tyrosine kinases.

Several lines of evidence suggest particular significance of IGF-1/PI3-K/AKT cascade in maintaining muscle cell growth and viability [59–61] likely through the suppression of FOXO-dependent activity of atrogin/MAFbx ubiquitin ligase gene required for the development of muscle atrophy [62–63]. Moreover, the statin-induced muscle damage is controlled by PGC-1α, a transcriptional coactivator that induces mitochondrial biogenesis and protects against the development of statin-induced muscle atrophy [64]. In *in vivo* model, simvastatin downregulated PI3-K/AKT signaling and upregulated FOXO transcription factors and downstream gene targets known to be implicated in muscle cachexia [63]. Insulin and IGF-1 are widely known agonists of their cognate receptors (IR and IGF-1R, respectively), although at concentrations higher than physiological cross-reactivity of insulin to IGF-1R and IGF-1 to IR were observed. On the other hand, LR have been shown to be platforms to initiate cellular signal transduction of IGF-1 and insulin-inducing skeletal muscle differentiation and hypertrophy. Notably, the impaired insulin/IGF-1 signaling [65–67] mimics the side effects of statin administration, whereas insulin and/or IGF-1 were reported to overcome statin-induced myopathy [61]. IR and IGF-1R with their intrinsic tyrosine kinase activities transduce the signal by recruiting insulin receptor substrate-1 (IRS-1) with its src-homology 2 domains (SH2) to the receptor phosphotyrosines. IRS-1 activates PI3-K/AKT/mTOR and Ras/Raf/MEK/ERK pathways, however, phosphoinositide 3-kinase (PI3-K) as a lipid kinase converts plasma membrane phosphatidylinositol-4,5-biphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate (PIP3). The latter attracts kinases with pleckstrin homology domain (PH) downstream to PI3-K including phosphoinositide-dependent kinase 1 and 2 (PDK1, PDK2) and AKT. Depletion

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of CHOL and sphingolipids blocks IGF-1-induced AKT membrane recruitment, whereas LR reconstitution in CHOL- and sphingolipid-deficient cells restored AKT membrane recruitment and phosphorylation [68]. Thus, LR-localized PIP3 is essential for AKT membrane association, while AKT seems to promote formation of PIP3-containing rafts.

7. Isoprenoids limit skeletal muscle regeneration

While human and animal studies have demonstrated that statin treatment may reduce serum CoQ10 levels [2, 69], ubiquinone levels in human skeletal muscle do not appear to be affected by statins [61, 70]. Possible significance of some reactions and intermediates in CHOL synthesis indicate that GGPP and FPP as isoprene units play very important role in muscle cell survival and regeneration. The posttranslational prenylation of proteins such as heterotrimeric G proteins, small G-proteins, and lamins enables these proteins to anchor to cell membranes, whereas N-linked glycosylation of insulin and IGF-1 membrane receptors mediated by dolichols establishes their proper biological functions (sensitivity to ligands). Dolichols serve as carriers and situate the core oligosaccharide to be assembled to protein molecules. From some studies, it appears that it is mevalonate and isoprene units (GGPP and FPP) as their downstream intermediates rather than CHOL play the key role in statin-induced myotoxicity. Consequently, replacement of depleted mevalonate reversed the changes induced by statins, where squalene synthase or squalene epoxidase (steps in CHOL synthesis) inhibitors at concentrations sufficient to inhibit entirely CHOL synthesis did not affect muscle cell viability [71–72]. These observations point to cardinal role played by isoprenoids in physiology of skeletal muscle cells. Interestingly, statins which are sometimes harm to skeletal muscle cells do not act adversely on myocardium, a type of striated musculature. Substantial difference in the sensitivity of skeletal muscle cells and cardiomyocytes to the statin-induced myopathy could be related to dissimilar mechanisms that control viability of these cells [73]. Alternatively, it was postulated that Ca^{2+} homeostasis alterations could account for statin-induced muscular side effects [74, 75].

8. Ca^{2+} homeostasis and statin-induced myopathy

Acute application of simvastatin on human skeletal muscle fibers led to a large release of Ca^{2+} into the sarcoplasm [76]. The authors showed that mitochondrial Ca^{2+} efflux through both permeability transition pores (PTP) and Na^{+}/Ca^{2+}-exchanger (NCE) was a major initiator of the large sarcoplasmic reticulum (SR) Ca^{2+} release by affecting ryanodine receptor 1 (RyR1, Figure 11). Furthermore, the effects of simvastatin on Ca^{2+} homeostasis were not linked to the disturbed cholesterol synthesis pathway as GGPP and FPP treatments did not prevent statin-induced Ca^{2+} waves. They were caused by simvastatin-dependent fall in mitochondrial membrane depolarization and Ca^{2+} efflux to the cytoplasm. Next, Ca^{2+} was recaptured by the SR that in turn triggered the SR release of Ca^{2+} by at present unknown molecular mechanism as "calcium-induced Ca^{2+} release" is implausible since the main RyR isoform in mammalian

skeletal muscle is poorly sensitive to Ca^{2+} [77]. It is apparent from this study that mitochondria played critical role, and that Ca^{2+} efflux from mitochondria resulted from alteration of mitochondrial respiratory chain, as mitochondrial membrane potential (MMP) decreased with concomitant rise in NADH concentration. Nonetheless, with regard to these experiments some criticism has to be reserved, as simvastatin concentrations (50–200 μM) were much above the pharmacological range. Summing up, these observations point to ubiquitin/proteasome (UP) proteolysis and mitochondria as skeletal muscle target of statins, while the exact nature of their detrimental action (direct or indirect) remains to be elucidated. Recently, some interesting data were obtained from transcriptomic analysis of biopsies collected from atorvastatin-treated and exercised vs. nonexercised skeletal muscles of healthy volunteers. The authors complement severalfold rise in UP pathway gene expression in 8-hours eccentrically exercised vastus lateralis muscles baseline compared to the right leg after statin/placebo treatment [78].

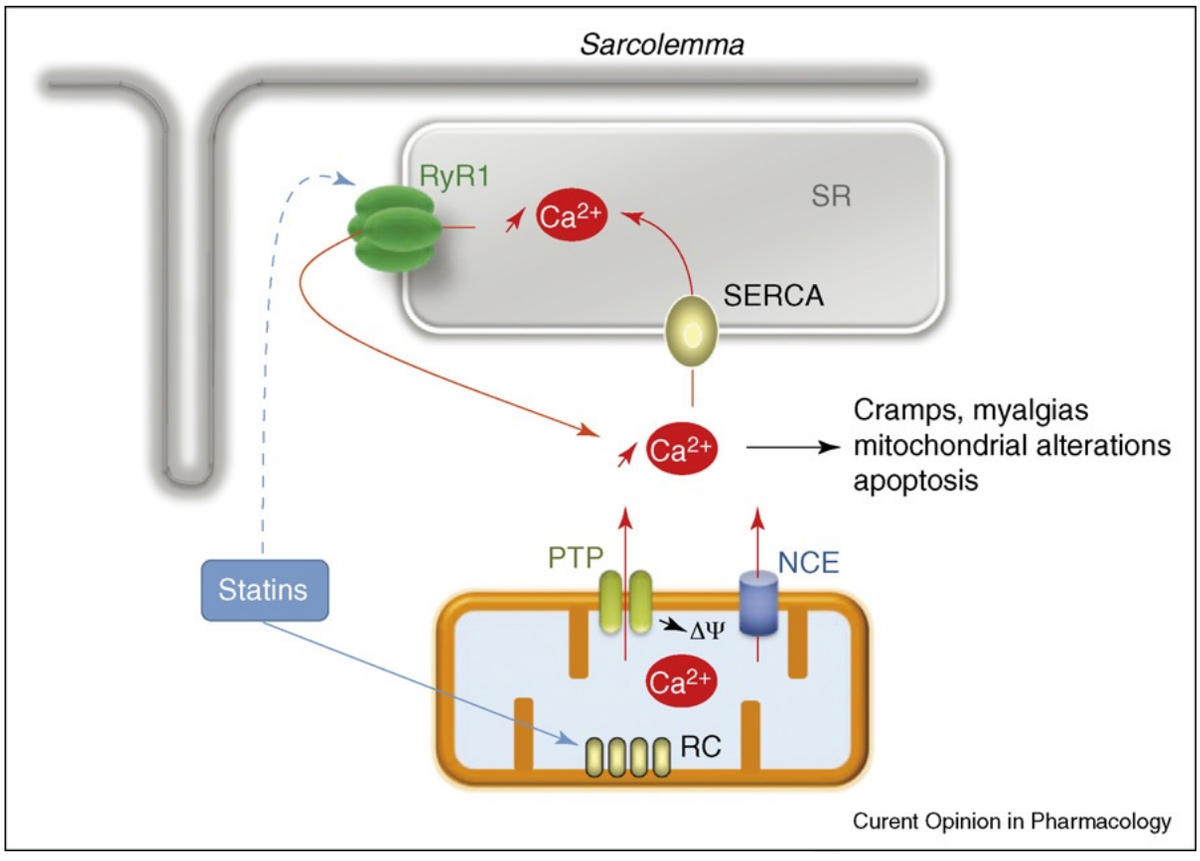

Figure 11. A possible direct pathophysiological effect of statins. Although statin myotoxycity may occur through the reduction of cholesterol synthesis, a direct effect of statins has been reported in vitro and in vivo in muscle fibers from both animal and human models. This diagram summarizes some of the most recent data suggesting a pathophysiological mechanism. Statins diffuse into muscle fibers and inhibit complex I of the mitochondrial respiratory chain (RC). This depolarizes the inner membrane (Dc) triggering a calcium release through the permeability transient pore (PTP) and sodium-calcium exchanger (NCE). This results in a first elevation of cytoplasmic calcium that will be partially uptaken by the sarcoendoplasmic reticulum calcium pump (SERCA) to the sarcoplasmic reticulum (SR). When overloaded, SR may spontaneously release calcium through the ryanodine receptor (RyR1) to generate a calcium wave. A direct effect of statins on RyR1 may not be excluded (dotted line). Impaired mitochondrial function and consequently calcium signaling may account for muscle symptoms, reprinted from Sirvent et al. 2008 [48].

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Deregulation of calcium ion (Ca^{2+}) homeostasis in mitochondria is indicated as initial step in cascade of events leading to statin myopathy [76, 79]. In several experiments carried out on C2C12 myoblasts and human muscle biopsies, statins impaired mitochondrial respiration and sensitized muscle fibers to calcium signaling. Accordingly, muscle fibers showed reduced level of ATP and higher frequency of Ca^{2+} waves [46, 79]. Disturbed regulation of Ca^{2+} homeostasis (elevated cytoplasmic concentrations) is known to trigger activity of calpains [80], whereas raise in ROS is associated with caspase cascade [81–82]. As RSC are enriched in SM, they obviously should have high LR/C representation. Modulation of SL modifications with sphingomyelinase inhibitors would provide closer look on LR/C impact cell viability/morbidity. Next to statins widely used as hypocholesteremic drugs, polyunsaturated fatty acids (PUFA) are frequently recommended to lower blood plasma concentration of low density lipoproteins (LDL) and triglycerides (TG). There is evidence that PUFA (n–3) synergize with statins in their positive effect, furthermore some PUFA (EPA and DHA) prevent statin-induced myopathy [83–84]. It was found that statins evoke endoplasmic reticulum stress (ERS) and ERS inhibitors as well as PUFA attenuate this response most likely through PPARγ-dependent mechanism. Detailed outline of PUFA protective effect has, however, not been explained. Scientific problem is to find out if LR contribute to the activation of RSC. Furthermore, if LR/C are essential to recruit RSC to enter the differentiation program, what would have been if LR are ablated? The study aimed to shed more light on the side effects of statin administration to skeletal muscle is urgently needed. Novelty of research should address etiology to abnormal function of sarcolemma in skeletal muscle cells of statin-treated subjects. We found only one report showing that CHOL depletion impaired muscle function [17]. CHOL is essential in holding together lateral assemblies of lipids in LR nanodomains. The latter are indispensable to cell signaling as they form platforms for signalosomes (proteins assembled in order to provide signal transduction from PM receptors). Their role has been corroborated for PI3-K/AKT and JAK/STAT but not Ras/Raf/MEK/ERK signaling pathway. We assume that former cascades (PI3-K/AKT and/or JAK/STAT) are involved in RSC activation while the latter are important to initiate proliferation. As muscle cell differentiation proceeds, the representation of SL in LR is subjected to additional modifications [85–88]. We guess these changes are related to the activation of sphingomyelinases and other SL converting enzymes. Ceramides and sphingosines were reported to frequently affect cell functions including proliferation, differentiation, and viability [89, 90], and other bioactive lipids are also important players in muscle growth and regeneration. At the same time, involvement of ROS and mitochondria, Ca^{2+} homeostasis, and proteolytic systems should be examined.

9. Skeletal muscle satellite cells and LR

Plasma membrane is not uniform in state of matter, i.e., fluid portion is represented by glycerophospholipids spontaneously mounted into lipid bilayer in disordered manner (Ld – liquid disordered). As mentioned before, in such membrane, numerous nanodomains known as lipid rafts contain sphingolipids and CHOL as well as lipid-modified integral membrane proteins. Nanodomains (Lo – liquid ordered) are buoyant in fluid portion of membrane and

have tendency to coalesce into larger platforms to form signalosomes essential for signal transduction [22]. Thus, in muscle cells deprived of mevalonate due to statin administration, one should expect lower level of LR/C and decreased availability of prenylated proteins (farnesylated and geranyl-geranylated). It is important to stress that muscle growth, adaptive hypertrophy, and regeneration are directly attributable to the PM representation of LR determined by CHOL and sphingolipids [87, 91] found in RSC. The mononucleated RSC are located beneath the basal lamina that surrounds multinucleated myofibers [6]. They are activated by signals from injured myofibers and macrophages to enter the cell cycle and produce myogenic precursor cells that then differentiate and fuse into multinucleated myotubes or existing myofibers [92]. The molecular mechanisms responsible for the transduction of such extracellular signals in satellite cells remain poorly defined, and the potential role of lipid-mediated signaling has not been previously considered in this context. There is an assumption that satellite cells are capable to rearrange PM composition in order to respond to extracellular signals and allow cell multiplication and migration which is followed by fusion. Actually, muscle cells were reported to change the lipid representation in PM according to the particular step of differentiation [87, 91, 93]. While phosphatidylserine (PS) is highly expressed during myoblast fusion [88], phosphatidylethanolamine (PE) is involved in cell motility [94]. Both mentioned are the glycerophospholipids of Ld phase located in the protoplasmic leaflet. On the other hand, sphingomyelin (SM) is found exclusively in the Lo phase where it forms LR nanodomains with other SL, GSL, CHOL, and proteins. CHOL is essential to organize LR as it helps both to position SL and GSL and provides the most advantageous energy status between Lo and Ld phase [95]. Nowadays, it is widely accepted that these nanodomains facilitate cytoplasmic signaling by acting to concentrate signaling molecules [96]. Additionally, SL metabolites, such as ceramide, sphingosine, and sphingosine 1-phosphate, are emerging as important regulators of a variety of cellular events, including cell proliferation, differentiation, and apoptosis [97–98]. With respect to SM, another important issue is that it is highly represented in PM of RSC but during satellite cell proliferation and subsequent differentiation it is almost undetectable [85]. One has to bear in mind that RSC as being stem cells undergo either symmetric or asymmetric division and that in the identical culture conditions they adopt characteristics consistent with a return to quiescent-like state [99]. Thus, it is apparent that certain activated satellite cells (ASC) by unknown mechanism are withdrawn from the cell cycle and they escape from the differentiation program. Cell decision whether to differentiate or not to differentiate is determined by the composition of PM and LR representation in particular. Under the appropriate conditions, SC differentiate into muscle cells with phenotype characterized by the accumulation of muscle contractile proteins and increased sensitivity to insulin. In these differentiated cells, insulin accelerates myogenesis [43]. Insulin initially stimulates proliferation, and subsequently, it stops cell divisions and stimulates metabolic pathways to promote protein synthesis. A clear explanation of how these signaling pathways elaborate such radically different physiological responses in this differentiated tissue has remained elusive, although compartmentalization and switching-off signaling molecules has been proposed [43]. Insulin activates their respective tyrosine kinase receptors to phosphorylate key residues on a "docking protein" or the receptor, respectively, which recruits multiple adaptor proteins. Recruited proteins include the GDP exchange factor Son of Sevenless (SOS), which activates the Ras/Raf/MEK/ERK mitogen-activated protein kinase cascade (mitogenicity), or the p85 regulatory subunit of PI3-kinase, which stimulates signaling pathways

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ultimately leading to AKT/PKB activation. PI3-K is strongly implicated in metabolic, but not mitogenic signaling in muscle cells, as is its downstream effector AKT [44]. In the latter paper, an important role of mitofusin 2 (Mfn2) protein has been shown as a partner and inhibitor of Ras. Thus, it become clear why studying the ability of different approaches to regulate numerous signaling molecules, statins and CHOL chelators, particularly PI3-K and AKT (PI3-K/AKT), are essential due to their relevance to anabolic metabolism in myotubes and LR reliance. Comparative studies concerning Ras/Raf/MEK/ERK and JAK/STAT would be crucial as these pathways are involved in muscle cell proliferation and they compromise muscle differentiation [100]. It is not clear if reactive oxygen species (ROS) are involved as a cause or an effect of disturbance [46, 79, 101]. Lower production of ATP would explain faster muscle fatigue observed during exercise in statin-induced myopathy [102]. Interestingly, appropriate muscle exercise (physical training) might protect skeletal muscles from undesired statin-induced side effects [103]. This is of particular importance as the widespread use of statins and more active lifestyle might foster the incidence of SIM.

10. Heat controls vital signaling molecules in plasma membrane

Although the molecular mechanisms that regulate the differentiation of satellite cells and myoblasts toward myofibers are not fully understood, cell membrane lipids and proteins that sense and respond to their environment must play an important role. Heat alters PM physical state into more fluidic form, and similar effect may be artificially induced by membrane fluidizers [104]. Interestingly, heat-induced hyperfluidization in animal PM is associated with the activation of the cholesteryl glucoside (CG) synthetase (glucosyltransferase) located in LR, the enzyme that catalyzes the transfer of the glucose moiety from glucose donor sphingolipid glucosylceramide to cholesterol [105]. CG production alters membrane physical properties and forms thermostable solid-ordered domains. Notably, CG and other steryl glucosides act as important lipid mediators in the process of heat shock factor-1 (HSF-1) activation. This transcription factor regulates the expression of heat shock proteins (HSPs), which are critical for the survival of cells [104]. Some authors showed that the alteration of membrane fluidity by heat or membrane fluidizer treatment causes the reorganization of lipid rafts linked to activation of heat shock response mediated by HSF-1 activation and HSP induction [106–108]. It is suggested by Kunimoto et al. [110–111] that PM fluidity leads to CG formation and the latter mediates HSF-1 activation and HSP induction. There is growing body of evidence that strategies aimed at increasing levels of HSPs may be successful in protecting cells in neuro-degenerative diseases. At least in the animal model of amyotrophic lateral sclerosis (ALS), increasing HSP levels by treatment with arimoclomol (hydroxylamine derivative) delayed disease progression in mice [112, 113]. Another hydroxylamine derivative, namely, BGP-15 inhibited acetaminophen-induced caspase-independent apoptosis of hepatocytes [106]. The prime HSPs induced by heat stress or membrane fluidizers are HSP70 and HSP90. Importantly, HSP72 preserves muscle function and slows progression of severe muscular dystrophy [114]. Under normal circumstances, chaperone proteins involved in protein quality control can prevent protein aggregation by binding of misfolded proteins as soon as they are produced during translation or later during their organization into supramolecular structures, thereby assisting protein refolding or else in targeting for degradation [115].

11. Sphingolipids in skeletal muscle regeneration

Sphingolipids (SL) and cholesterol (CHOL) create LR in plasma membrane, but it is the biochemistry of SL that is apparently decisive for skeletal muscle biology including its growth and differentiation. PM sphingomyelin is a target for both acidic and neutral sphingomyelinases (aSMase and nSMase) bringing ceramide (Cer) as product. Ceramides are LR modulators believed to alter PM fluidity and favor receptor oligomerization [116]. Cer has been suggested to fulfill a second-messenger function but the evidence for this action is scarce and controversial, while support is emerging for its indirect impact on cellular signaling resulting from changes in membrane structure. Cer could be further converted to sphingosine by ceramidase, whereas sphingosine 1-phosphate is synthesized from sphingosine by a phosphorylation reaction catalyzed by the sphingosine kinases (SKs) SK1 and SK2, which are highly conserved enzymes activated by numerous stimuli including transactivation induced by IGF-1 [117]. From studies carried out on C2C12 myoblast cell line as progeny of mouse satellite cells, it is clear that IGF-1 evokes two mutually exclusive biological responses (hyperplasia vs. hypertrophy). This cytokine plays a key role in skeletal muscle regeneration as it is able to recruit satellite cells and stimulate myoblast proliferation and myogenic differentiation. As mentioned before, myoblasts must not fuse unless they are withdrawn from the cell cycle. How then, IGF-1 regulates two opposite responses? In recent years, the sphingosine 1-phosphate (S1P) attracts special attention with regard to physiology of resident skeletal muscle satellite cells as well as proliferating and differentiating myoblasts. First, several lines of evidence indicate significant role of S1P in skeletal muscle regeneration and repair [85, 117–122]. The extracellular action of S1P present in micromolar concentrations in peripheral blood is exerted by binding to five specific cell surface heterotrimeric G protein–coupled S1P receptors ($S1P_1$–$S1P_5$). In turn, S1P agonist levels are tightly controlled by the balance between biosynthesis catalyzed by SKs, reversible conversion to sphingosine mediated by specific and nonspecific lipid phosphatases, and S1P lyase (SPL)-dependent degradation. Second, S1P receptors are coupled to one or more G-proteins so they can elicit distinct and even contrasting final cellular effects (Figure 12). In skeletal muscle cells, major role is played by $S1P_1$, $S1P_2$, and $S1P_3$ receptors [117, 119–122]. Actually, in myoblasts, $S1P_1$ and $S1P_3$ receptors via SK activation negatively regulate the mitogenic effect elicited by IGF-1, whereas $S1P_2$ receptor is involved in myogenic effect of the growth factor (Figure 13). Thus, in myoblasts, SK/S1P axis upon IGF-1 action regulates two opposing biological effects – transducing its myogenic response on one side and inhibiting its mitogenic effect on the other. The IGF-1-dependent transactivation of S1P receptors was also observed in other cell types pointing to the conservation of the IGF-1/SK/S1P circuit in tissues other than skeletal muscle [123]. How IGF-1 does affect SKs leading to two divergent biological effects in skeletal muscle? Among the various signaling pathways activated by S1P in skeletal muscle cells, the activation of ERK1/2 and p38 MAPK, both identified as downstream effectors of $S1P_2$ in response to growth factors, was required for cell proliferation and the stimulation of myogenic differentiation, respectively [124]. The inhibition of ERK1/2 activity with specific U0126 metabolic inhibitor prevented SK1 phosphorylation induced by IGF-1, demonstrating that the activation of SK1 induced by the growth factor was mediated by ERK1/2 [116]. Similarly, the S1P-induced differentiation was prevented

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in myoblasts where p38 MAPK was inactivated by the overexpression of the dominant negative mutant or by the use of specific p38 MAPK inhibitors SB203580 and SB239063 [118].

	Cell Proliferation	Cell Migration
C2C12 Myoblasts	↓	↓
Activated Satellite Cells	↑	↑

Figure 12. Role of sphingosine 1-phosphate on cell proliferation and migration in myoblasts and activated satellite cells, adapted from Donati et al. 2013 [125].

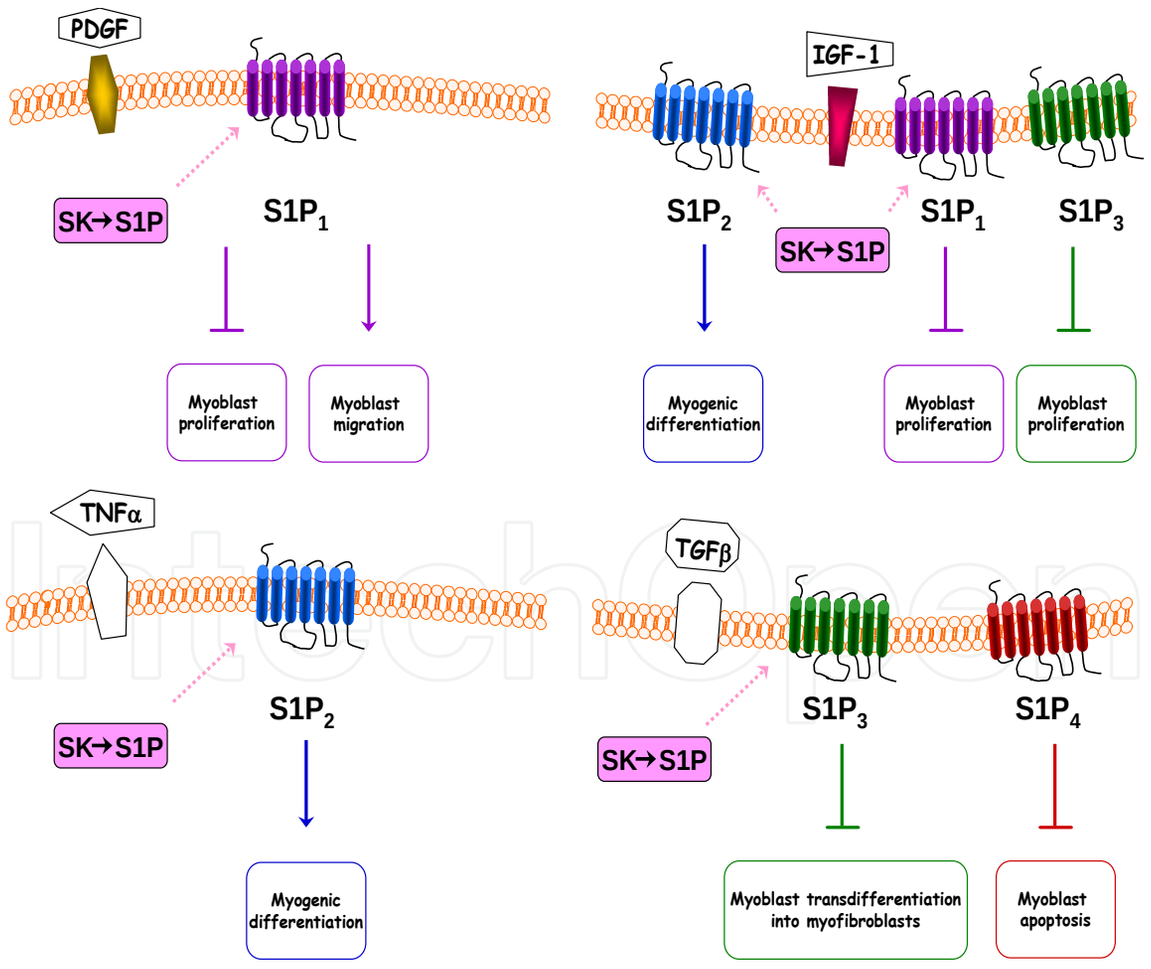

Figure 13. Schematic diagram of the biological actions evoked by S1PR transactivation by some growth factors in C2C12 myoblasts, adapted from Donati et al. 2013 [125].

One has to keep in mind, however, that S1P receptors are differently expressed in satellite cells, myoblasts, and muscle fibers, moreover their expression may vary in response to the action of particular factor. PDGF stimulates myoblasts proliferation and motility, while these effects are blocked by SK1/$S1P_1$ signaling axis [126]. In contrast, TGF-β1 was demonstrated to convey its detrimental profibrotic effect through $S1P_3$ receptors (Figure 13) [127]. These observations complement widely known activities of PDGF and TGF-β1 in wound healing. In the second intention healing as it is observed in the severe skeletal muscle injury or late stages of myopathy, the major role is played by myofibroblasts which cause fibrosis, a hallmark of in which myofibers are replaced by progressive deposition of extracellular matrix proteins [128]. The main task is therefore to facilitate skeletal muscle regeneration rather than repair, as the first one restores tissue structure and contractile function while the latter is limited to structural return. There are efforts observed to improve muscle healing by regeneration rather than fibrosis [129]. Collectively, taking into account the knowledge on how sphingosine 1-phosphate influences RSC and how it might prevent muscle fibrosis, it will be interesting to further investigate in this context the crosstalk between IGF-1 and S1P signaling pathway.

12. Concluding remarks

Primary stem cells in adult skeletal muscle known as satellite cells drive postnatal muscle growth and regeneration-associated hypertrophy. They reside beneath the basal lamina of the myofibers suggesting close contact between the adjacent cytoskeletons and chemical communication between the cells. One of the major unexplored areas of satellite cell biology is the identification of signals that are conferred from adjacent myofibers and the surrounding extracellular matrix. Equally important are soluble endocrine, paracrine, and autocrine factors that maintain satellite cells quiescent and control their preference to activate. For example, the maintenance of skeletal muscle requires notch signaling and greatly depends on delta upregulation for RSC activation [130]. In addition to the loss of notch activation, nonregenerating skeletal muscle produces excessive transforming growth factor (TGF)-β (but not myostatin), which induces unusually high levels of TGF-β pSmad3 and interferes with their regenerative capacity [131]. Thus a balance between endogenous pSmad3 and active notch controls the regenerative competence of muscle stem cells, and the deregulation of this balance in the old muscle microniche interferes with regeneration. The molecular mechanisms that regulate satellite cell quiescence, activation, and self renewal (asymmetric divisions) are not well understood, even though a possible clue for the ambiguous behavior of satellite cells could be associated with the membrane segregation of rafts and bioactive lipids such as PS that seems to accelerate myoblasts fusion into myotubes [132]. It seems plausible to affirm sarcolemmal differentiation as the leader constituent of stimulated skeletal muscle progenitors and subsequent populations of daughter cells (myoblasts, myotubes, and juvenile myofibers) involved in myogenic program. Lipid moiety of plasma membrane is not merely a boundary or the component in intercellular communication. Nowadays, it is widely accepted that specific lipids associate to form functional units (LR/C), creating substructures that actively modify its own composition including proteins and triggering a myriad of different signaling pathways. Lipid

segregation seems to account for the adaptability of skeletal muscle to a variety of stimuli, where the critical role is played by the myogenic signals represented by growth factors and cytokines. Cholesterol, isoprenoids, dolichols, and sphingolipids all contribute significantly to the physiological responses of skeletal muscle to injury. These bioactive lipids mediate most, if not all, of the signals elicited at the plasma membrane receptors. Recent advances in muscle research suggest key position occupied by sphingosine 1-phosphate, protein prenylation, and "caveolar" and "noncaveolar rafts" in skeletal muscle regeneration process.

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