REVIEW ARTICLE

# Regulation of muscle plasticity and trophism by fatty acids: A short review

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## Summary

The skeletal muscle tissue has a remarkable ability to alter its plastic structural and functional properties after a harmful stimulus, regulating the expression of proteins in complex events such as muscle regeneration. In this context, considering that potential therapeutic agents have been widely studied, nutritional strategies have been investigated in order to improve the regenerative capacity of skeletal muscle. There is evidence of the modulatory action of fatty acids, such that oleic and linoleic acids, that are abundant in Western diets, on muscle function and trophism. Thus, fatty acids appear to be potential candidates to promote or impair the recovery of muscle mass and function during regeneration, since they modulate intracellular pathways that regulate myogenesis. This study is the first to describe and discuss the effect of fatty acids on muscle plasticity and trophism, with emphasis on skeletal muscle regeneration and in vitro differentiation of muscle cells.

**Keywords:** cell differentiation, muscle repair, skeletal muscle, satellite cells, fatty acids.

## Introduction

Skeletal muscles have the plastic ability to adapt to the intrinsic and extrinsic demands of the environment. Such adaptive potential is attributed to the population of stem cells resident in adult skeletal muscle, known as satellite cells.[1] These are mononuclear and undifferentiated satellite cells located between the basal lamina and the sarcolemma of a muscle fiber, which proliferate, differentiate and fuse leading to the formation of a new myofiber and, thus, the reconstitution of the contractile apparatus.[2,3]

The process of muscle regeneration is triggered by a noxious stimulus whose nature can be mechanical,[3] chemical,[4] or thermal.[5] Skeletal muscle repair, triggered by sarcolemmal rupture and increased vascular permeability, involves cellular and molecular events that begin with increased calcium influx into the intracellular environment causing proteolysis dependent on that cation, necrosis of damaged tissue, and activation of inflammatory response at the lesion site. This phase is followed by the production of extracellular matrix proteins, revascularization and concomitant activation of myogenic cells.[2,3,5,6]

Several groups have investigated therapeutic strategies to accelerate the skeletal muscle repair process after injury. There is evidence that fatty acids modulate muscle function and trophism.[7-11] Our article is the first to describe and discuss the effects of fatty acids, especially oleic and linoleic acids, which are the most abundant fatty acids in Western diets, on muscle plasticity and trophism, with emphasis on skeletal muscle regeneration and in vitro differentiation of muscle cells. This is the main focus of our review. The searches were carried out in five bibliographic databases: PubMed, Web of Science, Scientific Electronic Library Online (SciELO), Excerpta Medica database (Embase), and Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS). References found in duplicity were excluded. Articles written in English and Portuguese were selected. As for the terms, we considered that there are differences in the indexing processes among the bibliographic databases and, therefore, we opted for searching free terms, and did not use controlled vocabulary (descriptors). In this way, more references were retrieved, guaranteeing that most published works were detected. The terms fatty acids; oleic and linoleic acid; muscle function and trophism; plasticity and muscle trophism; skeletal muscle regeneration; skeletal muscle repair; muscle satellite cells; and muscle cell differentiation were combined, as proposed by Sin et al.[12]

## Skeletal muscle satellite cells

Initially described in frog muscle fibers,[13] skeletal muscle satellite cells, undifferentiated and mononucleated, have this name because of their anatomical positioning at the periphery of the muscle fiber, between the basal lamina and the plasma membrane. They represent between 2 and 10% of the total myonuclei per muscle fiber and total 2 x $10^5$ to 1 x $10^6$ cells per gram of muscle.[14]

Muscle fibers are differentiated cells, unable to undergo division. The ability of muscles to self-repair has been attributed to satellite cells, which have high mitotic capacity, contributing to the maintenance and regeneration of adult skeletal muscle.[14]

In his article, Mauro[13] defined these satellite cells as "myoblastic cells in the adult organism, which failed to merge with other myoblasts. These cells are juxtaposed to recapitulate the embryonic development of skeletal muscle fibers". Subsequently, studies have shown that asymmetric divisions of satellite cells generate myogenic cells, which originate myoblasts, myocytes and myofibers.[15] Symmetric divisions, on the other hand, generate new satellite cells that expand the number of these cells, a process known as self-renewal. Multiple factors are part of this complex network of satellite cell growth and differentiation, governing the cell cycle progression and/or the return to a quiescent state (G0).[15]

In the absence of stimuli in the muscle tissue, the satellite cells remain in the G0 state. Once activated, these cells initiate the cell cycle, proliferate and express myogenic growth and differentiation markers.[1] Thus, a balance between G0 and the active state (self-renewal or myogenic differentiation) is indispensable for the conservation of muscle tissue.[16] Studies have shown that the number of satellite cells remains constant even after multiple activations.[17] Currently, many intrinsic and extrinsic factors that control the satellite cell function have been discovered. In all, these studies have demonstrated that there are specific cell cycle activations and inhibitions, and progression to myogeny.

Transcription factor PAX7 (meaning paired box) was the first marker identified in satellite cells in quiescent state, being activated during proliferation. It has a key function in the maintenance of the G0 state and in the prevention of early myogenic differentiation.[15] Studies have demonstrated the complete loss of muscle regenerative capacity in PAX7 knock-out mice ($PAX7^{-/-}$).[18,19]

In this context, increasing evidence shows that satellite cells are composed of two different populations that regulate the cell cycle: (1) those with stem cell potential, undifferentiated and which remain in G0 state during myogenic progression, and (2) those with potential for myogenic differentiation.[20]

After muscle injury, satellite cells are activated, initiating the expression of regulatory factors of myogenesis, such as myoblast differentiation (MYOD) and/or myogenic factor 5 (MYF5).[21] MYOD is expressed in extremely low amounts and is essentially undetectable in quiescent satellite cells. This protein marks the compromise of myoblasts with the myogenic lineage. In this context, the concomitant expression of MYOD and MYF5 is vital for the formation of myotubes and myofibers.[1,22]

Promotion of myofibroblast restoration and reorganization results from a decrease in PAX7 expression, cell cycle arrest and increased expression of myogenin (MYOG)[23] and myogenic regulatory factor 4 (MRF4),[24] both members of the superfamily of basic helix-loop-helix (bHLH) transcription factors. These factors are specific to skeletal muscle, being expressed at distinct moments during myogenesis. They have key functions in myogenic specification, muscle differentiation and maintenance during muscle development and regeneration[22] (Figure 1).

## Effects of fatty acids on skeletal muscle trophism and regeneration

The regulation of trophism and muscle regeneration involves the coordinated action of various cell types in response to local and systemic signals. It is slow and often incomplete depending on its severity, leading to loss of function.[26] Thus, the discovery of new dietary strategies to improve skeletal muscle regeneration capacity can be a powerful tool for the development of new nutritional therapies in order to accelerate regenerative processes and/or reduce the consequences of incomplete repair and extensive fibrosis deposited in the skeletal muscle, as occurs after severe muscle injuries.

The composition of phospholipids in the plasma membrane has a crucial influence on cell growth and metabolic activity. In the last two decades, it has been suggested that the lipid composition of the diet influences the fatty acid profile of the serum and the lipid content of the plasma membrane.[27-29] In fact, it has been shown that the length of the fatty acid chain and the degree of saturation or unsaturation alter the fluidity and activity of several membrane-bound proteins.[30,31]

In this context, few studies have evaluated the involvement of fatty acids in muscle trophism and myogenesis. Muscle differentiation is known to be accompanied by important metabolic changes, such as increased expression of genes related to the metabolism of carbohydrates and amino acids.[32,33] In this context, some nutritional strategies were evaluated in models of muscle injury in rodents. Pereira et al.[32] found that supplementation with

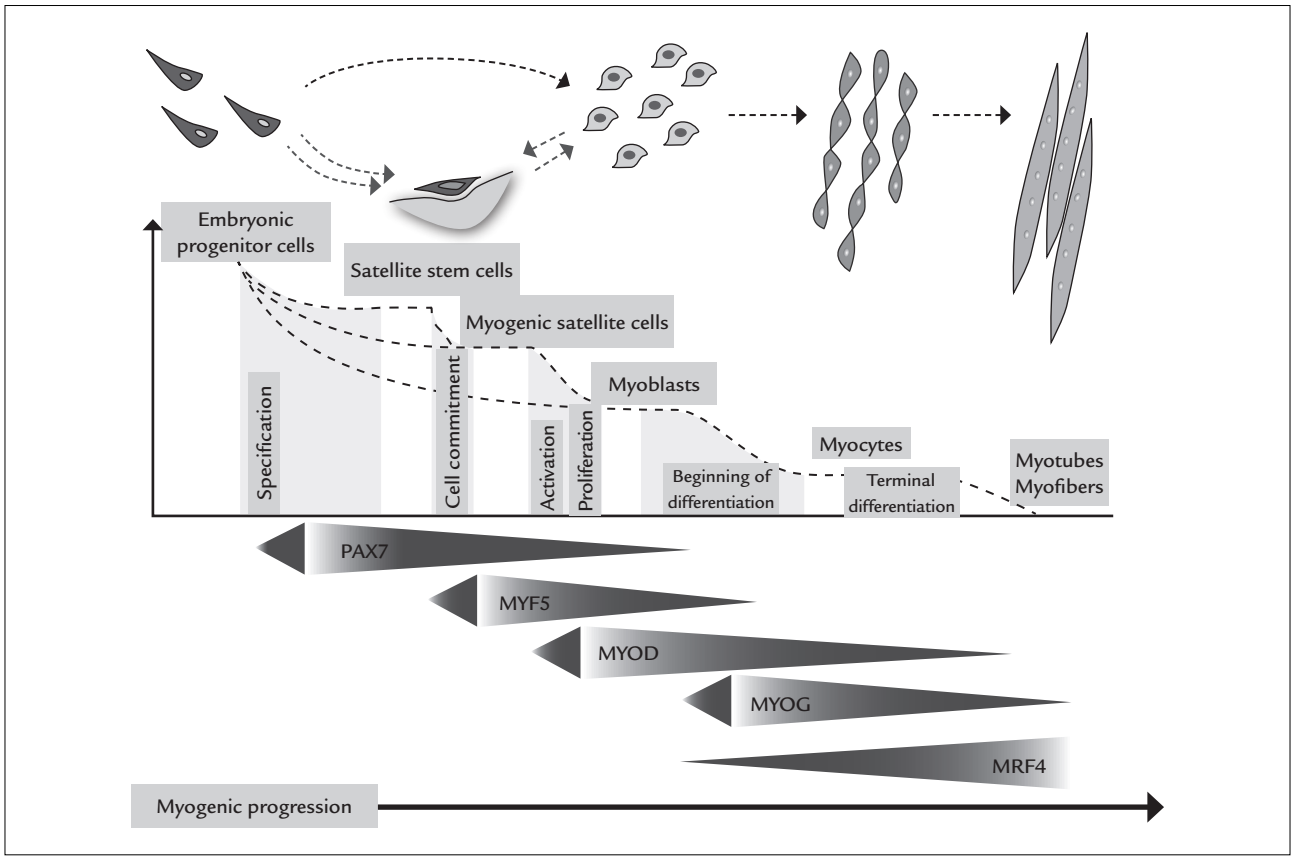


**FIGURE 1** Temporal activation of regulatory factors of myogenic differentiation. In skeletal muscle, satellite cells in the quiescent state or activated during proliferation express the paired-box 7 (PAX7) transcription factor. These cells have the ability to proliferate, self-renew, differentiate and fuse with newly formed myotubes or existing myofibers after stimuli such as muscle injury. Differentiation of satellite cells involves increased expression of basic helix-loop-helix (bHLH), myogenic factor 5 (MYF5) and myoblast determination (MYOD) transcription factors. Myogenin (MYOG), a transcription factor essential for myogenesis and skeletal muscle repair, is highly expressed during the formation of myocytes by the fusion of myoblasts. Myogenic regulatory factor 4 (MRF4) transcription factor is, then, activated during terminal differentiation and formation of myocytes and myotubes. (Modified from Wang and Rudnicki).[25]

leucine during the muscle regeneration process accelerates the repair of connective tissue in the anterior tibial muscle of rats. Baptista et al.[33] investigated the effect of supplementation with leucine and HMB (β-hydroxy-β-methylbutyrate) on the ubiquitin-muscle proteasome system under different sarcopenia conditions in rats, demonstrating the anti-atrophic effect of leucine.[32,33]

Oleic acid (monounsaturated 18:1 (n-9)) and linoleic acid (polyunsaturated 18:2 (n-6)) are the most abundant fatty acids in Western diets. Oleic acid is found mainly in olive oil, while linoleic acid is found in soy, sunflower and corn oils.[34] Using both isolated muscle cells and animal models, Salvadó et al.[35] demonstrated that oleic acid is capable of reversing the structural and metabolic changes in skeletal muscle induced by palmitic acid. In another study, the increase in docosahexaenoic acid (DHA) content (22:6 (n-3)) in the gastrocnemius muscle through supplementation with fish oil for 21 days is suggestive that this fatty acid attenuates lipopolysaccharide-induced muscle atrophy (LPS).[36] Other studies suggest that the reduction in DHA content impairs calcium homeostasis in the skeletal muscle cell.[37] Tuazon and Henderson[38] observed that increases in linoleic acid content and decline in DHA content in muscle phospholipids were positively correlated with increased creatine kinase activity, combined with decline in muscle grip strength of dystrophin knock-out animals. Another study shows that there is an inverse relationship between the concentration of oleic and linoleic acid in skeletal muscle.[39]

It has been demonstrated that some fatty acids, such as oleic and linoleic acids, exert pro-proliferative effects on vascular smooth muscle, and may regulate muscle

growth.[40] Perdiconi et al.[41] observed an increase in total phospholipid content during muscle differentiation. Myoblasts predominantly synthesize triacylglycerols, while myotubes synthesize phospholipids.[42] The fusion of myoblasts can also be regulated by factors that alter the fluidity of the plasma membrane, such as temperature and lipid composition.[43,44]

The fatty acid composition of phospholipids determines the physicochemical properties of the plasma membrane and, to a large extent, its asymmetry, fluidity, plasticity, organization and occurrence of microdomains.[45] The incorporation of omega-3 or -6 polyunsaturated fatty acids into membrane phospholipids affects lipid and protein interactions in the membrane, in addition to the physical properties mentioned above.[45] For example, the decrease in insulin sensitivity in skeletal muscle has been associated with a decrease in the proportion of polyunsaturated fatty acids in membrane phospholipids.[46]

There is evidence that intermediate products of fatty acid metabolism are important for the survival, proliferation, differentiation, and fusion of myoblasts.[47] Rodeman and Goldberg[48] suggested that lipid metabolites derived from polyunsaturated fatty acids, such as arachidonic acid, accelerate protein synthesis, fusion and growth of muscle cells in different animal models.

Oxidation of fatty acids is significantly higher in myotubes compared to myoblasts, and mitochondrial biogenesis is necessary for skeletal muscle differentiation.[42] The content of triacylglycerols decreases by more than 50% during myogenesis,[41] and the inhibition of mitochondrial respiration compromises myogenic differentiation and the formation of myotubes.[49] Leptin knock-out mice (ob/ob), which have high concentrations of plasma fatty acids, present deficient muscle regeneration.[50] In addition, a hyperlipidic diet compromises muscle regeneration in mice,[51] possibly by the effect of saturated fatty acids.

Pinheiro[43] observed that there is an increase in the synthesis of oleic and arachidonic acids during myogenesis in vitro. The addition of arachidonic and linoleic acids to the culture medium increases the proliferation of satellite cells, as assessed by the incorporation of $^{14}$Carbon-labeled thymidine. The author also observed that supplementation with linoleic acid for 20 days in dystrophic mice (mdx) significantly improves the strength of the gastrocnemius muscle of these animals, suggesting a possible trophic effect of this fatty acid.[43] On the other hand, the diet rich in saturated fatty acid and linoleic acid causes insulin resistance and imbalance of oxidative components in skeletal muscle, resulting in oxidative stress. Pariza et al.[52] demonstrated in vivo that supplementation with conjugated linoleic acid (0.3% of diet) causes a decrease in fat mass and an increase in fat-free lean mass in rodents.

Our group evaluated the effect of treatment with oleic and linoleic acids (0.44 g per kg body weight) for four weeks on lacerated gastrocnemius muscle regeneration in rats (unpublished data). Laceration *per se* causes an increase in the oleic/stearic and palmitoleic/palmitic ratio indicators of the desaturase activity and promotes a reduction of specific isotonic and specific absolute tetanic forces. There is also a drop in resistance to fatigue and an increase in the area of fibrous tissue. These findings indicate incomplete regeneration and partial recovery of the contractile function of the injured muscle. Linoleic acid supplementation decreases the mass, specific isotonic strength, fatigue resistance, and cross-sectional area of the contralateral and injured gastrocnemius muscle fibers, as well as increases the area of fibrous tissue in the injured muscle. Supplementation with oleic acid, on the other hand, does not modify the mass and the cross-sectional area of the fibers of the gastrocnemius muscle; it suppresses the decrease in specific isotonic force and the increase in the area of fibrous tissue induced by the injury, prevents tetanic forces (absolute and specific), and increases the resistance to fatigue in the contralateral and injured gastrocnemius muscles. Based on these findings, we conclude that supplementation with linoleic acid compromises the regeneration of the injured skeletal muscle, causing muscle mass reduction, fibrous tissue elevation, and, consequently, impairment of contractile function. Oleic acid, in turn, attenuates incomplete repair actions, optimizing the regenerative capacity and the contractile function of the injured muscle.

## Effects of fatty acids on muscle cell differentiation

The effects of fatty acids on fibroblast proliferation[53,54] and myogenic differentiation in isolated cells have been investigated.[7-11] In 1978, Horwitz et al.[55] observed that the fatty acids added to the culture medium have a stimulatory effect on the fusion of embryonic myoblasts. The authors observed that the lipid composition of the membrane influences the proliferation and fusion of myoblasts and, consequently, the formation of multinucleated myotubes. In 1985, Allen et al.[56] observed that linoleic acid and insulin stimulate the differentiation of satellite cells by regulating cell fusion. Incubation of the cells with linoleic acid (1 µg/mL) raises the degree of differentiation and fusion of satellite cells, without, however, changing the total number of cells. The authors also

observed that the presence of mitogenic agents in culture medium and the subsequent increase in proliferation prevent differentiation.

Lu et al.[57] observed that adding fatty acids to the culture medium induced proliferation of vascular smooth muscle, and that oleic acid had a more pronounced effect on the stimulation of proliferation, an effect associated with the activation of protein kinase C (PKC). Hurley et al.[8] compared the effect of different fatty acids on the differentiation of L6 myoblast in vitro. To assess the degree of differentiation, the authors quantified protein and DNA contents, as well as creatine kinase activity (CK/DNA). The effects on differentiation were accompanied by analysis of peroxisome proliferator-activated receptor alpha and gamma (PPAR-α and -γ) receptor activity to establish the possible association of these transcription factors with the differentiation process. They observed that linoleic acid stimulates differentiation at low concentrations (50 μM) and oleic acid at all concentrations tested (12.5 to 100 μM) without the involvement of the activation of the PPARs evaluated.

Lee et al.[7] investigated the effect of fatty acids on the proliferation and differentiation of C2C12 myoblasts, as well as the possible involvement of the mitogen activated protein kinases (MAPK) in this process. The authors have found that linoleic and oleic acids increase cell proliferation and differentiation, with phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) and c-Jun N--terminal kinases (JNK) occurring during proliferation, but not during differentiation. Markworth and Cameron-Smith[9] evaluated the effect of arachidonic acid treatment on C2C12 myoblasts and observed that arachidonic acid stimulates the growth of myoblasts in a dose-dependent manner at concentrations between 1.6 and 25 μM. There was an increase in myonuclei during myogenesis, regardless of changes in cell density or extent of myogenic differentiation. To verify the effect of arachidonic acid treatment on hypertrophy in myotubes, the authors cultured C2C12 myoblasts in differentiation medium for 72 hours. Then, they added arachidonic acid (25 μM) to the medium containing the already differentiated myotubes. Researchers have found that hypertrophy is greater in arachidonic acid-treated myotubes compared to untreated cells.

Briolay et al.[10] showed that oleic (18:1 (n-9)), arachidonic (20:4 (n-6)), eicosapentaenoic (EPA) (20:5 (n-3)) and DHA (22:6 (n-3)) (20 μM) acids stimulate the myogenic differentiation of L6 myoblast. These fatty acids alter the lipid composition of the membrane and, during myogenic differentiation, promote phosphorylation of ribosomal protein S6 kinase beta-1 – 70 KDa (p70S6K1) and activation of mammalian target of rapamycin complex 1 (mTORC1), an important cell cycle regulator and protein synthesis, without alteration of Akt phosphorylation. These results support the proposition that the fatty acid composition of the plasma membrane can control the activity of complex signaling pathways of myogenic differentiation. In this context, the treatment of isolated myoblasts with arachidonic acid rapidly stimulates protein turnover (synthesis and degradation)[48] (Figure 2).

Our group also assessed the effect of oleic and linoleic fatty acids (100 μM) on myoblast differentiation, myotubes growth and fibroblast proliferation in primary culture (data still unpublished). Treatment of fibroblasts with linoleic acid decreases mRNA expression of proliferating cell nuclear antigen (PCNA), collagen and fibronectin. Oleic acid, in turn, increases the content of MYOD mRNA in myoblasts, increases desmin in previously differentiated myotubes, and inhibits mRNA expression of PCNA, collagen and fibronectin in fibroblasts. We conclude that oleic acid, in vitro, has a modulatory effect on the differentiation of satellite stem cells and on the growth and maturation of myotubes.

## Final considerations

Recently, studies have revealed significant advances in the knowledge of mechanisms involved in the activation, proliferation and differentiation of muscle cells, as well as on fundamental processes of muscle trophism and plasticity. Dietary strategies have been investigated with a view to improving skeletal muscle regenerative capacity after injury. In this context, different fatty acids, such as oleic and linoleic acids, which are abundant in Western diets, have demonstrated in vitro modulatory effects on muscle cell differentiation, and in vivo effects on muscle plasticity and trophism, with an emphasis on regeneration of skeletal muscle. Recent evidence on the regulatory action of fatty acids on muscle function and muscle mass has been described and discussed in this review.

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## Conflict of interest

The authors declare no conflict of interest.

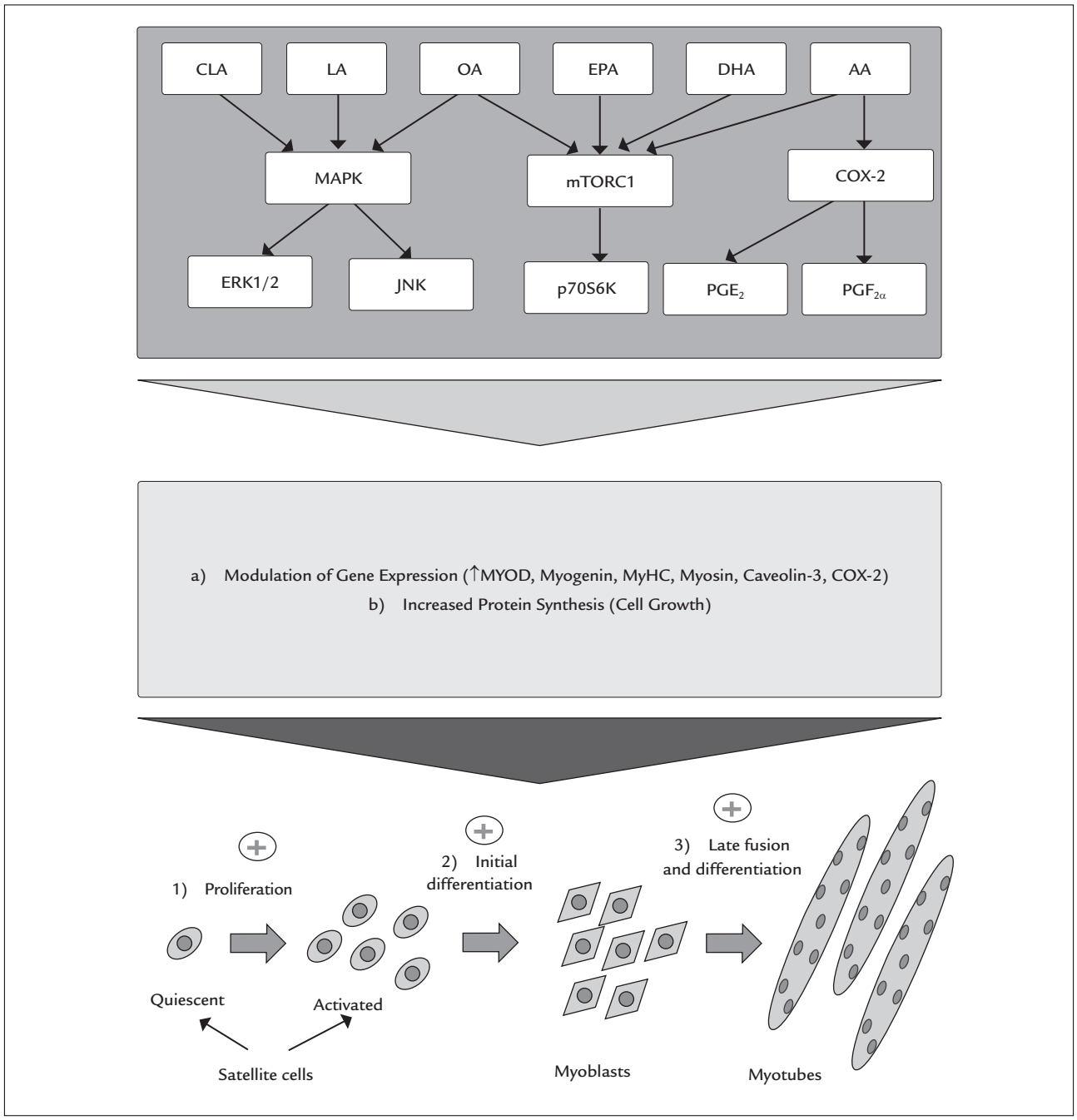


**FIGURE 2** Mechanisms possibly involved in the action of different fatty acids on the proliferation and differentiation of skeletal muscle cells.

For details, see "Effects of fatty acids on muscle cell differentiation".

CLA: conjugated linoleic acid; LA: linoleic acid; OA: oleic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; AA: arachidonic acid; MAPK: mitogen activated protein kinases; ERK1/2: extracellular signal-regulated kinases 1 and 2; JNK: c-Jun N-terminal kinases; mTORC1: mammalian target of rapamycin complex 1; p70S6K: ribosomal protein S6 kinase – 70 KDa; COX-2: cyclo--oxygenase-2; $PGE_2$: prostaglandin $E_2$; $PGF_{2\alpha}$: prostaglandin $F_{2\alpha}$; MYOD: myogenic differentiation; MyHC: myosin heavy chain.

## Resumo

Regulação da plasticidade e do trofismo muscular pelos ácidos graxos: uma breve revisão

O tecido muscular esquelético possui a notável capacidade plástica de alterar suas propriedades estruturais e funcionais após um estímulo lesivo, regulando a expressão de proteínas durante eventos complexos como a regeneração muscular. Nesse contexto, considerando que possíveis agentes terapêuticos vêm sendo amplamente estudados, estratégias nutricionais têm sido investigadas na perspectiva de melhorar a capacidade regenerativa do músculo esquelético. Há evidências da ação modulatória dos ácidos graxos, como os ácidos oleico e linoleico, que são abundantes nas dietas ocidentais, sobre a função muscular e o trofismo. Nesse sentido, os ácidos graxos parecem ser potenciais candidatos para promover ou prejudicar a recuperação da massa e a função muscular durante a regeneração, uma vez que modulam vias intracelulares reguladoras da miogênese. Este trabalho é o primeiro a descrever e discutir o efeito dos ácidos graxos sobre a plasticidade e o trofismo muscular, com ênfase na regeneração do músculo esquelético e na diferenciação de células musculares *in vitro*.

**Palavras-chave:** diferenciação celular, reparo muscular, músculo esquelético, células satélites, ácidos graxos.

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