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Endocrine control of skeletal muscle regeneration and clinical applications

Peggy Lafuste & Frederic Relaix

Muscle regeneration relies on finely tuned hormonal signalling to regulate muscle stem cell activity. This Comment explores how anabolic, catabolic, metabolic and stress-related hormones influence muscle stem cell function and the muscle repair process, highlighting their therapeutic potential for combating ageing, injury and muscle-wasting diseases through targeted endocrine modulation.

Skeletal muscle has a remarkable capacity for regeneration following injury, exercise-induced damage or trauma. The regeneration process is primarily driven by muscle stem cells (MuSCs). These cells reside in a specialized niche between the basal lamina and muscle fibres, where they remain quiescent until activated by injury or stress. On activation, MuSCs proliferate and differentiate into myogenic progenitors that fuse to repair damaged myofibres or form new ones, while a subset self-renews to replenish the stem cell pool. The regenerative process is intricately regulated by local interactions among various cell types within the muscle niche, such as macrophages, mesenchymal cells and vascular cells[1], as well as by hormonal signals that together coordinate repair. Hormones have a central role in modulating MuSC activity by regulating quiescence, activation, differentiation and self-renewal in response to physiological demands such as exercise or trauma. However, dysregulations in hormonal signalling caused by ageing, chronic stress or metabolic and genetic disorders can impair MuSC function, leading to muscle degeneration and conditions such as sarcopenia or muscle-wasting diseases.

Traditionally, hormones were defined as signalling molecules secreted by glands and transported through the bloodstream to distant target organs. Modern research has expanded this definition to include signalling molecules produced by diverse cell types, such as muscle cells (myokines), adipose cells (adipokines) and immune cells (cytokines), which act systemically by binding specific receptors to regulate physiology. These signalling molecules influence not only MuSC function but also the broader cellular and molecular environment required for effective muscle repair. A list of hormones and cytokines involved in muscle regeneration, along with their mechanisms of action, is provided in Supplementary Table 1. Understanding these expanded hormonal networks provides critical insights into how endocrine signals regulate MuSC function and muscle regeneration. It also highlights the therapeutic potential of hormonal modulation for preserving muscle function and enhancing repair in ageing, injury recovery and neuromuscular disorders.

Anabolic hormones have a central role in muscle repair and regeneration by promoting MuSC activation, protein synthesis and myofibre growth. Insulin-like growth factor 1 (IGF1) is a key regulator of muscle regeneration that balances anabolic and catabolic pathways. IGF1 enhances protein synthesis, inhibits protein degradation, and supports MuSC proliferation and differentiation[2]. Its sustained delivery has been shown to improve myogenesis, angiogenesis and inflammatory resolution, making it a promising therapeutic target for muscle loss.

Mechanical loading, such as that induced by resistance exercise, promotes MuSC activation and myonuclear accretion, facilitating muscle hypertrophy and repair[3]. Exercise further enhances muscle repair by increasing blood levels of IGF1 and promoting the release of exercise-induced hormones, such as irisin and osteocalcin, which improve mitochondrial function and reduce oxidative stress[4]. Nutritional strategies, such as protein supplementation, augment the MuSC response by increasing myogenic regulatory factor expression and improving satellite cell function in both young and older individuals[5].

Growth hormone also exerts notable effects on muscle repair. In addition to stimulating IGF1 production, growth hormone independently promotes MuSC proliferation and differentiation via the PI3K–AKT–mTOR pathway. Growth hormone also facilitates myoblast fusion through the calcineurin–NFATC2 pathway, enhancing myofibre growth[2]. Growth hormone therapy has demonstrated potential in counteracting sarcopenia, improving muscle re-innervation and supporting functional recovery following nerve injury[2].

Sex hormones, including oestrogen and testosterone, further modulate MuSC activity. Oestrogen, acting through oestrogen receptor-α, prevents satellite cell apoptosis and maintains regenerative capacity[1]. Oestrogen deficiency, as seen in menopause, results in reduced MuSC numbers and impaired self-renewal, as well as diminished muscle mass and strength. Additionally, oestrogen modulates inflammatory responses and enhances MuSC proliferation, as demonstrated in ovariectomized mice, in which oestrogen insufficiency leads to impaired muscle regeneration, increased fibrosis and muscle fibre composition shifts[1]. Testosterone promotes MuSC activation, myofibre hypertrophy and extracellular matrix remodelling while reducing fibrosis and muscle atrophy[1]. It interacts synergistically with IGF1 to amplify anabolic effects[2]. Although testosterone-based therapies and selective androgen receptor modulators are being explored for muscle-wasting conditions, safety concerns have limited their clinical application[1].

Vitamin D, acting as a steroid hormone, influences calcium homeostasis, inflammation and MuSC function. Vitamin D deficiency is associated with muscle weakness, impaired muscle regeneration and fibrosis[6]. Although vitamin D supplementation has been shown to enhance muscle recovery, myoblast fusion and protein synthesis, excessive dosing might impair regeneration[6], highlighting the need for optimized therapeutic strategies.

In contrast to anabolic hormones, catabolic hormones, such as glucocorticoids, negatively regulate muscle regeneration by impairing

MuSC function and promoting muscle atrophy. Although glucocorticoids possess anti-inflammatory properties that can facilitate sarcolemmal repair in conditions such as Duchenne muscular dystrophy, chronic exposure leads to muscle wasting through upregulation of catabolic pathways, including the MuRF1 and atrogin 1 pathways[6]. Glucocorticoids also suppress MuSC proliferation and differentiation by repressing akirin 1 and stimulating myostatin, a TGFβ family member that inhibits muscle regeneration via SMAD signalling[2]. Inhibition of myostatin, for example by follistatin, increases muscle mass, reduces fibrosis and accelerates regeneration, and follistatin-based therapies demonstrate promise for treating muscular dystrophy and sarcopenia[2,6].

Metabolic hormones, including insulin and thyroid hormones, regulate glucose uptake, energy metabolism and mitochondrial function, all of which are essential for muscle repair. Insulin enhances MuSC activation and regeneration, whereas insulin impairment in diabetes mellitus leads to dysregulated muscle repair[2]. Thyroid hormones also have an important role in muscle regeneration. Locally produced triiodothyronine (T_3) regulates MuSC activity and mitochondrial function, whereas inactivation of T_3 by type 3 iodothyronine deiodinase (DIO3) supports early MuSC proliferation before differentiation[7]. Disruptions in thyroid hormone signalling have been linked to delayed muscle repair and impaired differentiation[7].

Stress and immune-regulating hormones, including oxytocin, adrenaline and melatonin, further influence muscle regeneration by modulating immune cell recruitment, MuSC activation and extracellular matrix remodelling. Oxytocin enhances MuSC activation and differentiation while reducing fibrosis, with declining levels of oxytocin in ageing contributing to impaired muscle repair[8]. Adrenaline, through β2-adrenergic receptor signalling, regulates MuSC quiescence via the vascular niche[9]. Melatonin protects MuSCs from oxidative stress, enhances mitochondrial function and promotes MuSC activation, improving muscle regeneration in ageing and metabolic disorders[10].

Targeting hormonal pathways could rejuvenate MuSCs, offering therapies for muscle disorders. Despite advances in understanding the endocrine regulation of muscle regeneration (Supplementary Table 1), clinical challenges remain in treating conditions such as volumetric muscle loss, muscular dystrophies and sarcopenia. Although IGF1, growth hormone and oestrogen promote MuSC function, translating these findings into effective therapies is complicated by the systemic role of hormones and potential toxicity, variability in patient responses and challenges in hormone delivery. Future research should focus on refining targeted delivery strategies, optimizing dosing regimens and developing combination therapies to enhance muscle repair. By integrating endocrinology, regenerative medicine and bioengineering, novel therapeutic strategies might emerge to improve muscle function and counteract degeneration more effectively.

Peggy Lafuste [1] ✉ **& Frederic Relaix**[1,2,3,4]
[1]Université Paris Est Créteil, Institut National de la Santé et de la Recherche Médicale, Institut Mondor de Recherche Biomédicale (IMRB), Créteil, France. [2]EnvA, IMRB, Maisons-Alfort, France. [3]Etablissement Français du Sang, IMRB, Créteil, France. [4]Service d'Histologie, Hôpital Mondor, Assistance Publique–Hôpitaux de Paris, Créteil, France.
✉e-mail: peggy.lafuste@u-pec.fr

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Competing interests

The authors declare no competing interests.

Additional information

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