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EDITORIAL

Mechanisms of skeletal muscle repair and regeneration in health and disease

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Skeletal muscle is a structurally and functionally remarkable tissue composed of multinucleated post-mitotic muscle fibres. These fibres are filled with an exquisite, near crystalline array of assembled contractile proteins, capable of coupling ATP utilization to mechanical muscle contraction. Fully differentiated muscle has an incredible ability to protect and repair itself from significant muscle injuries. In fact, through activation of a resident population of stem cells known as satellite cells, muscle fibres can be completely regenerated, and normal function can be restored in a matter of a few weeks after a major myocellular necrotic injury. The loss of key mechanisms to protect muscle from injuries or loss of the capacity to repair muscle after injury is thought to underlie several forms of muscular dystrophy and also the age-related decline of muscle function. In this Subject Collection, *The FEBS Journal* highlights articles that review or investigate key mechanisms of muscle repair and regeneration in response to injuries, and the contributions of these pathways to health and disease of skeletal muscle.

Mechanisms of muscle repair and regeneration: recent advances

Myogenesis during development and injury

In this Subject Collection of *The FEBS Journal*, we highlight some of the key aspects of muscle repair and regeneration that are important for human health and disease. During development, muscle is produced through the fusion of myogenic precursors into large, multi-centimetre-long, multinucleated cells, known as muscle fibres [1]. Muscle fibres are filled with a near crystalline array of contractile proteins, calcium-handling proteins and organelles and mitochondrial networks, which convert the signal from a motor neuron action potential into a mechanical force generation or muscle shortening [2]. Remarkably, after a muscle injury leads to necrosis, muscle fibres can be completely replaced and regenerated within just a few weeks, and muscle function can be completely restored [3]. As reviewed by John Bachman and Joe Chakkalakal [4], as myogenic activity declines during postnatal development of muscle, a portion of the developing myogenic cells establish a resident population of quiescent stem cells known as satellite cells, which are identified by the marker Pax7 and reside under the basal lamina around muscle fibres. Myocellular injuries alter the stem cell niche in skeletal muscles and lead to downregulation of Pax7, increase in myogenic cell number and activation of a myogenic transcription factor programme prior to fusion and formation of new muscle fibres. Many pathways that regulate satellite cell activation and the transcriptional activation of myogenesis have been identified, and their significance has been shown through experimental cytotoxic

Abbreviation
DMD, Duchenne muscular dystrophy.

injuries triggering acute muscle regeneration in animal models. An example is shown by de la Vega et al. [5], who report that important components of the ubiquitin proteasome system are necessary for activation of the myogenic transcriptional programme after myofiber cytotoxic injury. Some of the satellite cells in muscle may also continue to contribute to continued normal postnatal growth and muscle maintenance. Myogenic cells may also contribute to the hypertrophic growth of muscle in response to several signalling pathways activated by vigorous contractions during exercise, as reviewed by Attwaters and Hughes [6]. Conversely, the loss of satellite cell function has been speculated to contribute to age-related decline in muscle mass and function. In the state-of-the-art review by Sahinyan et al. [7], advances and controversies in the field regarding the changes in satellite cell numbers and changes in the muscle stem cell niche with ageing are reviewed. The authors overview to what extent these changes contribute to the age-dependent decline in muscle mass and function. The regulation of the stem cell niche in the ageing muscle by both intrinsic factors and circulating factors has recently attracted great interest. With advances in lineage tracing, single-cell transcriptomics and analysis tools, such as NicheHotSpotter, highlighted by Popatov et al. [8], researchers are continuing to uncover and propose new models and hypotheses of how these relatively rare muscle stem cells are maintained and regulated within their niche throughout the lifespan, and then acutely activated in response to injuries.

Sarcolemma integrity: importance for muscle function

The preservation of muscle integrity and prevention of injury under the strain of significant mechanical forces is critical to the maintenance of normal muscle function. The integrity of the sarcolemma is a key factor in the maintenance of overall muscle fibre viability and excitability. Eric Hoffman [9] provides a firsthand account about the discovery of dystrophin as the causative gene in Duchenne muscular dystrophy (DMD). Antibodies generated against dystrophin led to the discovery that dystrophin was bound to the subsarcolemma cytoskeleton and the basal lamina outside muscle fibres through a large macromolecular protein complex known as the dystrophin–glycoprotein complex. In the absence of dystrophin, the muscle becomes susceptible to mechanical injuries of the sarcolemma, which suggests that the dystrophin–glycoprotein complex plays a key role in sarcolemma integrity. As shown by McDade et al. [10], acute sarcolemma injuries result in influx of calcium that can also activate the sarcolemma repair protein assembly, membrane reorganization and sarcolemma-resealing through mechanisms that are still under active investigation. If muscle fibres are not rapidly repaired, injured muscle cells undergo necrotic muscle fibre degeneration, followed by inflammation to clear out damaged cells, and activation of satellite cell-dependent muscle regeneration to replace damaged muscle fibres. Thus, the pathology of many muscular dystrophies that show loss of sarcolemma integrity, includes ongoing cycles of muscle injury, necrosis, degeneration and regeneration that over time may exhaust the satellite cell pool and lead to progressive muscle wasting.

Cross-talk between myokines, inflammation, myogenic cells and non-muscle cells in muscle injury

The activation of resident satellite cells after muscle injury in normal and diseased muscle results from a complex interplay between myokines released from muscle, cytokines from infiltrating immune cells and the function of other cells within or near the stem cell niche. The list of myokines, or cytokines that are released from muscle itself, is growing, and many of these myokines play an important role in both activating growth and preventing overgrowth during muscle development, as well as in regulating muscle regeneration following injury [11]. Interestingly, several of these myokines can also be released in response to normal muscle contractions or chronic exercise *in vivo* and may contribute to muscle growth and beneficial remodelling in response to exercise. For example, the myokine meteorin-like 1 is released from contracting muscle cells and can improve glucose metabolism through activating AMPK-dependent signalling and boosting the expression of glucose transporters [12]. The research by Nunez-Alvarez et al. [13], showing how HDAC11-regulated IL10 production in inflammatory cells can impact muscle regeneration, is one of many examples of how regulators of cytokine production from inflammatory cells can impact muscle regeneration through secondary impacts of cytokines on myogenic cell differentiation. Fibroadipogenic precursors also reside within the muscle stem cell niche and play an important role to help instruct myogenic cells to become activated after injury. However, as reviewed in Giuliani et al. [14], in conditions of chronic injury such as muscular dystrophy, fibroadipogenic precursors also expand and differentiate into fibroblasts and adipocytes leading to the fibrosis and fatty infiltration

observed in later stages of disease pathogenesis. Thus, efficient muscle repair and muscle regeneration are critical to the recovery from muscle injuries and maintenance of muscle. In the setting of chronic muscle injuries or muscular dystrophies, these repair pathways can be overwhelmed and lead to the loss of muscle fibre mass and replacement with fibrotic tissue and adipose tissue, which contributes to the further decline of muscle function.

Concluding remarks

As shown in this Subject Collection in *The FEBS Journal*, the ability to respond to and repair muscle injuries is essential to the sustained normal function of skeletal muscle. The population of resident satellite cells that are capable of completely regenerating muscle following injuries play additional important roles in muscle health, maintenance and growth under a variety of conditions. The uncovering of new pathways that regulate the response of muscle to injuries is providing new insights into the mechanisms of skeletal muscle health and disease.

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