Fibroblasts take the center stage in human skeletal muscle regeneration

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Competing Interests

None declared.

Outside of fibres themselves, satellite cells have historically been the most studied cell population in skeletal muscle tissue. Originally identified by Alexander Mauro in 1961 (MAURO, 1961), satellite cells play a central role in skeletal muscle regeneration, and have been in the spotlight of skeletal muscle cell biology for over 50 years. Muscle fibres are multinucleated, but the nuclei within fibres are terminally withdrawn from the cell cycle. When skeletal muscle tissue is injured, the nuclei in damaged segements of fibres undergo apoptosis, and satellite cells are the muscle fibre progenitor cells that proliferate, differentiate, and fuse to restore the nuclei lost during injury.

Skeletal muscle fibroblasts, which were originally described two decades before satellite cells (Landsteiner & Parker, 1940), have been known to play an important role in skeletal muscle extracellular matrix formation and modulation for some time. In 2011, two papers published from the laboratory of Gabrielle Kardon using mouse models and molecular genetics techniques, provided an important contribution to our understanding of the role of fibroblasts in skeletal muscle regeneration (Mathew *et al.*, 2011; Murphy *et al.*, 2011). These papers reported that skeletal muscle fibroblasts express the transcription factor Tcf4 (also known as Tcf7L2), and that fibroblasts play an important role in directing the regenerative activity of satellite cells in response to a severe muscle injury. This work identified a useful and specific marker of fibroblasts in muscle tissue *in vivo*, and also provided the first evidence that fibroblasts have a role in muscle regeneration in addition to extracellular matrix production and remodeling.

Although the findings regarding Tcf4/Tcf7L2 in murine studies made an important contribution to our understanding of the basic biology of fibroblasts and muscle regeneration, the barium chloride injury model used in this work is far more extensive and severe than the types of skeletal muscle injuries observed in humans. Further, given the potential therapeutic importance of manipulating the activity of fibroblasts in the treatment of muscle injuries and diseases, it was important to explore the interplay between fibroblasts and satellite cells in the context of human muscle regeneration. In the current edition of *The Journal of Physiology*, Abigail Mackey and colleagues (Mackey *et al.*, 2017) used a physiologically relevant eccentric injury model in human subjects, and sampled vastus lateralis muscle tissue from percutaneous biopsies obtained from

uninjured muscles, and at 2 days, 7 days, and 30 days after injury. The authors used elegant quantitative immunohistochemistry techniques, and informative *in vitro* satellite cell and fibroblast co-culture experiments to rigorously study the contribution of fibroblasts to skeletal muscle regeneration in humans. They demonstrated that there was an approximately 2:1 ratio of fibroblasts to satellite cells in uninjured muscle, and that both cell types increased proportionally until 30 days, at which point the fibroblast to satellite cell ratio was nearly 3:1. Further, fibroblasts were shown to be in close proximity to regenerating muscle fibres.

To complement their *in vivo* work, Mackey and colleagues then performed a series of *in vitro* experiments to evaluate the effect of fibroblasts on myogenesis. Interestingly, they found that when satellite cells were cultured in the same well as fibroblasts, there was an increase in satellite cell differentiation, and fusion. To further test whether this increase in myogenesis was dependent on physical contact between satellite cells and fibroblasts, the two populations of cells were cultured in distinct chambers separated by a media-permeable membrane, and satellite cell proliferation, differentiation, and fusion was again assessed. In this scenario, where media was shared between satellite cells and fibroblasts, but no physical contact occurred, there was no stimulatory effect of fibroblasts on satellite cell myogenesis. Coupled with the *in vivo* results, these findings suggest that fibroblasts promote the activity of satellite cells in the regenerating muscles of humans in a contact-dependent manner.

Although the study by Mackey and colleagues (Mackey *et al.*, 2017) provided an important advancement in our understanding of human muscle regeneration, many questions on the fundamental molecular mechanisms behind the regulation of satellite cell activity by fibroblasts remain. There are numerous cell contact-dependent signaling pathways, in which the receptor and ligand are both membrane bound, including the Notch and Ephrin signaling pathways. These pathways are known regulators of myogenesis, making them appealing targets of further exploration. While much work remains, it is clear that fibroblasts play an important role in skeletal muscle regeneration, and may serve as therapeutic cellular targets in the treatment of muscle injuries and diseases.

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