Skeletal muscle regeneration in adult zebrafish

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Master thesis in Biology

Skeletal muscle is the most abundant tissue in the human body, constituting around 40% of the total body mass. To properly fulfill a large diversity of functional demands, muscles are built with various proportions of distinct fiber types, whose classification is usually based on metabolic enzymes, contractile properties and myofibrillar protein isoforms. These contractile myofibers have the outstanding ability to remodel their intrinsic properties, as well as to fully regenerate through the activation of resident stem cells, called satellite cells. Among vertebrate models, the zebrafish (Danio rerio) has become a popular choice for studying muscle repair, due to numerous experimental advantages. However, these investigations are often limited by a modest ability to highlight zebrafish myofibers, since most labelling tools are developed for mouse models. Moreover, the research on muscle regeneration is usually restricted to localized injuries, performed by lasers or needles. In this work, specific markers were successfully uncovered to outline established major and minor muscle types in zebrafish tail skeletal muscles, namely fast-twitch, slow-twitch, fast-intermediate and slow-tonic myofibers. In uninjured fish, these fiber types were found to be segregated in distinct compartments, with heterogeneous groups of muscles encircled by Collagen 12. Moreover, the chaperone protein HSP90 was discovered to be a specific marker for fast-intermediate muscles, whereas the careg transgenic reporter was demarcating a new subpopulation of slow-twitch fibers. Next, to better replicate extensive loss of muscle mass, a new cryoinjury method was established to injure tail skeletal muscles, causing broad tissue damages. As a result, pigmentation and all fiber types were found to be substantially restored at their uninjured position by 30 dpci, although persisting structural differences suggested some regenerative limitations. Furthermore, the repair process involved a transient Collagen scar and the upregulation of the careg reporter in the wound. Concerning molecular mechanisms orchestrating skeletal muscle regeneration, the TOR pathway was found to be required for myofiber regeneration and scar resorption, in contrast to TGFβ / Activin-β signaling. Similarly, inhibition of angiogenesis impaired muscle restoration, but not the slow/fast fiber ratio. These promising molecular insights about myofiber regeneration might help to uncover molecules involved in stem cell activation and proliferation, which could subsequently lead to the establishment of new therapeutic strategies to treat massive muscle loss in humans.

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