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Insights from the Network

Renovating deteriorating infrastructure in the stem cell microenvironment towards treatments for muscular dystrophy and age-associated muscle wasting

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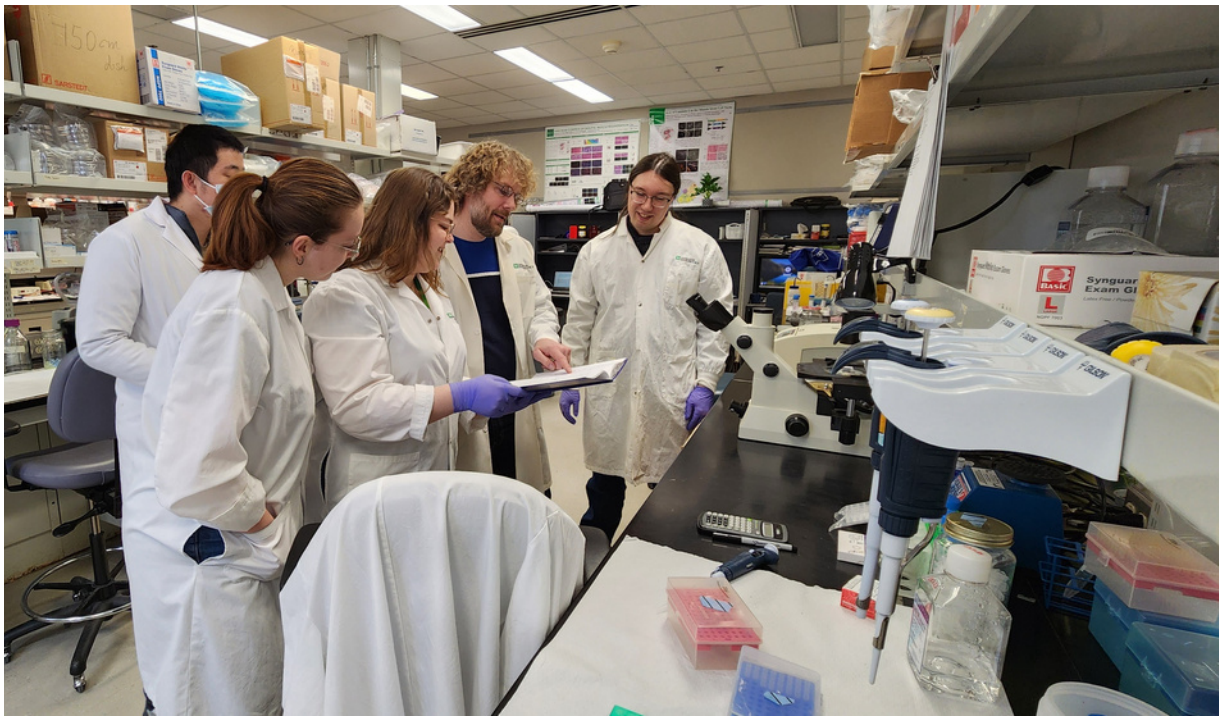
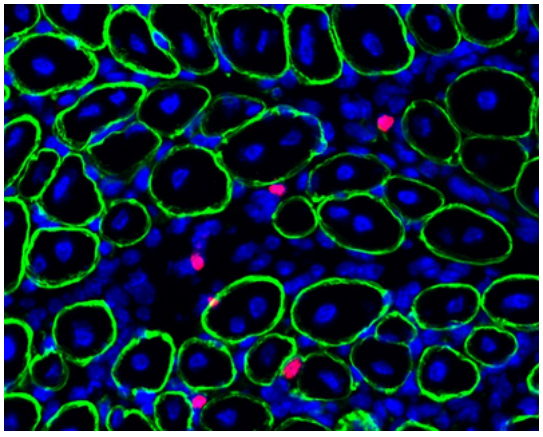
Skeletal muscle wasting conditions, whether they are caused by inherited genetic mutations or aging, are accompanied by a phenomenon called “regenerative dysfunction”. In the case of skeletal muscle this means that the tissue loses its ability to heal, which under normal conditions is extraordinary. Muscle fibers, the contractile units in skeletal muscle, contain hundreds of thousands of tiny adult stem cells that are primed for tissue repair. Owing to these muscle stem cells (MuSCs), healthy skeletal muscle can undergo multiple rounds of injury followed by complete repair and restoration of muscle fibers without any loss of functionality. This can happen, for instance, because of accidents or surgeries where muscles are damaged and typically heal without problems. However, with aging, or in the case of certain genetically induced muscle wasting conditions called “muscular dystrophies”, for reasons we don’t fully understand, MuSCs progressively fail to work properly. This leads to impaired tissue regeneration accompanied by a net loss of muscle fibers resulting in reduced levels of functional muscle mass.



The Bentzinger lab at the University of Sherbrooke in the province of Quebec tries to study regenerative dysfunction in skeletal muscle and devises novel strategies to mobilize MuSCs in aging and muscular dystrophy. The lab has a particular focus on mechanisms regulating stem cell function through signals from their microenvironment, which is composed of other cell types secreting regulatory soluble proteins or presenting cell-cell contacts. These different cell types include muscle fibers, fibroblast-like cell types, blood vessels and immune cells.



In addition to soluble proteins or cell-cell interactions originating from these different supportive cell types, MuSCs are also embedded in a material composed of a network of enormously large structural molecules that we call the extracellular matrix (ECM). ECM is typically insoluble and deposited by different cell types in skeletal muscle where it can influence MuSC function. ECM is what MuSCs and their supportive cell types in the tissue use to build a specialized microenvironment to which the stem cells can adhere, and which protects them ensuring their proper function. ECM regulates MuSCs on many levels, whether this is during homeostasis or during tissue regeneration when the stem cells activate and divide to generate new cells for tissue repair.

The previous work of the Bentzinger team and their collaborators has shown that during aging a particular ECM molecule called “Fibronectin” is dramatically reduced in the stem cell microenvironment, leading to a cascade of negative effects on skeletal muscle regeneration. Importantly, if fibronectin is brought back into aged regenerating muscles though injections, the stem cells rejuvenate and start to become much more efficient in healing the tissue. Moreover, in a project supported by the Canadian Stem Cell Network, the team has recently demonstrated that in muscular dystrophy, blood-vessel-associated endothelial cells have a severely impaired supportive function for MuSCs. Stimulation of blood vessels and endothelial cells using a small hormone called “apelin,” which was identified by the team using drug screening, helps to revascularize dystrophic muscles and greatly promotes stem cell function leading to muscles that remain functional and strong for much longer.

Present work in the Bentzinger lab aims at better understanding the different ECM derived signals in the MuSC microenvironment. To this end, the team and their collaborators use devices such as bioprinters to spot different types of ECM onto culture plates to study their effects on isolated MuSCs. In addition, genetically engineered mice are used to label and study the behaviour of different supportive cell types in the MuSC environment and untangle their complex interactions and contributions to the ECM. Lastly, the team has also begun to work on modeling some of the interactions of MuSCs with the ECM and supportive cell types in 3D culture using transparent gel substrates, which provides a much better model of the tissue context than traditional cell culture in flat plastic dishes and enables simulation of specific interactions in isolation so that they can be better targeted for therapeutic applications in the future.

If the healing capacity of the tissue could be preserved or, ideally, even restored using pharmacologic strategies targeting relevant cell types or the ECM, a wide range of potential applications can be envisioned. These range from treating muscular dystrophy patients and maintaining healthy muscle mass for longer, to helping elderly individuals recover faster from muscle damage. An example of the latter are hip replacement surgeries, which can be very damaging to the overlaying soft tissue. It is hoped that a better understanding of the microenvironmental interactions of MuSCs in health and disease will help to devise strategies that can be applied to treat muscular dystrophy or regenerative failure in age-associated muscle wasting.