

PRIZE ESSAY



FINALIST

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C. Florian Bentzinger received his master's and Ph.D. degrees from the University

of Basel in Switzerland. Following his postdoctoral studies at the Ottawa Hospital Research Institute, Dr. Bentzinger joined the Nestlé Institute of Health Sciences. In 2016, he was appointed as an assistant professor at the Université de Sherbrooke and as an investigator at the Centre de recherche du CHUS in Canada, where he is conducting research on the skeletal muscle stem cell niche.

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REGENERATIVE MEDICINE

Best supporting actors

Nearby cells help boost stem cell-mediated skeletal muscle repair

By **C. Florian Bentzinger**

Skeletal muscle stem cells (MuSCs) are critically dependent on their microenvironment, the so-called “stem cell niche.” The niche contains a multitude of cellular and acellular elements that regulate MuSC functions, including quiescence, proliferation, self-renewal, and differentiation (Fig. 1). By spatiotemporally controlling MuSCs, the components of the niche ultimately determine the regenerative capacity of skeletal muscle (SkM) tissue.

Upon SkM injury, certain cell types, such as fibroblasts, vascular cells, and immune cells, become highly abundant in the stem cell niche and play particularly important roles in regulating MuSCs. These supportive cell types interact with MuSCs by presenting cell-cell contacts, secreting growth factors, and providing various structural components to the extracellular matrix (ECM) (1, 2). Regulatory interactions of supportive cell types with MuSCs can be severely perturbed in aging and neuromuscular disorders (2–4).

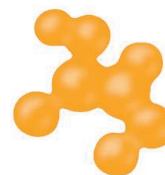
Impaired MuSC-niche interactions represent a root cause of regenerative failure of SkM tissue, and restoring microenvironmental signals can improve its healing capacity, thus slowing or stopping disease progression. Given its fundamental importance for regenerative medicine, it is imperative to study the cellular dynamics and molecular signals in the MuSC niche. In the long run, this research will pave the way for the development of novel therapies for degenerative SkM diseases.

In early studies, we investigated the regenerative deficit that accompanies a rare form of muscular dystrophy called congenital muscular dystrophy type 1A (MDC1A). This work revealed that a lack of the muscle fiber-derived ECM component laminin- α 2 in the niche severely impairs muscle healing in a mouse model of MDC1A and must therefore be essential for MuSC function (4). Reactivation of laminin receptors using transgenic expression of a miniaturized ligand restores the regenerative capacity of

SkM tissue, slows the disease, and prolongs the life of the animals.

Subsequently, we identified a novel receptor complex that integrates Wnt signals and the ECM component fibronectin (FN) to control MuSC self-renewal in the regenerative niche (5). MuSCs express the Wnt receptor Frizzled-7 (Fzd7), which binds to the plasma membrane proteoglycan syndecan-4 to form a receptor complex co-activated by Wnt7a and FN ligands. When Wnt7a was administered to a mouse model of Duchenne muscular dystrophy (DMD), a disorder associated with SkM degeneration and impaired regeneration, the treatment restored MuSC function and enhanced tissue repair (6, 7).

A follow-up study demonstrated that in vitro administration of Wnt7a to MuSCs before transplantation into DMD SkM greatly



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enhanced their engraftment and led to a remarkable mitigation of the disease (8). Not only were the Wnt7a-treated donor MuSCs more abundant following transplantation, we also observed improved migration of these cells into the host tissue. In addition, we discovered an unexpected role for Wnt7a: the regulation of postnatal growth of muscle fibers through the mTOR-AKT pathway (9). Thus, Wnt7a and FN appear to boost SkM regeneration through two different mechanisms: (i) by stimulating MuSC function and (ii) by increasing the growth rate of muscle fibers.

To exploit the potential of Wnt7a as a therapeutic agent, we developed a truncated variant with increased solubility, in which the C-terminal 137 amino acids lack the conserved palmitoylation sites (10). This mini-Wnt7a has full biological activity on MuSCs and is highly efficient in inducing muscle fiber hypertrophy. These properties make Wnt7a and its derivatives attractive candidates for developing drugs that stimulate SkM growth and regeneration. Several patents regarding therapeutic use of Wnt7a for SkM disease have been filed because of these discoveries (11–13).

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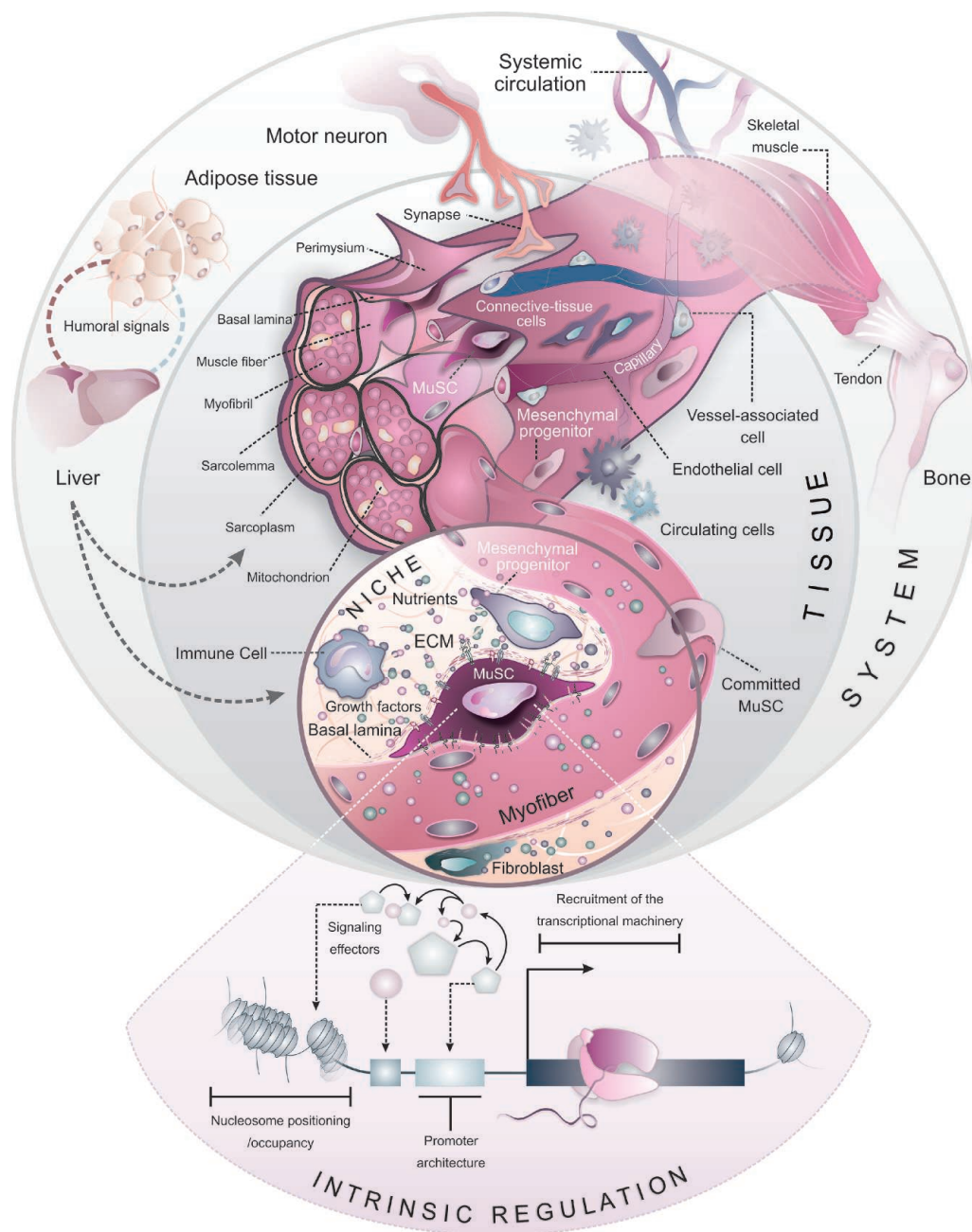


Fig. 1. The skeletal muscle stem cell niche. The niche microenvironment is composed of structural elements, locally bound and secreted signaling molecules, and cell-cell interactions. The niche that maintains MuSCs in their quiescent state in the absence of muscle injury is composed of two major compartments: the interface with the muscle fibers and the basal lamina. In the immediate phase following injury, the niche contains debris of degenerated muscle fibers and a high abundance of pro-inflammatory immune cells. Subsequently, the niche changes into a milieu that promotes MuSC proliferation and is characterized by extensive ECM synthesis by fibroblastic cells and angiogenesis. In the differentiative phase, anti-inflammatory macrophage subsets become dominant and MuSC-derived myoblasts fuse into young muscle fibers that are reinnervated as basal laminae mature. Systemic signals, including nutrients, hormones, and circulating growth factors, regulate MuSC function in quiescence and regeneration directly or influence them by mediating effects at the tissue level or by support cells. Intrinsic mechanisms, such as epigenetic adaptations, telomerase activity, and constitutively activated or repressed signaling loops, act in concert with extrinsic mechanisms to regulate MuSCs.

Our more recent work has continued to investigate the role of the Wnt7a potentiator FN for MuSC function. We discovered that aging severely perturbs the deposition of FN in the regenerative niche (3). Loss of FN affects a substantial number of pathways and cellular mechanisms implicated in MuSC aging. Reconstitution of FN levels in the aged niche remobilizes stem cells and restores youth-like SkM regeneration. These findings represent a previously unknown aging mechanism. Present studies aim to identify the age-affected cell type secreting FN. It has already been possible to narrow down a cell population positive for the surface markers CD45, CD31, and CD11b

that includes immune cells, hematopoietic cells, and endothelial cells.

The scientific understanding of the MuSC niche in health and disease has substantially advanced. The identification of regulatory hubs in the niche interactome that can be modulated to maintain, restore, or enhance the regenerative capacity of SkM tissue represents a unique opportunity for the targeted development of therapeutics and will likely improve the outcome of cell therapy treatments for muscular dystrophy. ■

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