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Control of muscle stem cell fate by Wnt signaling pathway(s)

Par

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Regeneration of the adult skeletal muscle tissue relies on a pool of quiescent muscle stem cells located in a niche around the myofibers: the satellite cells (MuSCs). Upon activation following injury or repeated exercise, MuSCs leave quiescence to proliferate and then differentiate to form new muscle fibers while a sub-population exit the cell cycle to self-renew and replenish the stem cell niche. In the course of this process, signals from the microenvironment instruct cycling MuSCs and control myogenesis. We previously demonstrated that numerous Wnt molecules are secreted in the local milieu during regeneration and showed that MuSC self-renewal is in part controlled by non-canonical Wnt7a/PCP signals sent by the regenerating myofibers. To elucidate the roles of the canonical Wnt/ß-catenin pathway in MuSCs, we generated mice with inducible MuSC-specific ß-catenin Loss-Of-Function or Gain-Of-Function. Strikingly, we observed that induction of either ß-catenin LOF or GOF mutations in MuSCs leads to the impairment of skeletal muscle regeneration following injury. By using a mouse model of conditional APC gene deletion in MuSCs we further demonstrated that the massive activation of canonical Wnt signaling in MuSC following APC loss results in defective cell cycle progression and apoptosis. Mechanistically, we observed that Wnt/ß-catenin signaling orchestrates the cytoplasmic relocalization of the histone 3 lysine 9 methyltransferase Setdb1 during differentiation. We further showed that Setdb1 is required for MuSCs amplification and suppresses myoblast terminal differentiation. Genome-wide analyses showed a Wnt3a-dependant release of Setdb1 from the promoter of selected target genes upon myoblast terminal differentiation. Taken together, our results demonstrate that both canonical and non-canonical Wnt pathways are necessary for MuSC function. Lastly, I will discuss the potential cross-talks between these two faces of an important signaling.

If you wish to meet Fabien Le Grand, please contact Bénédicte Chazaud (benedicte.chazaud@inserm.fr).

Selected publications:

Rudolf A, Schirwis E, Giordani L, Parisi A, Lepper C, Taketo MM, Le Grand F. β-Catenin Activation in Muscle Progenitor Cells Regulates Tissue Repair. **Cell Rep. 2016** 15:1277-90. PMID: 27134174.

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Wang H, Noulet F, Edom-Vovard F, Tozer S, Le Grand F, Duprez D. Bmp signaling at the tips of skeletal muscles regulates the number of fetal muscle progenitors and satellite cells during development. **Dev Cell. 2010** 18:643-54. PMID: 20412778.

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