



Seminar

Thursday November 17th 11.00

Amphithéâtre de la délégation du CNRS
Domaine Universitaire de la DOUA, 2 Rue Albert Einstein, Villeurbanne
(http://oscar.univ-lyon1.fr/appli-externe/plan/plans/plan_campus_ouest.html)

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" Molecular regulation of muscle stem cell asymmetric division "

Abstract

We discovered that a subset of satellite cells in skeletal muscle are self-renewing stem cells that give rise to myogenic progenitors through asymmetric apical-basal cell divisions. The regulation of asymmetric stem cell division is a key control point that impacts the efficacy of the entire regenerative program. Stem cell polarity is established by the PAR complex, comprised of PAR3/PAR6/aPKC, to regulate self-renewal and expansion. Duchenne Muscular Dystrophy (DMD) is caused by a lack of dystrophin which is expressed in muscle fibers where it plays a role in ensuring structural integrity. We have made the seminal finding that dystrophin regulates the establishment of PAR-mediated polarity in satellite cells. In the absence of dystrophin, the polarity effector Par1b is dysregulated, leading to the failure of Par3 to become localized to the cortex associated with the basal lamina. Importantly, this results in an abnormal increase in centrosome number, a 10-fold reduction in the numbers of satellite stem cells undergoing asymmetric divisions, and a marked decrease in the generation of myogenin-expressing progenitors. Accordingly, our data suggests that the failure of regenerative myogenesis to keep pace with disease progression in DMD is not due to muscle stem cell exhaustion, but rather is due to a cell-autonomous deficiency in asymmetric division.

If you wish to meet Michael Rudnicki, please contact Bénédicte Chazaud (benedicte.chazaud@inserm.fr).

Selected recent publications:

- 1: Pasut A, Chang NC, Rodriguez UG, Faulkes S, Yin H, Lalaria M, Ming H, Rudnicki MA. Notch Signaling Rescues Loss of Satellite Cells Lacking Pax7 and Promotes Brown Adipogenic Differentiation. **Cell Rep.** 2016 16(2):333-43.
 - 2: Dumont NA, Wang YX, von Maltzahn J, Pasut A, Bentzinger CF, Brun CE, Rudnicki MA. Dystrophin expression in muscle stem cells regulates their polarity and asymmetric division. **Nat Med.** 2015 21(12):1455-63.
 - 3: Dick SA, Chang NC, Dumont NA, Bell RA, Putinski C, Kawabe Y, Litchfield DW, Rudnicki MA, Megeney LA. Caspase 3 cleavage of Pax7 inhibits self-renewal of satellite cells. **Proc Natl Acad Sci U S A.** 2015 112(38):E5246-52.
 - 4: Price FD, von Maltzahn J, Bentzinger CF, Dumont NA, Yin H, Chang NC, Wilson DH, Frenette J, Rudnicki MA. Inhibition of JAK-STAT signaling stimulates adult satellite cell function. **Nat Med.** 2014 20(10):1174-81.
 - 5: Bentzinger CF, von Maltzahn J, Dumont NA, Stark DA, Wang YX, Nhan K, Frenette J, Cornelison DD, Rudnicki MA. Wnt7a stimulates myogenic stem cell motility and engraftment resulting in improved muscle strength. **J Cell Biol.** 2014 205(1):97-111.
 - 6: von Maltzahn J, Zinoviev R, Chang NC, Bentzinger CF, Rudnicki MA. A truncated Wnt7a retains full biological activity in skeletal muscle. **Nat Commun.** 2013;4:2869.
 - 8: von Maltzahn J, Jones AE, Parks RJ, Rudnicki MA. Pax7 is critical for the normal function of satellite cells in adult skeletal muscle. **Proc Natl Acad Sci U S A.** 2013 110(41):16474-9.
 - 9: Yin H, Pasut A, Soleimani VD, Bentzinger CF, Antoun G, Thorn S, Seale P, Fernando P, van Ijcken W, Grosveld F, Dekemp RA, Boushel R, Harper ME, Rudnicki MA. MicroRNA-133 controls brown adipose determination in skeletal muscle satellite cells by targeting Prdm16. **Cell Metab.** 2013 17(2):210-24.
 - 10: Bentzinger CF, Wang YX, von Maltzahn J, Soleimani VD, Yin H, Rudnicki MA. Fibronectin regulates Wnt7a signaling and satellite cell expansion. **Cell Stem Cell.** 2013 12(1):75-87.
 - 11: von Maltzahn J, Renaud JM, Parise G, Rudnicki MA. Wnt7a treatment ameliorates muscular dystrophy. **Proc Natl Acad Sci U S A.** 2012 109(50):20614-9.
 - 12: Kawabe Y, Wang YX, McKinnell IW, Bedford MT, Rudnicki MA. Carm1 regulates Pax7 transcriptional activity through MLL1/2 recruitment during asymmetric satellite stem cell divisions. **Cell Stem Cell.** 2012 11(3):333-45.
 - 13: Soleimani VD, Yin H, Jahani-Asl A, Ming H, Kockx CE, van Ijcken WF, Grosveld F, Rudnicki MA. Snail regulates MyoD binding-site occupancy to direct enhancer switching and differentiation-specific transcription in myogenesis. **Mol Cell.** 2012 47(3):457-68.
 - 14: Soleimani VD, Punch VG, Kawabe Y, Jones AE, Palidwor GA, Porter CJ, Cross JW, Carvajal JJ, Kockx CE, van Ijcken WF, Perkins TJ, Rigby PW, Grosveld F, Rudnicki MA. Transcriptional dominance of Pax7 in adult myogenesis is due to high-affinity recognition of homeodomain motifs. **Dev Cell.** 2012 22(6):1208-20.
 - 15: von Maltzahn J, Bentzinger CF, Rudnicki MA. Wnt7a-Fzd7 signalling directly activates the Akt/mTOR anabolic growth pathway in skeletal muscle. **Nat Cell Biol.** 2011 14(2):186-91.
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