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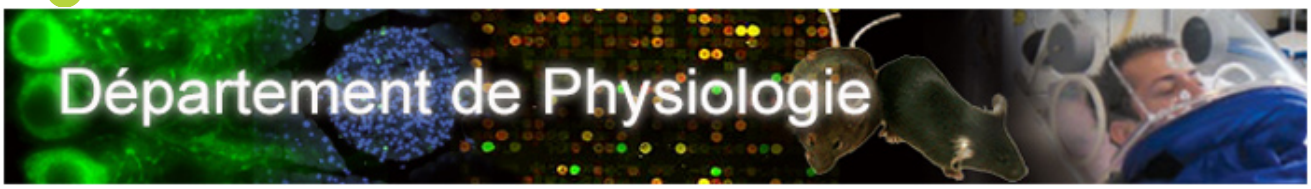

Monday November 23rd, 2015 - 14h00
Department of Physiology, Bugnon 7, 1005 Lausanne
seminar room, 6th floor

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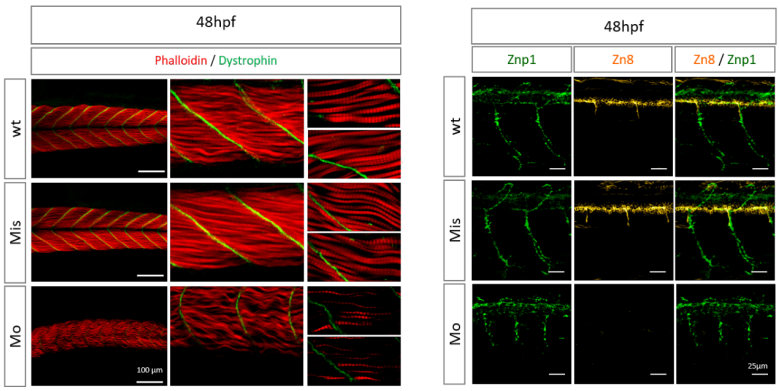
GIGAXONIN SUPERVISES NEUROMUSCULAR DEVELOPMENT THROUGH THE CONTROL OF Shh MACHINERY

Host: Prof. Francesca Amati

In vertebrates, Sonic Hedgehog (Shh) represents one of the major morphogen signal responsible for neuromuscular development. Genetic disruptions affecting Shh and partners converge onto developmental disorders whereas upregulation of the pathway leads to oncogenic processes. Consequently, Shh machinery has to be finely tuned, both spatially and temporally. Recent data highlighted the role of ubiquitination processes to ensure this modulation. The puzzling question remained to point out the enzymes involved in the subtle control of Shh machinery. In our report, we identified Gigaxonin E3-ligase as a multimodal regulator of Shh canonical pathway.

We investigate the function of Gigaxonin during early embryogenesis in the zebrafish model. Early depletion of the E3 ligase modifies spinal cord architecture by triggering a broad alteration of motor neurons differentiation and an impairment of neuritic growth. Gigaxonin activity also reveals necessary to drive muscle organisation and somitogenesis. Interestingly, comparable phenotypes are described when we induce a pharmacological disruption of Shh signalling. Hence, we identify a strong interaction between Gigaxonin and key actors of Shh pathways (Shh it-self, the receptor Patched 1 and the effector Smoothened). Gigaxonin E3-Ligase activity controls both the turn-over and the subcellular localisation of these substrates. Altogether these regulations promote Shh signalling and subsequently control neuronal progenitor differentiation, neuritic growth and muscle organization. Through this multimodal action, Gigaxonin-E3 ligase turns out to be the foreman of Shh machinery.



Gigaxonin controls neuromuscular development in zebrafish embryos:
Gigaxonin-depleted embryos (Mo) exhibit an alteration of somites and muscular structures in comparison with control groups (wt and Mis) as revealed by phalloïdin staining (Left Panel). Concomitantly, Gigaxonin disruption impacts secondary motor neuron differentiation (Zn8 staining: yellow) and affects neuritic growth of primary motor neurons (Znp1 staining : green) (Right Panel).