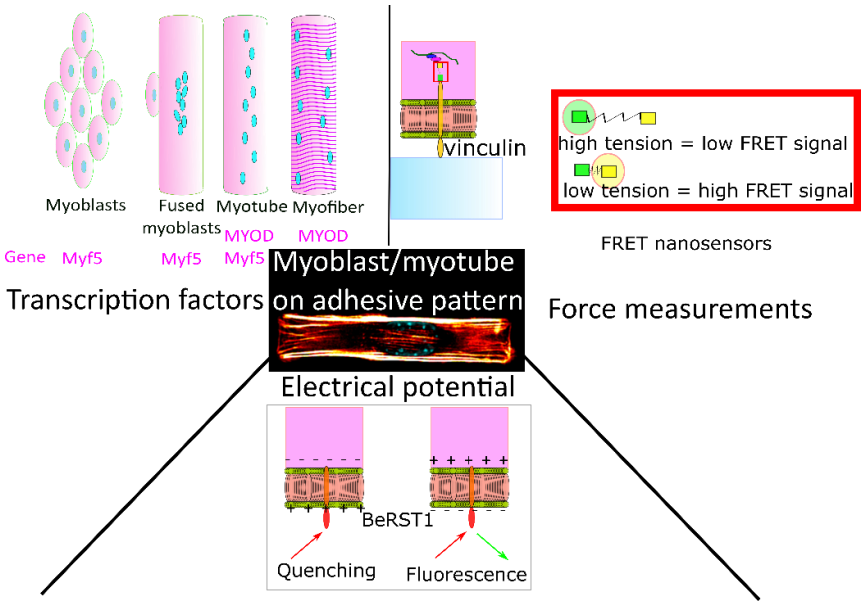
Muscle induced differentiation: interplay between mechanical and electrical effects

Supervisors: Sylvie HENON / Myriam REFFAY
E-mail: sylvie.henon@u-paris.fr / myriam.reffay@u-paris.fr
Phone number: 01 57 27 70 29
Web pages:
http://www.msc.univ-paris-diderot.fr/~henon
http://www.msc.univ-paris-diderot.fr/spip.php?rubrique274&lang=en
Laboratory name: Laboratoire Matière et Systèmes Complexes
Funding Thesis : YES (Labex WhoAmI ?)

Molecular and systems biology have provided unprecedented insights into the molecular and genetic basis of many cellular processes. However, the initiation of numerous metabolic, transcriptional or mechanical responses to environmental stimuli remain largely unexplained, pointing out the need to look at interplay between electrical coupling, mechanical stimuli and transcription factors.

Muscle cells are a reference model to look at the effects of electrical and mechanical stimuli at the single cell level but also in the production of collective behaviour. *In vivo*, differentiation of skeletal muscle is a highly controlled process, during which myoblasts, the precursor cells of muscles, first align and fuse to form multinucleated myotubes, that mature into myofibers. The process is well-known to be highly sensitive to electrical and mechanical stimulation. Myoblasts reveal as being influenced by physical properties such as applied mechanical stresses[(1)] or constraints on their shapes[(2)] in terms of proliferation, migration, nuclear positioning. In parallel, physiological cues may also determine their fate.

The project aims at quantifying the influence of mechanical and electrical stimuli in muscle differentiation process from myoblasts to myofibers.



The first part of the project will focus on 2D cultures of myoblasts, with shapes physically constrained thanks to the micro-patterning of adhesion proteins. The correlation between different cell differentiation cues will be followed thanks to (i) spatially-resolved

transcriptomics through RNA-FISH imaging [3] (dynamics or statics), (ii) force generation mapping using FRET nanosensors (iii) electrical conduction by imaging membrane potential sensors.

In a second part of the project, electrical stimulation will be applied to cultures of myoblasts, by implanting new optogenetics tools, using constructs containing rhodopsin channel activated by light. The differentiation process will be followed using the same read-outs as in the first part. The main challenge will be to enhance collective effects by junctions stimulation looking at the effect of depolarizing pre-orientated patches for example.

The project is supported by the Labex WhoAmI? and it is part of a broader network interested in the comprehension of muscle cell differentiation. It will benefit from collaboration with the team of Athanassia Sortiropoulos at Cochin Institute.

(1)L. Montel, Sotiropoulos A., Hénon S.PLoS One, 2019, Vol. 14, e0214385,.
(2)D. Pereira, et al.2020 Sci. Rep. Vol. 10, 20598.
(3) M. Dos Santos, et al.2020 Nat. Comm.,Vol. 11, 5102.