The fibro-inflammatory niche in idiopathic inflammatory myopathies – impact on myogenesis

PI: Bénédicte Chazaud - benedicte.chazaud@inserm.fr
Institut NeuroMyoGène - Unité Physiopathologie et Génétique du Neurone et du Muscle
UMR CNRS 5261 – INSERM U1315 - Université Claude Bernard Lyon 1

Context. Idiopathic inflammatory myopathies (IIM) are acquired dysimmune myopathies occurring at any stage of life. Muscles from IIM patients display chronic inflammatory infiltrates, notably macrophages and regenerating myofibers indicative of ongoing muscle regeneration process. Pejorative evolution identifies a fibro-fatty replacement of myofibers, that is clinically reflected by muscle weakness. Despite various treatments, patients rarely recover their initial muscle strength. This chronic muscle dysfunction remains unclear. Possible causes include a persistent inflammation-driven muscle damage, and/or defects in skeletal muscle regeneration, a process known to involve activation and myogenesis of muscle stem cells (MuSCs).

We previously demonstrated an impairment of the myogenic functions of MuSCs derived from IIM muscles rendering muscle repair inefficient. Our unpublished data show that the myogenesis defects is a hallmark of all IIM, indicating an intrinsic MuSCs alteration shared by all IIM.

Studies, particularly from our lab, have shown that MuSC microenvironment is crucial for an efficient muscle regeneration. MuSCs receive cues from their close environment composing the regenerative niche. This includes myofibers, vascular cells and mesenchymal stem cells called fibro-adipogenic precursors (FAPs). Moreover, immune cells (notably macrophages), which are rare resting in normal muscle, are also an important component of the MuSC regenerative niche.

Project hypothesis. We posit that the regenerative niche in IIM is altered and likely forms an inflammatory niche that may negatively impact on myogenesis and potentially sustains the alteration of muscle regeneration.

***Objectives*.** The project aims to identify the alteration of the regenerative niche in IIM muscle at the cellular and molecular levels and to evaluate how it impacts myogenesis.

We will first characterize the basal status of the cells of the niche (MuSCs, macrophages and FAPs) and their functional interplays to define the cellular niche in IIM, as compared with healthy cells.

Then, we will explore the molecular pathways modifications that drive the organization of the regenerative (inflammatory) niche with a cellular mapping of the regenerative niche *in vivo* as well as *in vitro* functional validation and *in situ* validation. The project will uses human cells, a very rare material, obtained through a close collaboration with the hospital.

***Techniques*.** Human cell culture and coculture, cell biology assays, molecular biology, immunofluorescence, microscopy, ELISA, multiplex assays, scRNAseq, immunohistology

***Expected outcome*.** The results of the present project will identify the cellular and molecular components of the regenerative niche in IIM, potentially defining an inflammatory niche which is detrimental for myogenesis and promoting fibrosis, explaining the failure of myofiber regeneration and the sustained muscle weakness in IIM patients.

Originality. The concept of the regenerative niche in skeletal muscle is quite recent and the host lab has been part of its establishment. Most studies are done in artificial contexts in the mouse. Using the unique opportunity to get IIM patient muscle derived MuSCs and histological samples, we will be able to bring this concept in human, and in a pathological context, beside the (usual) immune view of these auto-immune diseases.

References

IIMs

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