



PROJECT

Supervisor:

Davide Gabellini

Title:

Understanding and treating muscle inflammation in FSHD muscular dystrophy

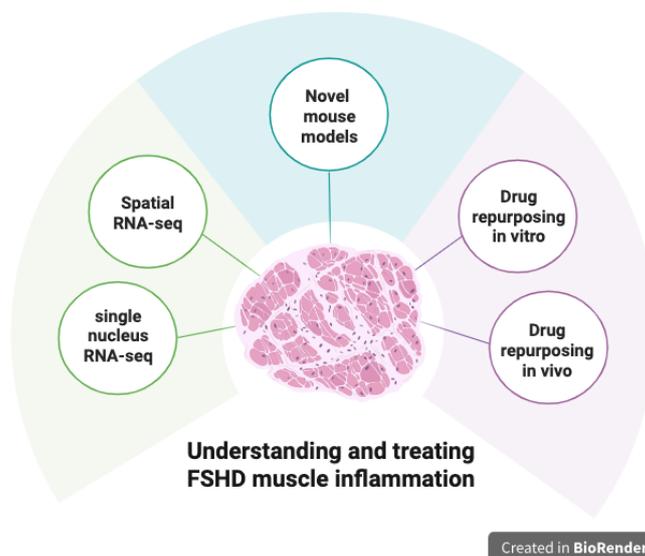
Curriculum:

Cell and Molecular Biology

Link to the personal page of the University or relevant hospital site website:

<https://research.hsr.it/en/divisions/genetics-and-cell-biology/gene-expression-regulation.html>

Description of the Project (max 3,000 characters including spaces)



Background/gap of knowledge

FSHD is a worldwide prevalent myopathy. The disease is caused by aberrant muscle expression of the DUX4 transcription factor, which is normally confined to early embryogenesis. The molecular mechanism through which DUX4 leads to FSHD is poorly known and no treatment exists.

Muscle inflammation is a prominent and early feature in FSHD that is associated to active disease and anticipates muscle loss and its fibro-fatty substitution, suggesting that inflammation is a primary event directly contributing to the disease, unlike other muscular dystrophies in which inflammation is generally secondary to muscle wasting.

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The current research has largely overlooked the specific inflammatory processes in FSHD and, consequently, all the clinical trials testing anti-inflammatory drugs have not shown any effect on FSHD patients [reviewed in (1)]. This gap of knowledge is critical, as understanding the inflammatory mechanism in FSHD could lead to the development of targeted therapeutic interventions.

Skeletal muscle is a complex and heterogeneous tissue composed of several cell types beside the multinucleated myofibers. The cell types contributing to the onset and progression of inflammation in FSHD are poorly known.

Rationale and hypothesis

Our preliminary results indicate that DUX4 directly activates a novel pro-inflammatory pathway significantly contributing to muscle wasting in FSHD. Importantly, we found that this pathway can be targeted with clinically approved treatments.

We hypothesize that dissecting the cellular and molecular mechanism responsible for muscle inflammation in FSHD could provide effective therapeutic options.

Here, we propose to further clarify the newly identified inflammatory pathway to provide insights into the pathogenesis of FSHD, and test targeted therapeutic strategies aimed at mitigating inflammation to preserve muscle integrity.

Objectives and specific aims

Critical questions remain about the precise molecular mechanisms underpinning muscle inflammation in FSHD. Moreover, despite the availability of globally approved inhibitors that target this pathway, their potential therapeutic application in FSHD has never been explored. Addressing these gaps is essential for developing novel interventions to mitigate muscle degeneration and improve FSHD patient outcomes.

Our Specific Aims are to:

1. Molecularly and spatially characterize the altered cell types and their interaction in FSHD.

These studies will allow to map cell-type-specific drivers and clarify the mechanism of muscle inflammation and myofiber degeneration in FSHD.

2. Generate novel animal models of inflammatory myopathies.

Here, we will directly assess the myopathic role of candidate activation in myofibers.

3. Pre-clinically evaluate repurposed treatments.

Here, we will test safety and efficacy of clinically approved treatments in cellular and animal FSHD models.

Expected outcomes

This project will characterize the cellular and molecular mechanism underlying FSHD muscle inflammation, understand the crosstalk between the various cell types altered in the disease, and test a possible therapeutic approach to preserve muscle tissue.

Skills that the student should acquire (max. 600 characters including spaces):



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The project entails a broad range of approaches, including bulk, single nucleus and spatial transcriptomics, cell biology, flow cytometry, immunoassays and animal models of disease. The student will learn how to critically evaluate the literature, design experiments, discuss the obtained results and assess their biological relevance. Training will also concern how to present scientific results at scientific meetings and write manuscripts or funding applications.

References (max. 15)

1. Mocciaro E, Runfola V, Ghezzi P, Pannese M, Gabellini D. DUX4 Role in Normal Physiology and in FSHD Muscular Dystrophy. *Cells* [Internet]. *Cells*; 2021 [cited 2024 Nov 4];10. Available from: <https://pubmed.ncbi.nlm.nih.gov/34943834/>