PROJECT

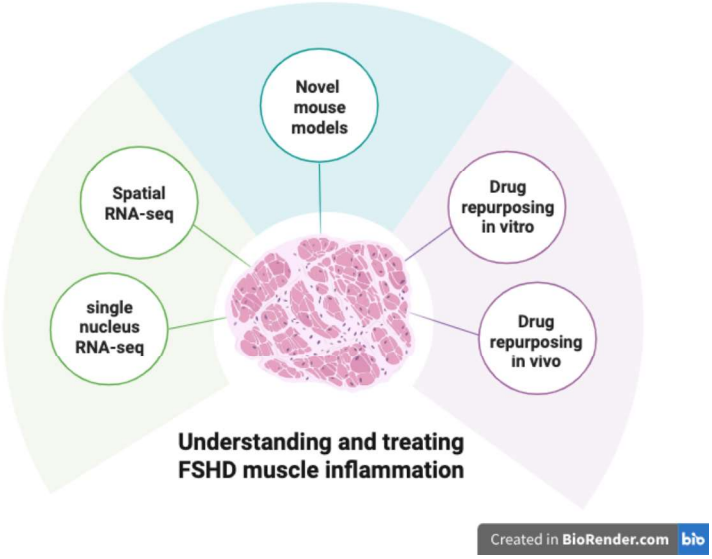
Supervisor: Davide Gabellini

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

Facioscapulohumeral muscular dystrophy (FSHD) one of the most prevalent neuromuscular disorders, is a chronic disease leading to significant lifetime morbidity for which there is no cure [reviewed in (1)].

FSHD is caused by aberrant expression of the transcription factor double homeobox 4 (DUX4), which is typically not expresses in healthy somatic cells. Although inflammation represents one of the most prominent hallmarks of the disease, the molecular mechanism underlaying this process is unknown, and effective strategies for intervention are yet to be determined.

Rationale and hypothesis

The molecular mechanism through which DUX4 leads to FSHD is poorly known. Aberrant DUX4 expression has been linked to the activation of multiple pathways [reviewed in (1)]. However, it remains unclear which of these pathways contributes to the disease, or whether targeting them offers any therapeutic benefit.

Despite the recognition that muscle inflammation is a prominent feature of FSHD, the underlying molecular mechanism remains poorly understood. The current research has largely overlooked the specific inflammatory processes in FSHD, particularly how inflammation may directly contribute to disease progression rather than serving merely as a byproduct of muscle degeneration, as observed in other muscular dystrophies. This is a critical gap, as understanding the inflammatory mechanism in FSHD could lead to the development of targeted therapeutic interventions.

Our preliminary data indicate that DUX4 drives muscle inflammation through the aberrant activation of repetitive elements and the production of interferon. Importantly, there are several clinically approved drugs targeting components of this pathway that could be used to the benefit of FSHD patients.

Objectives and specific aims

The main goal of this project is to dissect and target the molecular mechanism causing muscle inflammation in FSHD.

In this project, the student will investigate how IFN contributes to muscle degeneration in FSHD and evaluate the potential of repurposing existing clinically approved inhibitors as possible therapeutic agents for the benefit of FSHD patients.

The Specific Aims are:

1. To evaluate the role of myofiber IFN in FSHD.

The student will combine various animal models to directly assess requirement and sufficiency of myofibers IFN for muscle wasting in FSHD.

2. Pre-clinically evaluation of repurposed drugs.

The student will test safety and efficacy of clinically approved treatments in cellular and animal FSHD models.

All in all, this project will characterize the molecular mechanism underlying FSHD muscle inflammation and test a possible therapeutic approach to preserve muscle tissue.

Expected outcomes

FSHD has been the object of several unfocused clinical trials, which unfortunately have not produced a disease-modifying treatment.

Our strong preliminary results point to an original mechanism responsible for muscle inflammation in FSHD and open the possibility to repurpose clinically approved treatments.

This project will further dissect the pathway and use pre-clinical models to evaluate the safety and efficacy of drug repurposing to treat FSHD. This will provide proof of concept evaluation of possible anti-inflammatory therapeutics for FSHD. Thus, findings from this work have a strong potential for the development of novel therapeutic approaches to effectively treat FSHD.

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

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/