PROGETTO

Supervisore::	Davide Gabellini
Titolo/*Title*:	A possible epigenetic therapy for FSHD muscular dystrophy
Curriculum:	Cellular and Molecular Biology
Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:	https://research.hsr.it/en/divisions/genetics-and-cell-biology/gene-expression-regulation.html

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

FSHD is one of the most prevalent neuromuscular disorders. The disease is caused by aberrant re-activation of the embryonic transcription factor DUX4, which is toxic to skeletal muscle. Hence, blocking DUX4 expression with small molecule drugs is an attractive therapeutic avenue [1].
We recently identified the chromatin remodeling protein WDR5 as a key activator of DUX4 expression in FSHD. Importantly, WDR5 silencing or pharmacological inhibition rescues both cell viability and myogenic differentiation of FSHD muscle cells, and globally blocks the DUX4-induced gene expression, which is the major molecular signature in FSHD [3].
Collectively, our results support a pivotal role of WDR5 in the activation of DUX4 expression identifying a druggable pathway to an innovative therapeutic approach for FSHD.

Rationale and hypothesis

While our published results indicate that WDR5 is a key activator of DUX4 expression, long-term WDR5 inhibition could lead to toxicity. Indeed, WDR5 is involved in multiple gene regulatory complexes controlling a variety of key cellular activities. Hence, its targeting could lead to unwanted side effects. To identify a safer target, we performed a focused genetic screening to determine if a specific WDR5-containing complex is required for DUX4 expression. Through this work, we found a novel factor whose genetic or pharmacological targeting recapitulates WDR5 targeting effects in primary FSHD muscle cells.

Objectives and specific aims

Based on our results, we hypothesize that targeting the novel factor would protect from DUX4-induced toxicity with minimal side effects. Understanding safety and efficacy of targeting the novel factor will clarify the molecular pathogenesis and bring us closer to a rational treatment to block muscle degeneration in FSHD.

We propose the following Specific Aims:

1. Elucidate the role of the novel factor in controlling DUX4 expression. The student will characterize the mechanism though which the novel factor is recruited to the FSHD locus and its role in the regulation of DUX4 expression as a way to further support the relevance of targeting it for therapeutic purposes.
2. In vitro safety and efficacy studies. The student will perform dose and time escalation pharmacological inhibition studies in muscle cells from multiple FSHD patients and healthy controls. Expression of DUX4 and its targets, as well as evaluation of epigenetic features will be used as molecular efficacy and safety readouts. Cell growth, apoptosis, and myogenic differentiation will be used as functional efficacy and safety readouts.
3. In vivo safety and efficacy studies. The student will test pharmacological inhibition in vivo using a humanized animal model of FSHD and its relative control. Total body composition, tissue histology, serological, gene expression and functional studies will be used as safety and efficacy readouts.

Expected outcomes

Collectively, these studies aim at providing proof of principle supporting the relevance of the novel factor for DUX4 regulation in FSHD, while establishing the best drug modalities to reach significant molecular and functional efficacy with minimal side effects.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

The project entails a broad range of approaches, including gene expression profiling, next generation sequencing, 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.

Bibliografia (max. 15)

1. Mocciaro, E., Runfola, V., Ghezzi, P., Pannese, M. & Gabellini, D. DUX4 Role in Normal Physiology and in FSHD Muscular Dystrophy. Cells 10, (2021).
2. Mocciaro, E. et al. WDR5 is required for DUX4 expression and its pathological effects in FSHD muscular dystrophy. Nucleic Acids Res 51, 5144–5161 (2023).