PROGETTO

Supervisore::	Davide Gabellini
Titolo/*Title*:	Characterization of DUX4-r leukemogenic mechanism
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

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer and the major cause of cancer-related death among children and young adults. Structural chromosomal rearrangements and molecular aberrations identify distinct ALL subtypes. Characterization of the leukemic pathways associated to specific ALL drivers may help developing tailored therapeutic strategies with more effective treatment and reduced toxicity [1,2].
In 10% of ALL patients (14% in children [3]), the disease is caused by translocations of double homeobox 4 (DUX4), a transcription factor whose expression and activity is normally confined to early embryonic stages [4], producing the oncogenic version rearranged DUX4 (DUX4-r) [5].
Until recently, the molecular mechanism through which DUX4-r causes ALL was ill known strongly impairing the possibility to develop tailored therapeutic interventions.
We generated cellular and animal models of the disease, and used genetic and pharmacological perturbations in combination with several "Omics" and functional approaches to identify direct DUX4-r targets and characterize DUX4-r leukemogenic activity. Altogether, our recently published results [6] clarify DUX4-r mechanism of action and identify relevant disease pathways can be targeted pharmacologically.

Rationale and hypothesis

Treatment toxicities combined with regimens that span years mean that cure of leukemia is a life-altering experience for those who survive. Moreover, non-responding/relapsing patients face a dismal prognosis.
There is currently no targeted therapy for DUX4-r+ leukemia.
We found that DUX4-r directly activates the expression of grow factors, receptors and cell-adhesion molecules mediating the ability of DUX4-r+ cells to migrate and adhere to bone marrow stromal cells, and stimulate cell proliferation [6]. Intriguingly, among direct DUX4-r targets are novel isoforms of important cancer stem cell markers selectively expressed by DUX4-r positive cells. These molecules could minimally be used as diagnostic/prognostic DUX4-r markers, but could also be targeted for therapeutic purposes.

Objectives and specific aims

The goal of the project is to test the relevance of direct DUX4-r targets for the leukemia caused by this oncogene.
The project is composed of the following Specific Aims:
1. A focused CRISPR-based screen to identify direct DUX4-r targets responsible for the distinctive cell adhesion/proliferation activity driven by this oncogene.
2. A focused antibody-based screen to identify direct DUX4-r targets expressed exclusively on the surface of DUX4-r+ leukemia cells.

Expected outcomes

The project will identify direct DUX4-r targets required for leukemia cell adhesion and proliferation that could be targeted for therapeutic purposes, or that could be used as disease biomarkers or to deliver therapeutics selectively to DUX4-r+ leukemia cells.

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

The project entails a broad range of approaches, including CRISPR-based knockout, biochemistry, 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. Hunger, S. P. & Mullighan, C. G. Redefining ALL classification: toward detecting high-risk ALL and implementing precision medicine. Blood 125, 3977–3988 (2018).
2. Inaba, H., Greaves, M. & Mullighan, C. G. Acute lymphoblastic leukaemia. The Lancet 381, 1943–1955 (2018).
3. Li, Z. et al. Distinct clinical characteristics of DUX4 and PAX5 altered childhood B - lymphoblastic leukemia VIVA-NUS Centre for Translational Research in Acute Leukaemia. Blood Adv. 5(23):5226-5238 (2021).
4. Hendrickson, P. G. et al. Conserved roles of mouse DUX and human DUX4 in activating cleavage-stage genes and MERVL/HERVL retrotransposons. Nat Genet 49, 925–934 (2017).
5. Mocciaro, E., Runfola, V., Ghezzi, P., Pannese, M. & Gabellini, D. DUX4 Role in Normal Physiology and in FSHD Muscular Dystrophy. Cells 10(12):3322 (2021).
6. Campolungo, D., Salomé, M., Biferali, B., Tascini, A. S. & Gabellini, D. DUX4-r exerts a neomorphic activity that depends on GTF2I in acute lymphoblastic leukemia. Sci Adv 9(37):eadi3771 (2023).