



RESEARCH TOPIC MECM12

A longitudinal single-cell multi-omic approach to define the mechanisms of disease progression in patients with TP53-mutated MDS MECM standard

Research Area

Oncology

Laboratory name

Genomics of Hematological Malignances Lab

Research Supervisor

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Abstract

Myelodysplastic syndromes (MDS) are heterogeneous hematopoietic disorders characterized by recurrent genetic and cytogenetic abnormalities, bone marrow failure, and increased risk of transformation to Acute Myeloid Leukemia (AML). A subgroup of MDS patients harbour bi-allelic mutations in the TP53 gene, associated with poor outcome due to a heightened risk of leukemic progression and high relapse rates.

The aim of this project is to elucidate the clonal, transcriptional, and proteomic dynamics that drive disease progression, therapeutic relapse, and resistance in patients with TP53-mutated MDS, through a longitudinal (pre- vs post-evolution and pre- vs post-treatment) single-cell multi-omic approach. Single-cell technologies will include CITE-seq, for simultaneous transcriptomic and proteomic analysis; TARGET-seq, to identify TP53-mutated and non-mutated cells; single-cell proteomics. Multi-omics data will then be integrated. This study will lay the foundation for predicting novel biomarkers and developing effective therapeutic strategies for these high-risk patients.

Main technical approaches

Experience in NGS techniques, in manipulating primary cells, in cell purification.

Scientific references

1. Li H, Hu F, Gale RP, Sekeres MA, Liang Y. Myelodysplastic syndromes. *Nat Rev Dis Primers*. 2022;8(1):74. doi:10.1038/s41572-022-00402-5. PMID: 36396662.
2. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. *Leukemia*. 2014;28(2):241-247. doi:10.1038/leu.2013.336. Epub 2013 Nov 13. PMID: 24220272; PMCID: PMC3918868

3. Stengel A, Kern W, Haferlach T, et al. The impact of TP53 mutations and TP53 deletions on survival varies between AML, ALL, MDS and CLL: an analysis of 3307 cases. *Leukemia*. 2017;31(3):705-711. doi:10.1038/leu.2016.263. Epub 2016 Sep 29. PMID: 27680515.
4. Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat Med*. 2020;26(10):1549-1556. doi:10.1038/s41591-020-1008-z. Epub 2020 Aug 3. Erratum in: *Nat Med*. 2021;27(3):562. Erratum in: *Nat Med*. 2021;27(5):927. PMID: 32747829; PMCID: PMC8381722.
5. Zampini M, Riva E, Lanino L, et al. Characterization and Clinical Implications of p53 Dysfunction in Patients with Myelodysplastic Syndromes. *J Clin Oncol*. In press.

Type of contract

PhD scholarship of € 21.000 gross per year awarded by Humanitas University. This sum is exempt from IRPEF income tax according to the provisions of art. 4 of Law no. 476 of 13th August 1984, and is subject to social security contributions according to the provisions of art. 2, section 26 and subsequent sections, of Law no. 335 of 8th August 1995 and subsequent modifications.

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