Integrative Bulk and Single-Cell Multiomic Framework for Tracing (Sub)clonal Evolution in Multiple Myeloma

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Abstract

Background. Multiple myeloma, the second most common blood cancer, is characterized by the clonal proliferation of malignant plasma cells. Although recent immunotherapies have markedly improved outcomes in relapsed or refractory patients by redirecting immune responses toward tumor cells, primary and acquired resistance remain frequent within the first year. The underlying escape mechanisms are challenging to dissect due to the genetic and phenotypic heterogeneity of the disease.

Results. We developed an integrative framework combining whole-genome sequencing (WGS) with single-cell multiomic profiling (scMultiome: joint scRNA-seq and scATAC-seq) to enable multimodal characterization of tumor samples at subclonal resolution. We applied this approach to a large and diverse cohort of 38 patients (46 samples, including longitudinal samples from 7 patients) from the prospective MYRACLE study (ClinicalTrials.gov registration: NCT03807128). This cohort includes patients treated with emerging immunotherapies such as CAR-T cells and bispecific antibodies, many still at the trial stage.

Conclusions. Our integrative approach enables the identification of clonal and subclonal genetic and epigenetic events associated with disease progression and resistance. By reconstructing phylo(epi)genetic trajectories, we map the evolutionary paths accessible to multiple myeloma under therapeutic pressure, providing a scalable framework to study resistance mechanisms in a patient-specific and longitudinal manner.