Abstract: P1330

Title: CYTOREDUCTIVE CHEMOTHERAPY COULD ACCELERATE THE LOSS OF CLONAL DIVERSITY IN HEMATOPOIETIC STEM CELLS AND PROMOTES THE CONVERGENT EVOLUTION OF THERAPY-RELATED CLONAL HEMATOPOIESIS

Abstract Type: Poster Presentation

Session Title: Hematopoiesis, stem cells and microenvironment

Background:

Approximately 20,000 to 200,000 hematopoietic stem cells (HSCs) contribute to adult human hematopoiesis (Lee-Six et al. Nature 2018). HSCs lose clonal diversity with age, which is partly driven by the expansion of HSCs acquiring driver mutations (i.e., clonal hematopoiesis [CH]) (Mitchell et al. Nature 2022). HSCs are also subject to various types of external stressors such as chemotherapy. How the external stressors shape HSC clonality and dynamics remains unknown.

Aims:

To understand the influence of cancer chemotherapy on clonality and dynamics of hematopoietic stem and progenitor cells (HSPCs), we performed whole genome sequencing of 1,120 single-HSPC derived colonies from 10 patients with multiple myeloma (ages 46-65). Using shared and unique somatic mutations in these colonies, we reconstructed phylogenetic trees of the HSPCs to infer the evolutionary trajectories of these clones or their malignant clones in the samples of secondary myeloid malignancies.

Methods:

We generated methocult colonies from GCSF mobilized peripheral blood stem cells (PBSCs) collected at the time of autologous stem cell transplant (ASCT, median 86 colonies per PBSCs). Previous chemotherapy exposure included a melphalan-based (MEL) regimen in 2 patients, a cyclophosphamide-based (CY) regimen in 3 patients, and lenalidomide (LEN) and/or bortezomib (BTZ)-based regimens in 5 patients.

Results:

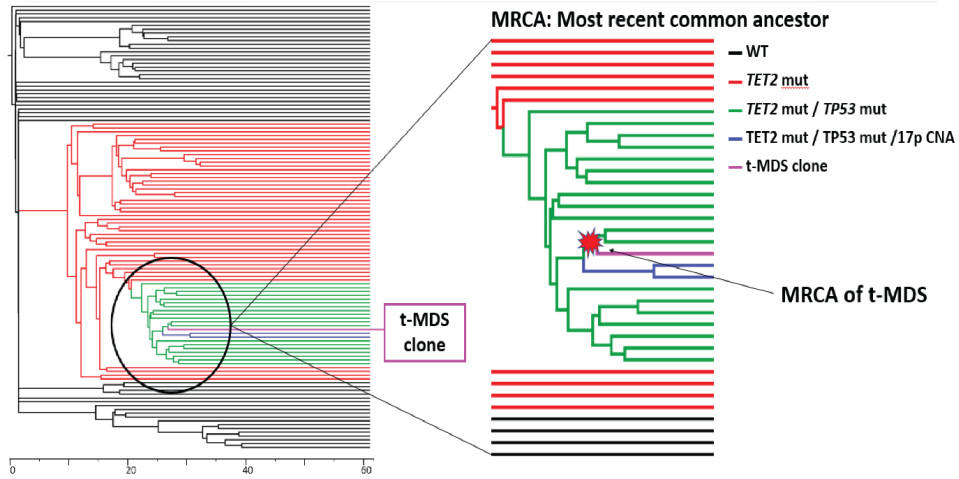
Despite the history of chemotherapy treatment, the number of somatic mutations in treated-HSPCs was comparable to that of age-matched HSPCs from normal individuals (Mitchell et al. Nature 2022), except in two patients with MEL treatment exhibiting significantly increased numbers of somatic mutations (median 2,339 vs. 1,146 somatic mutations per cell, $P < 0.001$). The excess mutations observed in MEL-treated HSPCs were consistent with the MEL-related mutation signature, SBS-MM1. None of the other patients' HPSCs showed treatment-related signatures.

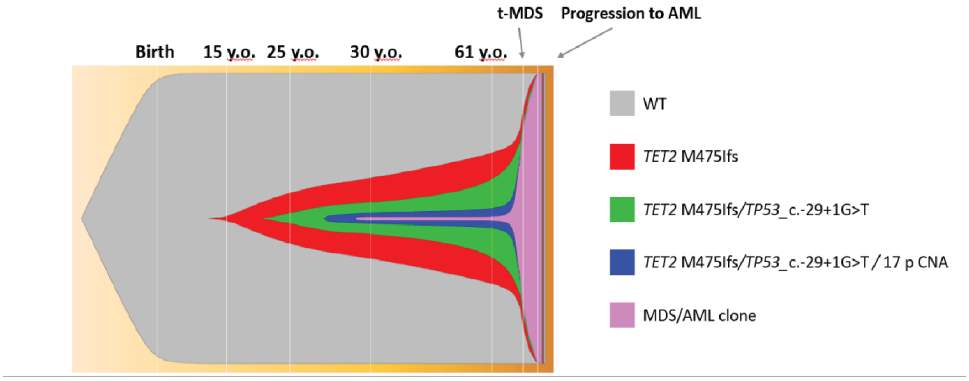
Overall, we observed decreased clonal diversity of HSPCs in the current cohort compared to age-matched normal individuals (Mitchell et al. Nature 2022). The clonality of treated-HSPCs resembled that of individuals with advanced age (age>75 years) in normal individuals. Low clonal diversity was particularly evident in MEL and CY-treated patients, whereas HSPCs treated with LEN and BTZ showed relatively preserved clonal diversity.

TP53 and *PPM1D* mutations were the most frequent driver mutations representing the clades of phylogenies. We observed multiple clades in the same patients having different mutations in the same genes (*TP53* and *PPM1D*), which is consistent with the convergent evolution, the findings suggestive of strong selective pressure from chemotherapy.

We also developed mathematical models simulating the population dynamics of HSCs with or without chemotherapy. These models showed that the loss of clonal diversity is accelerated by the administration of cytotoxic chemotherapy.

Combining somatic mutations identified in clonal hematopoietic and secondary myeloid malignancies, we have traced the evolutionary trajectory of malignant clones from the time of conception to their diagnosis. These can be represented by multi-step processes of driver mutations and acquisition of copy number alterations.





Summary/Conclusion:

Our results suggest that cytotoxic chemotherapy accelerates the loss of clonal diversity in HSPCs and promotes convergent evolution of clonal hematopoiesis driven by the mutations in DNA damaging pathway genes (TP53 and PPM1D), which likely forms the basis of therapy-related toxicities in hematopoiesis. However, the impact of cancer chemotherapy differs between drugs, and more studies are needed to systematically evaluate the differential effect of chemotherapies.

Keywords: Somatic mutation, Age related clonal hematopoiesis, Clonal hematopoiesis of indeterminate potential, Acute myeloid leukemia