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POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Identification of Therapy-Induced Clonal Evolution and Resistance Pathways in MRD Clones in Multiple Myeloma through Single-Cell Sequencing

Jian Cui[1], *Xiaoyun Li*[2], *Shuhui Deng, MD*[3], *Lugui Qiu*[4], *Xin Gao*[5], *Gang An*[6]

[1] Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Science & Peking Union Medical College, TIANJIN, CHN
[2] State Key Laboratory of Experimental Hematology, National Clinical Research Cent, Tianjin, CHN
[3] State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical Colleg, Tianjin, CHN
[4] State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology& Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China
[5] Institute of Hematology, Chinese Academy of Medical Sciences, Tianjin, CHN
[6] State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences&Peking Union Medical College, Tianjin, China

Introduction In multiple myeloma (MM), the leading cause of disease progression, exhibits intratumoral heterogeneity that enables adaptability, limits therapeutic success, and remains incompletely understood. Previous studies have confirmed that clonal evolution frequently occurs at disease follow-up, and the patterns of clonal evolution between diagnosis and relapse correlates with patient outcomes. However, it remains unclear whether clonal evolution occurs as early as after induction therapy. Additionally, the mechanisms of malignant plasma cells (PCs) resistance after induction therapy have only been partly resolved. Here, we use single-cell RNA sequencing (scRNA-seq) to identify the clonal architecture at diagnosis and after induction therapy, and elucidate the resistance pathways occurs early after upfront therapy. Methods In this study, we analyzed single-cell RNA sequencing from 19 patients with newly diagnosed MM (NDMM), paired bone marrow (BM) samples after 2-4 cycles of proteasome inhibitor (PI) plus immunomodulatory drugs (IMiDS)-based induction therapy were collected and underwent scRNA-seq. By tracing transcriptional and cytogenetic PCs clones over time and performing differential expression analysis, we defined different patterns of clonal evolution and identified potential resistant pathways. Results In our cohort, 12 patients were identified with more than 30 PCs in the BM samples sequenced after induction therapy. Among them, our analysis of the transcriptional and cytogenetic clonal dynamics in MM patients identified three main trajectories: patients with sensitive PC clones or clone that responds to treatment with >90% of the malignant PCs replaced with seemingly health PCs (3/12 patients, 25%); in patients with a resistant clone that did not respond or only very partly responded to treatment, > 50% of the malignant PCs were found in the BM post-treatment (5/12 patients, 42%); and patients with clonal selection, indicating that the significant clone has been replaced by a small or undetectable clone at baseline (4/12 patients, 33%). For these four patients identified with clonal selection, one was observed with branching evolution, and the other three were observed with differential evolution. Transcriptional differences among sensitive clones, resistant clones, and selective clones were detected based on a pairwise comparison of the gene expressions. A large number of differentially expressed genes with reported MM resistant-related functions were observed in the resistant clones, including previously reported 1q-related genes such as CKS1B, HNRNPU, and H3F3A; cell cycle- and cell proliferation-related genes such as TUBA1B, STMN1, and HMGB2. For selective clones, an evident activation of the NF-kB signaling pathway was observed. Conclusions Together, our study confirms that clonal dynamics of the evolving PC clones may occur early after upfront therapy, and reveals that the acquisition of therapeutic resistant pathways is associated with early adaptation to treatment.

Disclosures No relevant conflicts of interest to declare.

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