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POSTER ABSTRACTS

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

CRIP1 Upregulated Along with chr1q-Gain Indicates Immune Dysregulation and Portends Poor Outcomes in Multiple Myeloma

Shanshan Zhang[1], Linjing Cai[2], Zhang Hanzhen[3], Yuqi Wang[4], Chen Huan, MBBS[5], Xiaolei Wei, MD[6], Qifa Liu, MD[7]

[1] Department of Hematology, Department of Hematology, Nanfang Hospital, Southern medical university, Guangzhou, China
[2] Department of Hematology, Nanfang Hospital, Guangzhou, China
[3] Department of Hematology, Nanfang Hospital, Southern Medical University, Guangdong, China
[4] Nanfang hospital, Guangzhou, China
[5] Southern Medical University, GuangZhou, China
[6] Department of Hematology, Nanfang Hospital of Southern Medical University, Guangzhou, China
[7] Nanfang Hospital, Southern Medical University, Guangzhou, China

Background: The gain of chromosome 1q (chr1q-gain), one of the frequently occurring copy number aberrations in multiple myeloma (MM), is associated with a poor prognosis. However, the specific high-risk genes involved and the underlying molecular mechanisms remain elusive.
Method: In this study, we gathered a comprehensive dataset comprising bulk transcriptome data from 1271 multiple myeloma (MM) patients, including 413 patients from the GSE4581 dataset and 858 patients from the MMRF dataset. Additionally, we acquired single-cell RNA sequencing data from various disease stages, which included 12 MM patients, 7 patients with monoclonal gammopathy of undetermined significance (MGUS), 4 patients with amyloidosis (AL), 6 patients with smoldering multiple myeloma (SMM), and 11 healthy control donors from GSE117156. Cox regression and Kaplan-Meier curves were employed to identify and validate significant candidates associated with adverse prognosis among the overexpressed genes in patients with chr1q-gain. Furthermore, the expression profiles of the candidates in malignant plasma cells from MM patients compared to plasma cells in healthy donors were evaluated at single cell resolution. Gene Set Enrichment Analysis (GSEA) was conducted to uncover the pathways enriched in high-CRIP1 groups. To better understand the immune infiltration in MM, we utilized CIBERSORTx to infer the immune cell composition.
Results: A total of 541 genes were found to be upregulated in multiple myeloma (MM) patients with chr1q-gain in the GSE4581 dataset, with a false discovery rate (FDR) of less than 0.05 and a log fold change (LogFC) greater than 0.5.We identified five genes (CRIP1, ANP32E, CKS1B, RBFA, TOP2A) associated with poor prognosis through univariate Cox and multivariate Cox regression analyses and successfully validated in MMRF dataset(n=858). Upon characterizing the expression of these candidate genes in malignant plasma cells at a single-cell resolution, we made an interesting observation: CRIP1 was uniquely expressed in multiple myeloma (MM) patients when compared to healthy donors, individuals with MGUS, SMM and AL patients. Moreover, the GSEA results showed significant enrichment of the "Anti-viral Mechanism by IFN-stimulated Genes" (Normalized Enrichment Score, NES=1.98, False Discovery Rate, FDR=0.017) and "Interferon Signaling" (NES=2.11, FDR<0.001) in CRIP1-low MM patients. These findings suggest that CRIP1 may play a role in the development of multiple myeloma by influencing the tumor immune microenvironment through the regulation of these pathways. Analysis of immune cell infiltration in MM showed the expression level of CRIP1 is negatively correlated with CD4 naïve T cells (R=-0.24, P<0.001) and positively correlated with Monocytes (R=0.19, P<0.001). Tumors with high CRIP1 expression showed increased infiltration of CD8 T cells, CD4 memory T cells, activated NK cells, M0 macrophages, and Eosinophils.
Conclusions: The study showed that CRIP1 upregulated along with chr1q-gain was highly expressed in MM patients compared to healthy individuals and associated with immune dysregulation. The patients with higher CRIP1 expression have poorer survival. CRIP1 could serve as a potential therapeutic target and prognostic biomarker in multiple myeloma.

Disclosures No relevant conflicts of interest to declare.

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