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

Identification and Validation of High-Risk Genes Contributing to Poor Prognosis in Multiple Myeloma Patients with chr1q Gain/Amplification

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The gain/amplification of 1q21 (1q gain/amp) is a common cytogenetic abnormality (CA) in multiple myeloma (MM) and implies poor outcome. Despite the dysregulation of numerous genes located in chromosome 1q due to gain/amplification, the pivotal genes influencing the prognosis of multiple myeloma remain undefined.

Gene expression matrices and clinical data of multiple myeloma (MM) patients were acquired from publicly available databases, including the Gene Expression Omnibus (GEO) and CoMMpass. A comparative analysis was performed between MM patients with and without 1q gain/amplification to identify genes that exhibited differential expression due to this genetic alteration. The Least Absolute Shrinkage and Selection Operator (LASSO) technique and multivariate Cox regression analysis were employed to select potential candidate genes strongly associated with an unfavorable prognosis in MM patients. The overall survival of MM patients was assessed using the Kaplan-Meier method, and survival curves were compared using the log-rank test.

In the training set comprising 413 MM patients from the GSE4581 database, 93 individuals (22.5%) displayed 1q gain/amplification. Differential gene expression analysis identified 541 upregulated genes in patients with 1q gain/amp, with 187 of these genes located on chromosome 1q. Subsequently, the 187 upregulated genes on chromosome 1q underwent LASSO and multivariate Cox regression analysis. As a result, ten genes (ANP32E, ARPC5, CDC42BPA, CDKN2C, CHD1L, COAS, ISG20L2, NUF2, TAGLN2, UBE2T) were identified as significant contributors to poor overall survival in MM patients. Additional analysis utilizing single-cell RNA sequencing (scRNAseq) was conducted on plasma cells from 12 MM patients and ten healthy donors from the GSE117156 dataset. The findings unveiled elevated expression levels of CDKN2C, ISG20L2, NUF2 and UBE2T in malignant plasma cells compared to those from healthy donors. The prognostic significance of the four high-risk genes (CDKN2C, ISG20L2, NUF2 and UBE2T) was further confirmed in the CoMMpass database, which comprises 858 MM patients. Although patients with 1q gain/amp showed more inferior survival (P=0.012), without the four high-risk genes overexpression in patients with 1q gain/amp showed the similar survival with patients without 1q abnormal(P=0.74). Furthermore, in the CoMMpass database, we observed a notable pattern wherein patients with higher expression levels of the four high-risk genes (N=27) were more prevalent in the late stage, with 51% of them classified at stage III. Conversely, only 27% of patients with low expression levels of the four high-risk genes were at stage III. Notably, no significant differences were observed in terms of age, sex, or race between the two groups.

In summary, our findings demonstrate that overexpression of CDKN2C, ISG20L2, NUF2 and UBE2T contribute to the poor outcome in multiple myeloma patients with 1q gain/ amplification.

Disclosures No relevant conflicts of interest to declare.

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