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POSTER ABSTRACTS

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

CREB1 Promotes Immune Escape of Multiple Myeloma Cells By Inducing HLA-E

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Introduction: Multiple Myeloma (MM) is a disease of clonal plasma cells, which accumulate in the bone marrow (BM) and rely on the support of the microenvironment to survive. Immune escape is a common resistance mechanism employed by tumor cells to avoid cytotoxicity by effector immune cells. HLA-E, a non-classical major histocompatibility complex (MHC) class I molecule, inhibits the function of specific subtypes of Natural Killer (NK) and T cells, leading to tumor immune escape. HLA-E expression correlates with worse progression-free survival in newly diagnosed patients with MM. Therefore, we decided to better elucidate the function and regulation of HLA-E expression in MM.
Results: We observed that HLA-E mRNA expression increases in the transformation from normal plasma cells to MM. Since INF-gamma induces HLA-E in MM cells and CREB1 itself promotes the production of IFN-gamma, we hypothesize that CREB1 could regulate HLA-E expression in MM. We first analyzed RNA-sequencing data from patients with MM in the CoMMpass database: gene set enrichment analysis (GSEA) showed increased expression of several pathways related to interferon signaling in patients with high CREB1 expression. We then specifically looked at differences in HLA-E and we confirmed that patients with high CREB1 expression had statistically significant higher HLA-E levels compared with patients with low CREB1 expression. CHIP-sequencing assays in MM cell lines demonstrated that CREB1 can directly influence HLA-E expression by binding to HLA-E promoter. To further prove these data, we evaluated HLA-E levels in gain-of and loss-of function models of CREB1. We observed an increase of HLA-E levels by overexpression of wild type CREB1 and reduction of HLA-E levels by CREB1 silencing or pharmacological inhibition of CREB1 with 666-15 (CREBi).
We then investigated the relationship between CREB1 and STAT1. Indeed, IFN-gamma signals through the STAT1-JAK pathway. Interestingly, while treatment with IFN-gamma strongly induces HLA-E without affecting CREB1 levels or its function, CREBi + INF-gamma reduces HLA-E, STAT1, and phospho-STAT1 levels. Conversely, immunomodulatory drugs (lenalidomide-LEN and pomalidomide-POM) and HDAC inhibitor, Panobinostat, promote the phosphorylation of STAT1, resulting in the transcription of IFN-target genes, including HLA-E. The increase in HLA-E was then reverted by CREB1 inhibition. Since HLA-E impairs NK cell function, we treated MM cells in the presence of NK cells with CREBi alone or in combination with immunomodulatory drugs (IMiDs). Treatment with CREBi or CREBi + IMiDs potentiated the killing effects of NK cells. Animal studies are ongoing to confirm these data in vivo.
Conclusion: In conclusion, our study defines the role of CREB1 in modulating HLA-E expression; CREB1 inhibition improves NK cell-mediated cytotoxicity in MM, representing a novel strategy to tackle immune escape.

Disclosures Cottini: *The Dedham Group:* Consultancy.

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