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

Unveiling Novel Therapeutic Targets for CAR Therapy in Multiple Myeloma through Single-Cell RNA Sequencing

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Multiple Myeloma (MM) is a hematological malignancy characterized by the clonal proliferation of plasma cells. Among the different therapeutic options in this setting, chimeric antigen receptor (CAR) T cells recently showed unprecedent achievements in term of progression free survival. However, despite advancements in current therapies, the disease's heterogeneity remains a major challenge and all patients unavoidably relapse, rendering innovative approaches to identify precise therapeutic targets eagerly awaited. Along this line, the revolution of single-cell (sc) technologies brings new opportunities to identify precise therapeutic targets, including abundant and unique surface proteins for CAR therapy. In this study, by analyzing individual cancer cells at sc level, we aim to identify novel surface targets, facilitating the development of novel personalized cellular therapies as well as treatment sequences. To this end, we used samples collected from 9 publicly available single-cell RNA sequencing (scRNA-seq) datasets (GEO accession numbers: GSE176131, GSE189460, GSE223060, GSE210079, GSE145977, GSE124310, GSE161801, GSE163278, GSE161722) obtained from 156 patients affected by monoclonal gammopathies (19 monoclonal gammopathy of undetermined significance (MGUS), 10 smoldering multiple myeloma (SMM), 78 MM and 25 relapsed/refractory multiple myeloma (RRMM)) and 24 normal bone marrows (NBM), to conduct an unbiased search for genes showing specific expression in plasma cells (PCs), regardless of disease status. We found 15 genes showing differential expression in PCs (adj.pval<0.01 and logFC>1) and coding for surface proteins: TNFRSF17(BCMA), SDC1 (CD138), FCRL5 (GPRC5D), TNFRSF13B (TACI), CD38, SLAMF7 (CS1), CD59, FCGR2B, FGFR3, SLC44A1 (CTL1), CD320, FCRL2, IL15RA, INSR and SLAMF1. As expected, most of these molecules already represent critical therapeutic targets. After completing our initial analysis, we compared PCs transcriptomes from MM/RRMM patients with NBM, MGUS, and SMM samples. Among previously identified genes, CD320 only was significantly overexpressed in MM PCs. Next, we investigated associations between cytogenetic-related cell subclusters and previously identified surface markers. Interestingly, we found a significant association between the expression levels of TACI/CD59 and the overexpression of CCND2 and MAF, both associated with the presence of t(14:16). Next, we decided to focus on the first five genes (according to expression ranking) that do not currently have an active clinical development program in advanced phases, namely: TNFRSF13B, CD59, FCGR2B, SLC44A1, and CD320 (Fig. 1 A, values dichotomized based on their median) to uncover their (potential) impact/association with patient's outcome. In our analysis of different available expression profiling datasets (GSE4204, GSE2658, GSE57317, GSE4581, GSE4452, GSE9782, the CoMMpass study NCT01454297) involving around 2000 MM patients, we observed TNFRSF13B, CD59, and FCGR2B expression correlated with improved outcome while CD320 and SLC44A1 expression associated with worse outcome (Fig. 1 B).
In conclusion, we integrated results from both scRNAseq and bulk-RNAseq/microarray data to identify new targets genes to be used in the context of personalized medicine. Interestingly, CD320 emerges as a potential candidate biomarker useful for monitoring disease evolution and predicting worse outcomes. Additionally, this approach led us to identify a series of potential new targets for MM patients, depicting a new scenario where each patient could be "screened" to identify the best molecule to be targeted. While further investigation is necessary to assess off-target toxicity and confirm clinical relevance, our analyses significantly streamline the search for tumor markers with a method potentially applicable to different malignancies, bringing us closer to identifying the best candidates for effective CAR therapy.

Disclosures No relevant conflicts of interest to declare.

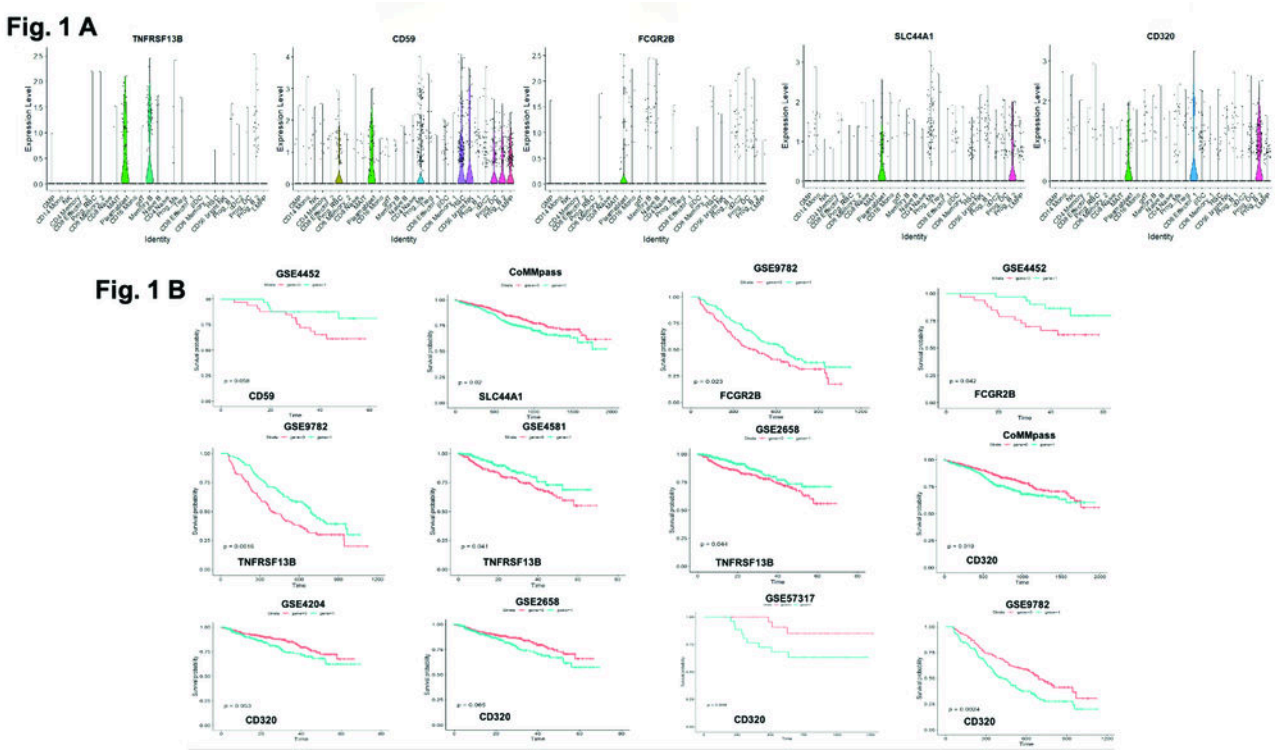

Figure 1

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