GENOMICS OF MULTIPLE MYELOMA INFLUENCES THE EXPRESSION OF CAR T-CELL TARGETS

Christina Yu*, Brian Walker, David Roosman, Kun Huang, Michel Sadelain, Fabiana Perna. Indiana University School of Medicine, Ohio State University, Indianapolis, IN, USA; Indiana University School of Medicine, Indianapolis, IN, USA; Indiana University School of Medicine and Regenstrief Institute, Indianapolis, IN, USA; Memorial Sloan Kettering Cancer Center, New York, NY, USA

Background Multiple Myeloma (MM) is an incurable disease, with a particularly poor prognosis for patients with refractory/relapsed MM or high-risk cytogenetics. Chimeric Antigen Receptor (CAR) T-cell therapy targeting BCMA can induce deep responses in highly pretreated RRMM; however, remissions are not sustained, and the majority of patients eventually relapse. We hypothesized that genomic determinants of MM play a role in dictating the expression of surface targets that can be of use for immune targeting.

Methods We analyzed the gene expression of 24 immunotherapeutic targets in a combined dataset of 1900 MM patients from three independent expression datasets obtained from the Multiple Myeloma Research Foundation CoMMpass study and Gene Expression Omnibus. Given that CAR T-cell therapy may be especially important for patients with high-risk myeloma, we defined the expression of each target in high-risk MM patients by stratifying patients based on several genomic features impacting prognosis. Additionally, we conducted a gene co-expression network analysis and identified 30 gene modules highly correlated with 16 cell surface targets from our panel, further suggesting that genetic determinants of MM may shape a targetable cell surfaceome. In order to determine whether targeting any of these candidate antigens might cause major toxicity to normal cells, we utilized several repositories providing protein data to annotate their expression in several normal cell types.

Results We determined that a number of genomic factors could stratify the 24 targets into three general groups: 1) targets that show consistent overexpression in high-risk patients: IGF1R, ITG87, GPRC5D, and CD70, and are thus suitable for most high-risk patients; 2) targets that are down-regulated in patients with high-risk genomic features: CD200, CD19, CD40, CD1D, and IGKC, perhaps playing a role in cancer immune escape; and 3) targets associated with one specific genetic abnormality, i.e. t(4;14): FUT3, SLAMF7, CD56, CD138, and BCMA, thus of use for precision CAR therapy in this high-risk patient subset.

Conclusions Our work provides a means of target selection for precision CAR therapy, by considering both patient genomic backgrounds and cancer cell surface profiles. Furthermore, our results provide a roadmap for immunotherapy of MM by unbiasedly comparing the expression of top MM cell surface targets in patient data and normal cells and suggest that the genetic landscape of MM may predict the expression of specific targets for precision immunotherapy. The quest for novel MM targets for immunotherapies remains open, and CAR target discovery driven by specific genetic events remains an active area of investigation.

REFERENCE

IN VIVO LOCALIZATION OF GENETICALLY ENGINEERED NATURAL KILLER CELLS AGAINST GLIOBLASTOMA USING PET IMAGING

Yeohhee Yun*, Jiao Wang, Karen Pollok, Tony Sinn, Randy Brutkiewicz, Sandro Matovecic, Michael Veronesi, Indiana University School of Medicine, Indianapolis, IN, USA; Purdue University, West Lafayette, IN, USA

Background Glioblastoma (GBM) is a deadly brain malignancy with a dismal prognosis. While immunotherapy holds great promise for GBM treatment, most have failed due to a suppressive tumor microenvironment (TME). Antigen heterogeneity and adenosine signaling are two immunosuppressive mechanisms in GBM. The CD73-adenosine axis plays a multifaceted role in GBM pathogenesis and drives the dysfunction of NK cells in GBM TME.1,3 Our NKG2D-chimeric antigen receptor (CAR)-natural killer (NK) cells have shown anti-tumor activity when combined with CD73 blockade in vivo.2 To further extend the potency of these cells against GBM and address antigen heterogeneity in GBM, we combined the local blockade of CD73 with multi-antigen-targeting engineered NK cells. In order to improve treatment assessment, PET/MR imaging was employed to enable detailed, non-invasive assessment of tumor progression. Imaging assessment of adoptively-transferred CAR-NK cells was also developed to determine the fate of NK cell delivery to the tumor site over time.

Methods We generated multifunctional engineered NK (E-NK) cells that express an anti-CD73 scFv, which is cleavable by GBM-associated proteases, an NKG2D-CAR, as well as a GD2