(PF720) TARGETING GLUTAMINE METABOLISM AS A NEW STRATEGY TO IMPROVE ANTI-BCMA T CELL ENGAGER ACTIVITY IN MYELOMA CELLS.

Topic: 13. Myeloma and other monoclonal gammopathies - Biology & translational research

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Background

Multiple myeloma (MM) is an hematological malignancy characterized by the high tendency to relapse and to develop drug resistance. The introduction of novel immunotherapeutic treatments, such as CAR-T cells and T cell engagers (TCE) improves the response rate of relapsed MM patients, but the presence of T cell exhaustion and the loose of surface antigens in MM cells may lead to the lack of response to immunotherapy. Growing evidence indicate that MM cells are highly glutamine (Gln)-dependent depleting this nutrient within the bone marrow (BM), creating a metabolic competition that drives immune cells toward alternative substrate. Interestingly it has been recently hypothesized that modulation of Gln metabolism may improve CAR-T cell activity in MM.

Aims

Based on these data, in this study we aim to explore how altered Gln metabolism impacts immunotherapy response to Elranatamab an anti-BCMA/CD3 TCE. We hypothesized that targeting Gln metabolism may increase MM susceptibility to T cell-mediated cytotoxicity while maintaining T cell effector function.

Methods

We investigated the effects of Gln restriction on pharmacological modulation of elranatamab activity. Firstly, BCMA expression was assessed in human myeloma cell lines (HMCLs) and $CD138^+$ PCs from 29 MM patients, by flow cytometry analysis. Cytotoxicity and T cell activation (CD69, CD25) were assessed both in co-cultures of $BCMA^+$ HMCLs with healthy donor T cells and in BM mononuclear cells (MNCs) from MM patients. Gln restriction was achieved by culturing HMCLs and BM MNCs in media containing 0.5 mM and 0.2 mM Gln, respectively, for 48 and 72 hours. GLS inhibition was tested using the glutaminase inhibitor CB-839. Single-cell RNA-seq analysis on MM patients bone biopsies and western blotting of purified T cells were also performed.

Results

We found that elranatamab induced strong anti-HMCLs cytotoxicity and robust T-cell activation, which were preserved under Gln restriction; moreover, combined treatment with elranatamab and CB-839 further enhanced anti-MM cytotoxicity without affecting T-cell activation. Single-cell RNA-seq analysis confirmed that primary MM exhibit high baseline expression of GLS and SLC1A5 along with ASNS and GFPT1, consistent with a strong Gln dependence. Both $CD4^+$ and $CD8^+$ T cells expressed GLS but displayed low expression of ASNS and GFPT1.
In BM MNCs from MM patients, Gln restriction lowered the median EC_{50} of elranatamab and maintained T-cell activation, suggesting MM selective sensitization, while co-treatment with CB-839 synergistically increased cytotoxicity without impairing T-cell activation profile. Lastly, T cells exposed to the combination displayed increased expression of enzymes involved in alternative Gln-utilization pathways (ASNS and O-GlcNAc).

Summary/Conclusion

Overall, these data suggest a rationale to integrate targeting Gln metabolisms with the use of BCMA/CD3 TCE as a novel strategy to overcome metabolic immunosuppression and enhance immunotherapeutic responses in MM patients.