Background Immunotherapy has emerged as a promising approach for cancer treatment, and natural killer (NK) cells play a critical role in immune surveillance against tumor cells. However, tumors employ various immune evasion mechanisms, including the interaction between T-cell immunoglobulin and mucin domain 3 (TIM-3) and its ligand, galectin-9, which suppresses NK cell function. In this study, we investigated the potential of targeting TIM-3 to enhance NK cell-mediated killing and infiltration into GBM.

Methods We developed a 3D spheroid GBM tumor model as a mimic of the GBM tumor microenvironment to study NK cell interaction and infiltration into this tumor. Patient-derived GBM43 cells were used to generate 3D spheroids. NK cells were isolated from healthy donor peripheral blood and introduced into the GBM spheroid system. The killing ability of NK cells was assessed by measuring lactate dehydrogenase (LDH) release and interferon-gamma (IFN-γ) production using enzyme-linked immunosorbent assay (ELISA). The infiltration of NK cells into the spheroids was evaluated using a confocal fluorescence microscope.

Results Our results demonstrated that NK cells exhibited decreased killing ability against GBM spheroids compared to monolayer cultures, indicating the impact of the 3D tumor environment on immune cell function. However, upon treatment with a TIM-3 inhibitor, the killing capacity of NK cells was significantly restored. The LDH release and IFN-γ production levels were significantly higher in the TIM-3 inhibitor-treated group compared to the control group. Moreover, confocal microscopy analysis revealed enhanced infiltration of NK cells into the GBM spheroids following TIM-3 inhibition.

Conclusions This study provides evidence that inhibiting the TIM-3 pathway enhances NK cell-mediated killing and infiltration into 3D GBM spheroids. Inhibition of TIM-3 effectively restored the compromised killing ability of NK cells in the 3D tumor model. These findings highlight the importance of targeting the TIM-3 pathway to overcome immune evasion mechanisms employed by tumors and improve the efficacy of NK cell-based immunotherapy in the context of glioblastoma multiforme. Further investigation is warranted to evaluate the therapeutic potential of TIM-3 inhibition in preclinical and clinical settings for cancer treatment, with a focus on personalized approaches and combination therapies.

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