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Rapid expansion of TILs from patients with glioma and recognition of autologous tumor

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Background

Tumor-infiltrating T cells (TIL) may represent a viable source of T cells for the biological treatment of patients with tumors of the central nervous system. We established a rapid TIL expansion protocol for patients with glioblastoma, and tested the recognition of short-term expanded tumor autologous tumor cell lines defined by cytokine production from responding T cells.

Material and methods

Glioma tumor tissue was obtained from 15 patients with glioblastoma, tumor cell lines were established and TIL could be successfully expanded in 15/15 cases using a cytokine cocktail IL-2/IL-15/IL-21, OKT-3 and irradiated, allogeneic feeder cells. Intracellular Cytokine Staining (ICS) was used to detect antigen-specific immune responses. Autologous tumor cells or TAAs (NY-ESO-1, Survivin and EGFRvIII peptides) were co-cultured with TILs for 6 hours in the presence of Brefeldin A as well as in medium (negative control), or PMA +Ionomycin (positive control). CD3, CD4 and CD8 markers were combined with either IL-2, IL17, TNFalpha, IFNgamma production or 41-BB expression. VB family composition, exhaustion/activation as well as differentiation markers were tested by flow cytometry.

Results

15/15 TIL could be successfully expanded (up to 10e10 cells) using IL-2, IL-15 and IL-21. The majority of TIL exhibited a mixture of CD4+, CD8+, as well as CD3+ (TCRalpha/beta) CD4-CD8- T cells with an CD45RA-CCR7+ phenotype. TILs showed low frequencies of exhaustion markers, i.e. PD-1 (in CD8+ TILs: median: 3.03%, mean: 3.40%, in CD4+ TILs: median: 2.10%, mean: 7.73%), TIM-3 (in CD8+ TILs: median: 0.30%, mean: 1.21%, in CD4+ TILs: median: 0.70%, mean: 1.00%), CTLA-4 (in CD8+ TILs: median: 1.47%, mean: 1.73%, in CD4+ TILs: median: 0.04%, mean: 0.07%) and LAG-3 (in CD8+ TILs: median: 8.87%, mean: 30.00%, in CD4+ TILs: median: 1.21%, mean: 1.25%). Some TIL cultures exhibited preferential usage of VB families (i.e up to 60% VB22 or VB1 in CD4+ or CD8+ TIL). TIL from individual patients exhibited NY-ESO-1 specificity up to 2% in CD4 and CD8+ T cells, yet up to 25% IFN and TNF production directed against autologous tumor cells, defined by ICS. Whole genome sequencing is currently performed in gliomas to subsequently test for subsequent TIL recognition.

Conclusion

TIL from glioma samples can be reliably and successfully expanded in IL-2/IL-15 and IL-21, they exhibit a Th1-cytokine production pattern and recognize autologous tumor cells ex vivo. Glioma - reactive TIL represent a viable source the cellular therapy for patients with glioblastoma and a Phase I safety trial is currently prepared at Karolinska.

Consent

Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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