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Generation of tumor-infiltrating lymphocytes from pancreatic cancer lesions for cellular therapy

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Purpose

The generation of T lymphocytes with specific reactivity against autologous tumor is a prerequisite for effective adoptive transfer therapies. Pancreatic cancer-specific lymphocyte cultures from tumor infiltrating lymphocytes (TILs) may represent a viable source of T cells for the biological therapy for patients with pancreatic cancer.

Methods

Pancreatic cancer tissue was obtained either by surgery or from biopsy specimens from 16 patients and cultured with cytokines (IL-2, IL-15and IL-21). TIL were expanded using OKT-3 and irradiated allogeneic peripheral blood mononuclear cells (PBMCs). TIL reactivity was gauged for recognition of molecularly defined tumor-associated antigens (TAAs, mesothelin, survivin and NY-ESO-1) by IFN-gamma production and intracellular cytokine production (ICS). TCR VB T cell populations were tested by a panel of TCR Vb specific antibodies, along with T cell differentiation and exhaustion markers by flow cytometry.

Results

TIL from 16/16 patients, up to 10e11 cells, could be successfully expanded using IL-2/15/21. 4 week TIL cultures showed up to 90% CD8+ T cells, yet 1/16 TIL cultures exhibited exclusively CD4+ TIL with a CD45RA-CCR7+ phenotype. 12 / 16 of TILs showed preferential expansion of TCR VB families, i.e. 99.3% in Vb13.2 in CD8+ TIL, 77% in VB1, 68.7% in VB22, 64% in VB14 for individual patients. Even biopsy specimens (about 10 mg), yielded at least 1.5 x10e9 CD8 TIL. ICS analysis showed a low frequency (up to 2.5%) of mesothelin, survivin or NY-ESO-1 reactive CD8+ TIL. TIL from a 1/16 patients showed up to 10% NY-ESO-1 specific IFNgamma and TNFalpha production in CD4+ and CD8+ T cells. Tumors from these patients are currently sequenced for mutations and subsequent testing for TIL recognition.

Conclusion

We have optimized methods for the robust and fast generation of TIL from pancreatic cancer lesions, including small biopsy specimens, using a cytokine cocktail of IL-2/IL-15 and IL-21. TIL showed a Th1-cytokine production pattern and a central memory phenotype. A Phase I clinical safety trial at Karolinska is currently prepared for IL-2/15/21-expanded TIL for the cellular therapy for patients with pancreatic cancer.

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