Ex vivo expanded telomerase-specific T cells are effective in an orthotopic mouse model for pancreatic adenocarcinoma

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ABSTRACT

Telomerase activity is over-expressed in nearly all pancreatic carcinomas, but not in chronic pancreatitis. Here, we investigated various protocols for expansion of telomerase-specific T cells for adoptive cell transfer and their use in a syngeneic pancreatic carcinoma mouse model. Telomerase-specific T cells were generated by stimulation of splenocytes from peptide-immunized donor mice with either interleukin (IL)-2, IL-15, artificial antigen-presenting cells, anti-signalling lymphocyte activation molecule (SLAM) microbeads or allogeneic dendritic cells in combination with a limited dilution assay. T cells were tested for antigen specificity in vitro and for anti-tumour activity in syngeneic mice with orthotopically implanted tumours pretreated with cyclophosphamide. The immune cells from recipients were immunophenotyped. During a period of 2 weeks, the expansion approach using IL-2 was very successful in generating a high number of telomerase-specific CD8+ T cells without losing their function after adoptive cell transfer. Significantly slower tumour growth rate and less metastasis were observed after adoptively transferring telomerase specific CD8+ T cells, expanded using IL-2. Further investigations showed that anti-tumour efficacy was associated with a significant shift from naive CD8+ T cells to CD8+ central memory T cells, as well as recruitment of a high number of dendritic cells. Remarkable amounts of telomerase-specific T cells were detectable in the tumour. Generation of telomerase-specific T cells is feasible, whereat IL-2-based protocols seemed to be most effective and efficient. Antigen-specific T cells showed significant cytotoxic activity in a syngeneic, orthotopic mouse model, whereas central memory T cells but not effector memory T cells appear to be of high importance.