

Abstract

Anti-FAP CAR modified T cells target the tumor stroma.

Redirected T cell therapy recently showed spectacular success in the treatment of leukemia in early phase trials; targeting solid cancer lesions, however, proved less efficacious demanding additional strategies. Cancer cells are embedded in a dense network of stroma, the predominant cell type of which are tumor-associated fibroblasts (TAFs). Fibroblast activation protein- α (FAP) is expressed by tumor-associated fibroblasts in over 90% of epithelial carcinomas but not by healthy tissue fibroblasts. We explored targeting of TAFs by engineering T cells with a chimeric antigen receptor (CAR) specific to FAP, a type-2 dipeptidyl peptidase expressed on TAFs. CAR modified T cells recognize and lyse activated FAP⁺ fibroblasts in a FAP-specific fashion. In established tumors with FAP-negative cancer cells, the tumor stroma cells express FAP as revealed by PCR and immunohistochemistry. Tumor formation by FAP-negative cancer cells of a variety of carcinomas is impaired in presence of anti-FAP CAR T cells independently of a particular cancer cell antigen. Cancer cell seeding in various organs upon i.v. application is reduced in presence of anti-FAP CAR T cells. Notably, no severe side effect was observed. Data point to a potential clinical application of the strategy, in particular in the situation of primary tumor removal with high incidence of relapse.