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EDITORIAL

Anti-CD137 monoclonal antibodies and adoptive T cell therapy: a perfect marriage?

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Abstract CD137(4-1BB) costimulation and adoptive T cell therapy strongly synergize in terms of achieving maximal efficacy against experimental cancers. These costimulatory biological functions of CD137 have been exploited by means of introducing the CD137 signaling domain in clinically successful chimeric antigen receptors and to more efficiently expand T cells in culture. In addition, immunomagnetic sorting of CD137-positive T cells among tumor-infiltrating lymphocytes selects for the fittest antitumor T lymphocytes for subsequent cultures. In mouse models, co-infusion of both agonist antibodies and T cells attains marked synergistic effects that result from more focused and intense cytolytic activity visualized under in vivo microscopy and from more efficient entrance of T cells into the tumor through the vasculature. These several levels of dynamic interaction between adoptive T cell therapy and CD137 offer much opportunity to raise the efficacy of current cancer immunotherapies.

Keywords CD137 (4-1BB) · Adoptive T cell transfer · CARTs · Combined immunotherapy

Abbreviations

CAR	Chimeric antigen receptor
CART	Chimeric antigen receptor T cell
CTL	Cytotoxic T lymphocyte
TIL	Tumor-infiltrating lymphocyte

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Immunotherapy of cancer is living through a revolutionary period prompted by the extraordinary efficacy results of antibodies blocking CTLA-4 or PD-1/PD-L1 against a variety of solid cancers [1, 2]. In parallel, durable clinical responses are achieved by adoptive T cell therapy against B cell lineage leukemias and lymphomas, using gene-transduced T lymphocytes to express chimeric antigen receptors recognizing the B cell marker CD19 [3–5]. Very likely, significant additional benefit of innovative immunotherapy will result from combinatorial approaches [1, 2], as recently reported by combining anti-PD1- and anti-CTLA-4-targeted therapy in a phase III clinical trial for metastatic melanoma patients [6] that was conducive to FDA approval. As yet clinically unexplored avenue, combining adoptive T cell therapy with immune-augmenting strategies could additionally increase the efficacy of immune control in solid tumors and improve outcome.

CD137 (4-1BB, tnfrsf9) is a surface receptor of the TNF receptor family that is expressed by activated but not resting T lymphocytes and NK cells [7]. Expression on T cells requires antigen recognition since it requires intense signaling through the antigen receptor complex. Therefore, only T cells that have been antigen-primed acquire the expression of CD137, the downstream signaling of which promotes T cell proliferation, memory differentiation, and effector functions and further prevents T cell apoptosis [8]. Under physiological circumstances, this receptor is ligated by CD137 ligand (4-1BB ligand), an agonist membrane molecule expressed by professional antigen-presenting cells, but also by some tumor cells. In order to exploit this pathway therapeutically, monoclonal antibodies which achieve much stronger, supraphysiological stimulation of CD137 signaling were designed to enhance costimulation of CD8 T lymphocytes and strongly improve the defense against syngeneic