Letter to the Editor

Anti-CD137 Cancer Immunotherapy Suppresses Tumor Growth—Letter

Bhushan Dharmadhikari, Qun Zeng, Meihui Wu, and Herbert Schwarz

We read with great interest the publication by Kang and colleagues (1). The authors describe that agonistic anti-CD137 (TNFRSF9, 4-1BB) antibodies enhance antitumor T-cell responses in murine xenograft models that is consistent with the findings of many other groups and that corresponds to the consensus in the field. In the same publication, the authors report that in CD137-deficient mice, growth of CT26 colon carcinoma and Renca renal carcinoma was significantly inhibited.

This is puzzling and in contrast to a multitude of findings that show the importance of CD137–CD137 ligand (CD137L) interactions for transplant rejection, pathogen clearance, and protection against malignant disease. In addition, the current report is also in contrast with an earlier one by some of the same authors who found an increased growth of B16F10 melanoma in CD137-deficient mice (2). The research community would benefit if the authors could provide an explanation for the contrasting growth patterns of different tumors in CD137-deficient mice.

Furthermore, the authors propose that “blockade of the CD137L signaling pathway may be used to promote therapy-induced immunosurveillance.” While CD137 forward signaling, that is, costimulation of T cells, is conserved between human and mouse, there is evidence that reverse CD137L signaling into monocyctic cells differs between the two species. Reverse CD137L signaling in murine monocytes induces cell activation and IL10 secretion but does not lead to a proinflammatory phenotype (3). However, in human monocytes and dendritic cells (DC), reverse CD137L signaling causes a proinflammatory cell activation. In monocytes, it induces the release of proinflammatory cytokines, prolonged survival, endomitosis, and migration. Furthermore, reverse CD137L signaling induces maturation of human immature DCs and even differentiation of peripheral human monocytes to inflammatory DCs that resemble inflammatory DCs isolated from a tumor ascites or the synovial fluid of a rheumatoid arthritis patient and that have an enhanced capability to induce antiviral T-cell responses (4).

This species difference may have its cause in the unusually low homology of 36% between human and murine CD137L, whereas for most other members of the TNF and TNF receptor families, the human–mouse homology is 60%–80% (5). We are therefore sceptical that data on reverse CD137L signaling obtained from murine cells or mice are translatable to the human system and would strongly caution against using CD137L blockade for human cancer immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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