Tumor-antigen ST4-dependent Activation of the CD137 Costimulatory Pathway by Bispecific ST4 x CD137 TRIDENT™ Molecules

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Abstract

Introduction

The therapeutic glycoprotein ST4 is expressed on the cell surface of multiple cancer cells as a sponge for soluble TGF-β. CD137 (4-1BB) is a costimulatory molecule expressed on activated T cells and NK cells. Enhanced tumor cell killing with bispecific CD137 (4-1BB) DART molecules was shown in HNSCC cancer cell lines in vitro with minimal bystander killing. ST4 expression on tumor cells was also shown to facilitate antigen presentation to CD8+ T cells in vitro and in vivo. We hypothesized that bispecific ST4 x CD137 TRIDENT molecules could be designed to enhance tumor cell killing mediated by both CD8+ and CD4+ T cells.

Methods

Bispecific ST4 x CD137 TRIDENT molecules were designed using a modular approach to target CD137 expression on activated T cells while potentially limiting non-specific T-cell activation. ST4-specific antibodies were prepared using an in vitro expression system with primary human or cynomolgus monkey T-cells. T cells were incubated with or without antigen-expressing tumor cells and supernatants collected after 48-hr incubation were subject to ELISA assay to determine IFN-γ levels.

Results

5T4 x CD137 TRIDENT molecules enhanced redirected T-cell killing of 5T4-positive tumor cells in vitro. The 5T4 x CD137 TRIDENT molecules increased redirected T-cell killing of 5T4+ tumor targets compared to B7-H3 x CD3 DART (a model system) and control TRIDENT molecules. In addition, 5T4 x CD137 TRIDENT molecules enhanced T-cell activation and proliferation with relative expansion of CD8 central/effector memory cells in B7-H3 x CD3 DART (as a model system) and 5T4 x CD137 TRIDENT-treated tumor cells. Enhanced tumor cell killing with bispecific ST4 x CD137 TRIDENT molecules was confirmed in an orthotopic breast cancer model.

Conclusions

Bispecific ST4 x CD137 TRIDENT molecules may offer an opportunity to maximize conditional CD137 costimulation with limited systemic toxicity. Further studies are warranted to establish the potential of ST4 x CD137 TRIDENT molecules in vivo.

References

1LA ST4 x CD137 TRIDENT molecule demonstrated enhanced T-cell activation in vitro with relative expansion of CD8+ T effector cells. In vivo, ST4 x CD137 TRIDENT molecules enhanced redirected T-cell killing of 5T4+ tumor targets compared to control TRIDENT molecules.

2In vivo, ST4 x CD137 TRIDENT molecules may offer an opportunity to maximize conditional CD137 costimulation with limited systemic toxicity.