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Combination immunotherapy with tumor targeting monoclonal antibodies and anti CD137

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Tumor targeting monoclonal antibody (mAb) therapy has changed the natural history of patients with B cell lymphomas, breast cancer and colorectal and head and neck cancers, respectively. Despite their promise, response rates are suboptimal at less than 25%, highlighting the need to enhance mAb activity. Natural killer (NK) cells are important effector cells mediating antibody dependent cell mediated cytotoxicity (ADCC), a primary antitumor mechanism of action of mAbs. Approaches that specifically augment NK cell function can thus complement and enhance mAb therapy. The co stimulatory molecule CD137 (4-1BB), a member of the tumor necrosis factor receptor super family is expressed following NK and memory T cell activation. We found that isolated human NK cells substantially increased expression of CD137 when exposed to tumor cells bound by their tumor targeting mAb, including rituximab coated CD20 expressing lymphoma, trastuzumab coated, HER2 expressing breast cancer and cetuximab coated, EGFR expressing head and neck and colorectal cancer cell lines. Furthermore, activation of CD137 with an agonistic mAb (anti CD137) enhanced NK cell degranulation and cytotoxicity. In multiple murine syngeneic and xenograft models, combined tumor targeting mAb and anti CD137 mAb administration was synergistic and led to complete tumor resolution and prolonged survival, which was dependent on the presence of NK cells. In patients receiving mAb therapy, the level of CD137 on circulating NK cells increased post mAb infusions. This sequential antibody strategy, combining a tumor targeting mAb with anti CD137 to activate the host innate immune system, may improve the therapeutic effects of tumor targeting mAbs and is now being investigated in clinical trials.

The therapeutic potential of Treg cells in preserving microvascular health in a mouse model of orthotopic tracheal transplantation

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Microvascular loss may be a root cause for chronic rejection in all solid organ transplants, which leads to the bronchiolitis obliterans syndrome (BOS), a fibrotic remodeling resulting in progressive narrowing of small airways. Previous research implicates T regulatory cell (Treg) as a potential mediator of microvascular repair. However, Treg has never been examined as an actual cause of graft hypoxia and ischemia during allograft rejection. We have reported the importance of functional microvasculature in the prevention of epithelial loss and fibrosis due to CD4+ T cells mediated rejection. The orthotopic tracheal transplant (OTT) model is ideal for studying the role of Treg mediated immune suppression in the rejection-associated airway hypoxia and ischemia implicated in chronic lung transplant rejection. In this study, we investigated that Treg mediated immune suppression ($CD4^+$ T cells) promotes microvascular reestablishment and thus affects the progress of chronic rejection. Balb/C→C57/Bl6 allografts were adoptively transfer with Tregs (1x10^6) I.V. at d0 and allografts were monitored from day-2 to da-28 for tissue pO_2, blood perfusion and functional microvasculature during acute rejection. Our data demonstrate that targeted immune suppression by Tregs significantly improves tissue pO_2, microvascular flow at day 10 post transplantation, followed by sharp rise in IL-10 and IL-5 gene expression compared to untreated WT controls. However, Tregs treatment in WT is able to significantly ($p<0.05$) delay acute (from d10 to d14) rejection alone but not able to prevent acute rejection. These findings conclude that protecting airway microvasculature with Treg therapy facilitates microvascular re-establishment and shortens the phase of hypoxia in allograft. These findings can be translated to adjunct therapy in combination with existing transplant therapies especially with low-dose rapamycin (promotes Treg expansion) to improve the efficacy of Treg therapy.