Dual Role for Galectin-3 in CD8 T cell Function

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ABSTRACT

Immunosuppression and reduced cytolytic function of tumor infiltrating lymphocytes are major obstacles to creating effective therapies for patients. Galectin-3 (Gal3), a lectin family member, is expressed in numerous cancers including breast and prostate. Moreover, it is expressed ubiquitously by prostate epithelia, macrophages, and activated lymphocytes. Endogenous Gal3 promotes alternative macrophage activation and limits TCR-mediated CD8 T cell activation, which limit antitumor immunity. However, the regulatory effects of Gal3 on inflammation and CD8 T cell function remain unknown. We hypothesized that Gal3 within the tumor microenvironment promotes tumor progression by negatively regulating the function of CD8 T cells. To test this, we first examined the effects of endogenous Gal3 deletion in CD8 T cells. In vivo, antigen-specific Gal3-/CD8 T cells exhibited decreased effector function (decreased proliferation, granzyme B, IFN-gamma, and IL-2) compared to wildtype controls. We also analyzed differential gene expression in antigen-specific Gal3-/ or Gal3+/CD8 T cells and found that granzyme B, CD25, KLRF-1, and Blimp-1 were reduced in Gal3-/CD8 T cells as compared to controls. In vitro studies demonstrated that antigen-specific Gal3+/CD8 T cells had a significant reduction in CD25 and OX40 expression. Interestingly, Gal3 inhibition in vivo augmented CD8 T cell expansion and CD2L2L expression, suggesting dual roles for Gal3 in CD8 T cell function. Future studies will examine Gal3 inhibition directly on CD8 T cell function and macrophage polarization within the tumor microenvironment and on tumor growth in prostate tumor-bearing mice.

BACKGROUND

Figure 1. Phenotype comparison of naive Galactin-3 deficient CD8 T cells vs. WT CD8 T cells by flow cytometry.

RESULTS

Figure 2. Galactin-3 deficient CD8 T cells exhibit reduced effector function following antigen stimulation in vivo.

Figure 3. Selected genes down-regulated in Galectin-3 deficient CD8 T cells

CONCLUSIONS

- Endogenous Gal3 deficiency decreased CD8 T cell proliferation and activation in response to antigen, and decreased cytokine production
- Gal3 deficient CD8 T cells have reduced KLRF-1, CD25, IFN-g, granzyme B, and FasL, which are all increased in effector CD8
- Gal3 deficient CD8 T cells have reduced CD25 and OX40 expression in vitro, and CD25 expression can be rescued by the addition of IL-2, while OX40 expression cannot
- Gal3 inhibition in vivo enhances CD8 T cell proliferation and activation in response to antigen.

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