TIM-3 EXPRESSION DRIVES PHENOTYPIC AND FUNCTIONAL CHANGES IN TREG IN SECONDARY LYMPHOID ORGANS AND THE TUMOR MICROENVIRONMENT, EFFECTING TUMOR BURDEN

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Background Regulatory T cells (T reg) are critical mediators of self-tolerance but can also limit effective anti-tumor immunity. We and others previously reported that 40–60% percent of T reg-infiltrating head and neck cancer (HNC) and other tumors highly express Tim-3, compared with about 5% in lymphoid organs, it therefore gets imperative to characterize if Tim-3 is driving any T reg specific function in tumor microenvironment and under homeostasis.

Methods Using a conditional TIM-3 inducible and knockout mouse model developed in our lab, we have performed syngeneic tumor challenges in T reg-specific Tim-3 transgenic and knockout mice (FoxP3ERT2CreSFS-Tim-3 and FoxP3ERT2Cre-FLEX4). We have also characterized the tumor immune infiltrate of these mice to understand the impact of T reg specific Tim-3 induction and deficiency on the immune landscape.

Results Tim-3 induction on T reg leads to rapid growth associated with higher progression of CD8 compartment towards exhaustion, while Tim-3 knockout in T reg specific manner leads to overall decline in T reg compartment in tumors associated with lower exhaustion in the CD8 compartment and decrease in tumor burden.

Conclusions Tumor-infiltrating Tim-3+ Treg have enhanced suppressive function and display a more effector-like phenotype. Using a novel mouse model with cell type-specific Tim-3 expression, we show here that expression of Tim-3 by Treg is sufficient to drive Treg to a more effector-like phenotype, and increases suppressive activity, effector T cell exhaustion and tumor growth. We also show that inducible deletion of Tim-3 specifically from Treg enhances anti-tumor immunity and decrease in tumor burden along with a decrease in tumor associated Treg compartment. These findings may help to reconcile previous reports that some Tim-3 antibodies enhance T cell responses in vivo, while expression of Tim-3 has a cell-intrinsic ability to enhance TCR signaling and T cell activation. A major role of Tim-3 was found to be mediated through IL-10 and IL-10 R pathway in both Treg and CD8 compartment. Thus, we propose that Tim-3 regulates anti-tumor immunity at least in part through enhancement of Treg function. To our knowledge, this is the first example in which expression of a single co-stimulatory molecule is sufficient to drive differentiation of Treg in this manner.

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