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Elucidating the role of Neuropilin-1 in intra-tumoral regulatory T cell stability

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Regulatory T cells (T_{regs}) play an integral role in the adaptive immune system through suppression of self-reactive immune responses in order to prevent autoimmunity and maintain homeostasis. However, they are deleterious in cancer through suppression of the anti-tumor immune response. In fact, we show that deletion of 50% of T_{regs} results in normal tumor growth. Therefore, it is advantageous to understand the role of T_{regs} in the tumor microenvironment in order to create targeted cancer therapies. Our lab has shown that the Neuropilin-1 (Nrp1) pathway is required for T_{reg} stability in the tumor microenvironment, but is disposable for maintaining immune homeostasis in the periphery, identifying it as a prime therapeutic target.

In order to further understand the role of Nrp1-deficient T_{regs} intratumorally, we constructed a competitive environment by utilizing *Foxp3*, which is located on the X chromosome, and as a result of X-inactivation, female $Foxp3^{Cre\text{-}YFP}$ heterozygous mice are cellular heterozygotes. We generated $Nrp1^{L/L}Foxp3^{Cre\text{-}YFP/+}$ heterozygous mice comprised of 50% WT T_{regs} and 50% Nrp1-deficient T_{regs}. Surprisingly, when given B16 melanoma, heterozygous mice **phenocopy**$Nrp1^{L/L}Foxp3^{Cre\text{-}YFP}$ homozygous mice (Figure 1A). This suggests that **Nrp1-deficient T_{regs} are playing an active role in shifting the anti-tumor immune response by destabilizing surrounding WT T_{regs} as determined by DNA methylation status** (Figure 1B). Neither WT nor Nrp1-deficient T_{regs} in the tumor from $Nrp1^{L/L}Foxp3^{Cre\text{-}YFP/+}$ mice can suppress in a standard microsuppression assay *ex vivo*, unlike WT T_{regs} from $Foxp3^{Cre\text{-}YFP}$ mice. Through various co-culture experiments, we revealed that destabilization of WT T_{regs}

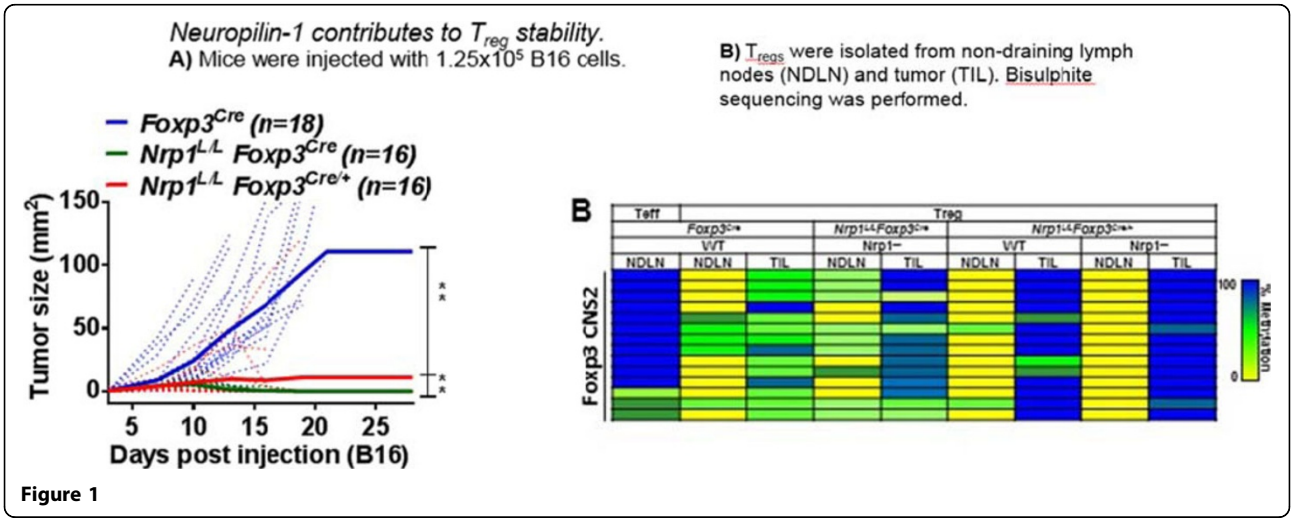

Figure 1

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is possibly due to a soluble factor derived from Nrp1-deficient T_{regs}. Our data revealed that Nrp1-deficient T_{regs} produce large amounts of IFNγ in the tumor microenvironment. Indeed, **when treated with IFNγ, WT T_{regs} lose suppressive capacity**. In order to uncover potential novel pathways leading to this phenotype, we are performing global transcript studies using RNASeq. Overall, we have shown that Nrp1 is required for intratumoral T_{reg} stability, and in its absence, there is an alteration in the tumor microenvironment, leading to an **enhanced anti-tumor immune response**. These studies uncover a novel potential target for future cancer immunotherapies that preserves peripheral immune health.

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