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Ex-Th17 Foxp3+ T cells - a novel subset of Foxp3+ T cells induced in cancer

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Th17 and regulatory T (T_{reg}) cells are integral in maintaining immune homeostasis and Th17-T_{reg} misbalance associates with inflammation.

We demonstrate that in addition to natural (n)T_{reg} and induced (i)T_{reg} cells developed from naïve precursors, Th17 cells are a novel source of $Foxp3^+$ cells by converting into ex-Th17 $Foxp3^+$ cells, and this helps to reconcile the contradictory information about the relevance in particularly of Th17 subset in immune surveillance.

We identified IL-$17A^+Foxp3^+$ double-positive and ex-IL-17-producing IL-$17A^-Foxp3^+$ T cells to be the underlying mechanism of immune regulation in mesenchymal stem cell-mediated prolonged allograft survival. Further, we identified accumulation of IL$17A^+Foxp3^+$ and ex-Th17 $Foxp3^+$ cells in tumor bearing mice, indicating progressive direct Th17-into-T_{reg} cell conversion as a novel phenomenon in cancer.

Moreover, we determined the importance of the Th17 cell plasticity for tumor induction and/or progression in ROR-$g^{-/-}$ mice. Our data indicate that RORgt is required not only for Th17 development, but also for effective T_{reg} cell induction. TGF-b_1 induced Foxp3 expression was reduced in ROR-$g^{-/-}$ cells. Further, tumor bearing ROR-$g^{-/-}$ mice showed significantly less $Foxp3^+$ T_{reg} cells, but higher $IFNg^+$ Tcells compared to wild type animals.

Increased infiltration of $IL17^+$ and $FoxP3^+$ $CD4^+$ T cells in the human ovarian cancer ascites, with the presence of a distinct $IL17^+FoxP3^+$ subset, and a significant correlation between tumor-associated Th17 and T_{reg} cells demonstrates the existence of Th17-$Foxp3^+$ T cell inter-relationship in cancer patients.

Yin-yang of $IL17^+$ and $Foxp3^+$ is important principle for improved clinical approaches targeting responses against self, allo and/or neo-self.

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