CCR8 as a novel biomarker for the specific targeting of a highly suppressive tumor infiltrating regulatory T cell subset.

Aside from cancer cells, the tumor microenvironment (TME) contains a vast array of immune cells which are known to contribute significantly to tumor growth and dissemination. These immune cells are therefore considered interesting targets for cancer therapy. Strikingly, detailed studies regarding the role of chemokines and chemokine receptor expression on tumor-resident immune cells are largely lacking.
Through the use of single cell RNA sequencing we unraveled the T cell complexity in Lewis Lung carcinoma and were able to identify two distinct regulatory T cell (TI-Treg) subsets within the TME. The Chemokine (C-C motif) receptor 8 (CCR8) appeared specifically expressed by the highly activated TI-Treg subset. These findings were confirmed at the protein and functional level, where the CCR8+ TI-Tregs showed higher expression of a plethora of activation markers and immune checkpoint molecules, including LAG-3 and OX40, and showed a superior suppressive capacity. Interestingly, this upregulation of CCR8 on the activated Tregs was specific for the TME and appeared to be antigen-induced. Moreover, these findings also translate to human cancer where we found that CCR8 upregulation also appeared to be specific for the TI-Tregs. These results indicate that CCR8 can be used as a biomarker for this pro-tumoral TI-Treg subset. However, comparison of WT TI-Tregs to CCR8-KO TI-Tregs showed that a loss of CCR8 expression did not influence TI-Treg recruitment to the TME, nor their activation status or their suppressive capacity, indicating that CCR8 does not play an important functional role on TI-Tregs.
Aside from CCR8, single cell RNA sequencing of the whole TME showed that the CCR8-specific ligand, CCL8, was specifically and highly expressed by pro-tumoral M2-like TAMs. However, the exact role of CCL8 remains elusive.
Overall, the unique expression-profile of CCR8 allows it to be used as a potent biomarker for the therapeutic targeting of the pro-tumoral LAG-3HighOX40High TI-Treg subset. This highly specific targeting would allow us to prevent systemic Treg depletion in cancer patients and avoid the induction of autoimmune complications.

Keywords : CCR8, single cell RNAseq, T reg subsets, macrophage subsets
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