

Regulatory T cell Expression of CCR4 is required to Prevent Cutaneous & Pulmonary Inflammation

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Though many studies have shown that CD4+CD25+ regulatory T cells (Tregs) are important in the regulation of different immune responses, it is not known if their migration into non-lymphoid tissues is required for their function *in vivo*. We and others have seen that a large subset of CD4+CD25+ T cells in the primary lymphoid organs and PBL express the chemokine receptor CCR4. The ligands for CCR4, CCL17 and CCL22, are expressed in inflamed skin and lung tissue suggesting that Treg expression of CCR4 may direct this subset to the skin and lung to help control inflammatory responses within these tissues. We utilized the FoxP3GFP mouse model, in which all Foxp3-expressing T cells express GFP, and found that a large subset of T cells in the skin and the lungs are Foxp3-expressing Tregs. Many of these Tregs express CCR4 and the adhesion receptor α E integrin (CD103), the later of which has been associated with antigen-experienced, non-lymphoid tissue homing Treg, as well as T cell homing to the skin.

To determine the importance of CCR4 expression in Treg homing to the skin and lung tissue, we utilized the Scurfy (*sf*) mouse, which lacks Foxp3+ Tregs due to a natural mutation in the X chromosome-encoded Foxp3 gene. For our studies, we constructed mixed bone marrow chimeras with *sf* mice and CCR4 knockout mice. In this system in which only the Tregs are lacking CCR4 while all other cells remain CCR4-sufficient, we found that mice spontaneously develop severe inflammation and lymphocytic infiltration in the skin and lung tissue, while all other tissues remain normal. Analysis of the Tregs residing in these tissues reveal that Tregs lacking CCR4 expression are significantly less able to traffic into the skin and lung compared to WT, while they retain normal ability to traffic into other tissues. These data suggest that lack of CCR4 expression, and therefore the inefficient trafficking of Foxp3+ Tregs leads to an inability to maintain tolerance in the skin and lungs under non-inflammatory conditions. These data are the first to demonstrate that a chemokine receptor plays an important role in the function of Tregs in the maintenance of peripheral tolerance.