Antigen-specific expansion of human regulatory T cells as a major tolerance mechanism against mucosal fungi.

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Abstract

Foxp3(+) regulatory T cells (Treg) have a central role for keeping the balance between pro- and anti-inflammatory immune responses against chronically encountered antigens at mucosal sites. However, their antigen specificity especially in humans is largely unknown. Here we used a sensitive enrichment technology for antigen-reactive T cells to directly compare the conventional vs. regulatory CD4(+) T-cell response directed against two ubiquitous mucosal fungi, *Aspergillus fumigatus* and *Candida albicans*. In healthy humans, fungus-specific CD4(+)CD25(+)CD127(-)Foxp3(+) Treg are strongly expanded in peripheral blood and possess phenotypic, epigenetic and functional features of thymus-derived Treg. Intriguingly, for *A. fumigatus*, the strong Treg response contrasts with minimal conventional T-cell memory, indicating selective Treg expansion as an effective mechanism to prevent inappropriate immune activation in healthy individuals. By contrast, in subjects with *A. fumigatus* allergies, specific Th2 cells were strongly expanded despite the presence of specific Treg. Taken together, we demonstrate a

largely expanded Treg population specific for mucosal fungi as part of the physiological human T-cell repertoire and identify a unique capacity of *A. fumigatus* to selectively generate Treg responses as a potentially important mechanism for the prevention of allergic reactions.

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