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Gene editing to enforce FOXP3 expression and a rapamycin-inducible IL-2 signaling complex in human primary T cells allows selective expansion of immunosuppressive Treg-like cells.

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Abstract:
Regulatory T cells are a distinct T cell lineage that suppress adaptive immune responses. Their importance in maintaining immune self-tolerance is evidenced in IPEX patients, who rapidly develop multiple severe autoimmune diseases caused by the lack of regulatory T cells due to FOXP3 mutations. FOXP3 is a "master regulator" transcription factor that is required for the acquisition of regulatory T cell phenotypes. There is evidence that regulatory T cell defects may have roles in common autoimmune diseases such as Type I diabetes and Lupus. Numerous strategies are thus being developed to improve the numbers or functions of regulatory T cells, including ex vivo expansion and re-infusion of autologous regulatory T cells. This latter approach is limited by the biology of regulatory T cells: they comprise a low proportion of peripheral lymphocytes, are rapidly outgrown in normal culture conditions by other T cells, expand slowly in culture, and have unstable FOXP3 expression. We have previously shown a novel homology-directed repair-based gene editing strategy to generate regulatory-like T cells (edTreg) from bulk peripheral blood CD4 cells, using CRISPR/CAS9 and an AAV6 delivered donor template to stably express FOXP3. These edited cells express characteristic markers of regulatory T cells, down-regulate expression of inflammatory cytokines, and suppress expansion of activated effector T cells in vitro and in vivo. We have also previously demonstrated the development of a synthetic cell surface receptor we have termed a chemically-induced signaling complex (CISC), that delivers an intracellular IL-2 signal when dimerized by the drug rapamycin. In this study, we determined whether co-expression of FOXP3 with the IL2R-CISC could provide a selective advantage for edited vs. non-edited cells in the presence of rapamycin, improving in vitro manufacturing and/or in vivo expansion. Here we show a potentially manufacturing-scalable gene editing methodology for generating human CD4 T cells co-expressing FOXP3 and IL2R-CISC, resulting in a >90% pure population and ~20-fold expansion after two weeks in rapamycin-containing cytokine-free media. When transferred into immunodeficient mice, these cells were selectively expanded in mice that were administered rapamycin. CISC edTreg were also able to suppress inflammatory T cell responses when co-administered with effector T cells, relative to mock-edited T cells. These results show the promise of this strategy for generating a regulatory T cell therapy. Further work is ongoing to determine the longevity and function of CISC edTreg in vivo in animal models, both with and without dimerizer therapy.
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