DEVELOPMENT OF A METHODOLOGY FOR THE PRODUCTION OF SPECIFIC ALLOANTIGEN--- REACTIVE HUMAN TREGS

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Abstract

Background: Organ transplantation is limited by the need for life---long immunosuppression and its off---target side effects, which include life---threatening infection, malignancy and cardiovascular disease. Regulatory T cell (Treg) therapy has the potential to reduce the need for immunosuppression by naturally regulating the immune response and promoting tolerance to the graft. In a number of early clinical trials, polyclonal Treg therapy has demonstrated efficacy in maintaining graft function. However, optimal Treg immunotherapy should employ alloantigen---reactive rather than polyclonally---reactive Tregs to ensure both safety and enhanced specificity to the transplant.

Aim: Several approaches have been reported for the selective expansion of alloantigen---reactive Tregs, but none have demonstrated effective generation at a practical scale for clinical use. This study aimed to develop an effective method to rapidly expand functional human alloantigen---reactive Tregs.

Methods: CD4+CD25hiCD127lo human Tregs were flow sorted and stimulated ex vivo with allogeneic immature dendritic cells (iDCs). Cells were subsequently expanded by alloantigen stimulation for two weeks, followed by one week of polyclonal stimulation.

Results: Using in vitro suppression assays, alloantigen---reactive Tregs were found to be superior suppressors of effector cells and revealed potent allo---specific inhibition in comparison with polyclonally---expanded Tregs. Alloantigen---reactive Tregs maintained a high expression of Treg---specific and functional markers after expansion. Cytokine analysis revealed that alloantigen and polyclonal expanded Tregs express distinct pro---inflammatory cytokine profiles. Assessment of the T cell receptor repertoire revealed a restricted clonal expansion in alloantigen--- reactive Tregs compared with polyclonally---expanded Tregs.

Conclusions: Our results suggest that the generation of alloantigen---reactive Tregs with definable allo---specificity is technically feasible. This methodology may provide a practical and GMP---compatible technique for alloantigen---reactive Treg generation without genetic manipulation.

Biography:

Alaa Alzhrani is a Last year DPhil candidate at Nuffield Department of Surgical Science, Oxford University. MSc degree in Immunology and Allergy, Nottingham University. BSc in Biomedical Sciences, King Saud University.

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