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Targeting regulatory T-cells to induce transplantation tolerance and chimerism

Over the last few decades there has been substantial progress in the field of organ transplantation. The largest success could be achieved in short-term graft survival, whereas long-term graft survival is still a major problem. Chronic rejection continues to be the main reason for graft loss during long-term follow-up. Furhermore, the long-term exposure of patients to immunosupressive drugs carries a high risk of severe side effects, including tumors, infections and metabolic disorders. Therefore, a state would be desirable in which the host permanently accepets the transplanted organ without requiring immunosupressive drugs (termed 'donor-specific tolerance'). Mixed chimerism, which is the co-existence of donor and recipient hematopoietic cells, is a promising approach to achieve donor-specific tolerance. The effectiveness of mixed chimerism as tolerance protocol has recently been demonstrated by pilot trials achieving operational tolerance in patients simultanously receiving a bone marrow and renal graft from the same donor (one of these patients is currently under investigation in our institute). Despite its encouraging results, this strategy has not yet been established in the clinic due to the cytoreductive conditioning used as the default setting in bone marrow transplantation (irradiation, cytotoxic drugs or antibodies). It is well established in the murine model that the use of costimulation blockade dramatically alleviates the devastating pre-treatment of bone marrow transplantation. Recently it could be shown by our group that the adoptive transfer of regulatory T cells together with costimulation blockade and a short course of Rapamycin (‘Treg therapy’) obviates the need for any cytoreductive conditioning. In regards of clinical implementation, it would be more tempting to indetify pharmacological agents that selectively expand regulatory T cells in vivo and thus replace therapeutic administration of regulatory T cells. Consequently, it is the aim of my Phd project to investigate the underlying mechanisms of 'Treg therapy' and to develop it further with regard to clinical application. The first major step within my project was to characterize the phenotype of activated Tregs by means of various surface markers (CTLA-4, GITR, CD25, CD69,CD44, CD62L,...) and to compare it to natural and induced Tregs, respectively.

Thereby I want to figure out the most important features of regulatory T cells to exhibit their tolerizing function.

A broad range of antibodies would be very helpful to illuminate the complex mechanisms of regulatory T cells in the field of transplntation tolerance.