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Session Title : Mechanisms and biomarkers of immune tolerance

Th17-based biomarkers in transplantation

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Individuals who undergo liver transplantation (LT) often require prolonged treatment with immunosuppressive drugs, but continuous use of these drugs throughout their lives can lead to severe side effects. Some LT recipients, however, develop immune tolerance over time. This immune tolerance, known as operational tolerance, has the potential to reduce the dependency on ongoing immunosuppressive drug therapy. Yet, the specific factors indicating the development of operational tolerance have remained unclear. The primary objective of this study was to monitor immunological markers in LT patients over an extended period to identify the markers that signify the development of operational tolerance. In a prospective pilot study, we focused on measuring immune markers, specifically the ratio of regulatory T (Treg) cells to T helper (Th) 17 cells in the peripheral blood. We conducted this study on the most immunologically stable LT patients among those who were already clinically stable. Over time, the doses of immunosuppressive drugs administered to these LT recipients were gradually reduced, and we closely monitored changes in immunological markers associated with the development of immune tolerance. We examined the effect of combination therapy with STAT3/Th17 targeting drug and tacrolimus on immune parameters including T regulatory (Treg) and type 17 helper T (Th17) cells *in vitro* and *in vivo* in mice and in liver transplantation (LT) patients. In LT patients, addition of new drug increased the peripheral percentage of CD4+Treg and CD8+Treg cells and decreased CD4+Th17. Our study suggests that the addition of immune modulatory drug to tacrolimus may improve immunological balance by increasing Treg cells and decreasing Th17 cells. These findings provide potential biomarkers for evaluating the immune status of LT patients and offer insights into targets for enhancing immune homeostasis. As the doses of immunosuppressive drugs were gradually reduced, the Treg/Th17, Th1/Th17, and CD8/Th17 ratios in tolerant recipients significantly increased compared to non-tolerant recipients. These results suggest that monitoring changes in immune markers, particularly the Treg/Th17 ratio during the tapering of immunosuppressive drug treatment, may enable the prediction of the development of tolerance.