Immunosuppressive therapy in organ transplantation: Strategies for personalization approaches

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The serious side effects and complications related to the use of immunosuppressants in organ transplantation have fueled research into their possible minimization. Immunosuppressive therapy in organ transplantation is therefore tentatively moving from a phase of empirical administration towards individualized therapy. This process is highly dependent on the development of monitoring methods to detect individual immune states.

Anti-donor alloreactivity, which depends on the number and phenotype of alloreactive precursors in the recipient, could be used to monitor the immune state for individualizing immunosuppressive therapy. For this purpose, we have applied the mixed lymphocyte reaction (MLR) assay, an assay in which CFSE-labeled PBMCs from recipients are cultured with allogeneic lymphocytes from donors as stimuli, to clinical liver and kidney transplantation. This method allows for the separate quantification of the proliferation of CD4 and CD8 responder T cells in response to allo-stimulation by using multiparameter FCM. By analyzing the proliferation and CD25 expression for the CD4 and CD8 T-cell subsets in response to anti-donor and anti-third party stimuli, the immune status was categorized as hypo-, normo-, or hyperresponsive. In patients with hyperresponsive immune status on either CD4 or CD8 T cells, immunosuppressants were increased. In patients with normoresponsive immune status, immunosuppressant tapering was abandoned. Only in patients with hyporesponsive immune status, immunosuppressant therapy was tapered off.

In addition to cellular ex vivo assays such as the MLR, analyses by molecular genetics such as the single nucleotide polymorphism (SNP) testing would lead to an improvement in risk prediction, early detection and prevention of various complications after organ transplantation. We have recently demonstrated that Fc-gamma R SNPs are predisposing factors for bloodstream infections and can predict mortality after living donor liver transplantation. We have also investigated the impact of SNPs in the FOXP3 gene, a master regulator gene of regulatory T cells, on rejection severity in liver transplant recipients. We found that FOXP3 SNP rs3761548 A/C could be a predisposing factor for steroid-resistant acute rejection after liver transplantation.

In this session, I would like to introduce how we practice individualizing immunosuppressive therapy by making use of cellular immunology and molecular genetics in clinical organ transplantation.