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Beneficial effects of myeloid-cell-expressed S100A9 in kidney transplantation

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Our goal is to enhance diagnostic accuracy of acute rejection (AR) after kidney transplantation, and to predict the impact of AR on graft outcome. In patients suffering from AR (n=28) we identified by microarray S100A9 expression as a prognostic indicator of outcome. In a second cohort, we confirmed that patients with high S100A9 expression during AR (n=36) have better 12-year graft survival (91.5%) than low expressers (n=61; 69.2%). Furthermore, by comparing AR biopsy samples and biopsies without signs of rejection (n=120), we found that S100A9 may function as a diagnostic marker of acute rejection.

Next, we studied the mechanism by which S100A9 exerts its biologic effects. In the biopsies, the majority (75%) of the S100A9+ cell population consisted of CD68+ myeloid cells expressing HLA-DR. Expression of S100A9 was related to expression of immune regulatory molecules, including IL-10, regulatory T cell marker FoxP3/CD3, and p40 component of the reactive oxygen species (ROS)-producing machinery. Overexpression of S100A9 in cultured macrophages led to increased ROS production, whereas inhibition by siRNA transfection resulted into decreased ROS production. The presence of low concentrations of the ROS metabolite H_2O_2 for 0.5h led to downregulation of the proliferative response of activated T cells.

S100A9 levels in the graft are specifically elevated during conditions of increased inflammation. The presence of distinct myeloid cell subsets, expressing S100A9, early after transplantation provides prognostic information with respect to graft survival. The current data suggest that an increased expression of S100A9 by myeloid cells leads to local ROS production in the immune synapse, and as a consequence downregulation of alloimmune responses by T cells in the graft.

Biography

The line of work by Dr. Michael Eikmans (Leiden University Medical Center, the Netherlands) has been to compose a risk profile for kidney transplant rejection and late outcome based on genomic and proteomic tools. During his Ph.D. (1999-2002) he showed that gene expression assessment in biopsies complements current conventional diagnostic criteria. This year an American research grant was awarded to non-invasively monitor patients after kidney transplantation, making use of molecular and immunologic tools in urine and blood. As medical immunologist he gives consultations to Eurotransplant (organization allocating donor organs) and to transplant physicians, in case of (planned) kidney transplantations.

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