Infinite Science Publishing

Role of antibodies against PAR-1 and PAR-2 in cancer in the kidney transplant recipients

R. Catar[a,c,*], R. Carroll[b], L. Chen[a], Q. Li[a], I. Schramm[a], M. Simon[a], O. Wischnewski[a], A. Kusch[a], A. Philippe[a], D. Dragun[a,c]

[a] *Department of Nephrology and Medical Intensive Care, Campus Virchow-Klinikum, Charité Berlin Germany*
[b] *Royal Adelaide Hospital, Centre for Experimental Transplantation - Adelaide, Australia*
[c] *Berlin Institute of Health, Berlin, German*
[*] *Corresponding author, email: rusan.catar@charite.de*

Background: Activated angiogenesis and impaired host immune response contribute to cancer in renal transplant recipients. Induction of VEGF is crucial for neoangiogenesis in tumors. Functional autoantibodies targeting GPCRs are able to induce endothelial dysfunction. We hypothesized that autoimmune GPCR targeting process may disturb VEGF induced angiogenesis. We identified in an in vitro model PAR-1 as novel activating autoantibody target and assessed the presence of this naturally occurring blocking antibody in 20 Kidney Transplant Recipients (KTR) with and 29 KTR without metastatic cancer. In further in vitro studies, we determined the influence of IgG derived from KTR on PAR-2-dependent G-protein activation

Methods/Materials: Human endothelial cells were stimulated with IgG isolated from sera of kidney transplant recipients (KTR-IgG). Transcriptional regulation of VEGF was studied by promoter deletion assay. Transcription factor activation and binding was assessed by qRT-PCR, western blot, EMSA and cFOS knockdown. VEGF secretion was determined by ELISA. Tube formation on matrigel served to study endothelial neoangiogenic response. G-protein activation was measured by reporter assay. All 49 patients enrolled had sera for assessment of PAR antibodies (PAR-Ab) via ELISA in 2016 and at the time of transplantation.

Results: Treatment with KTR-IgG reduced ERK1/2-dependent VEGF secretion and tube formation. VEGF secretion and endothelial tube formation could be restored by pretreatment with specific PAR-1 inhibitor. KTR-IgG contributed to deregulated neoangiogenesis via reduced VEGF promoter activity and increased cFos protein expression via its binding to the VEGF promoter. Mutation of extracellular loops of PAR2 receptor increased PAR2-Ab dependent Gq11 Signalling. Levels of PAR1-Ab were statistically significantly lower pre transplant and at diagnosis in those KTR who subsequently developed cancer compared to controls without cancer.

Infinite Science Publishing

Conclusion: We identified the PAR-1 receptor as a new target for functional antibodies in the context of kidney transplantation and tumor angiogenesis. PAR-1 regulated angiogenesis could offer new possibilities for treatment of kidney transplants to obviate tumor angiogenesis.