Non-HLA Antibodies Targeting G-Protein Coupled Receptors Induce mTORC1 and mTORC2 Signalling in Human Microvascular Endothelium

Wischnewski O.1, Catar R.A.1, Schaub T.1, Hegner B.1, Dragun D.1
1Charité - Universitätsmedizin Berlin, Department of Nephrology and Intensive Care Medicine, Berlin, Germany

Functional non-HLA antibodies targeting G protein-coupled receptors (GPCR) Angiotensin II Type 1 receptor (AT1R) and Endothelin-1 Type A receptor (ETAR) are implicated in pathogenesis of renal and cardiac transplant vasculopathy. Both antibodies activate canonic G-protein related ERK 1/2. While Erk-signaling may represent general cellular response to agonist stimulation, the molecular link between receptor stimulation and development of vascular obliterative lesion has not been fully established yet. We hypothesized the involvement of PI3K/Akt downstream signalling target mammalian target of rapamycin (mTOR) and assessed the relative importance of the two different signalling complexes mTORC1 and mTORC2. Human microvascular endothelial cells (hMEC) with reliable expression of target antigens were stimulated with AT1R-Ab and ETAR-Ab containing IgG from patients with obliterative vasculopathy. Phospho-specific antibodies directed against mTOR downstream targets was used to assess activation of mTORC1 (pp70S6K at Thr389) and mTORC2 (pAkt at Ser473). Signalling activity of both, mTORC1 and mTORC2, was increased after short-term treatment with patient IgG compared to cells treated with IgG from healthy controls. This effect could be inhibited by preincubating the cells with specific blockers of the AT1R (Valsartan) and ETAR (Sitaxentan). Phosphorylation of p70S6K as well as of pAkt at Ser473 was completely abolished by the pharmacologic mTOR inhibitor. Additional experiments demonstrated an ERK 1/2 independent activation of both mTOR complexes indicating a direct activation via PI3K/Akt. We provide evidence that functional non-HLA antibodies targeting AT1R and ETAR induce mTORC1 and mTORC2 signalling which is independent of canonic ERK 1/2 activation in human microvascular endothelium. Our data may provide a translational rationale for therapeutic mTOR inhibition in patients with non-HLA antibodies.

Assigned speakers:
Oskar Wischnewski, Charité - Universitätsmedizin Berlin, Berlin, Germany