OMICS Group Conferences
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International Conference and Exhibition on
Nephrology & Therapeutics

August 20-22, 2012 Hilton Chicago/Northbrook, USA

Diversity of endocytic trafficking and degradation of angiotensin type I receptor directed by its ligand and heterodimerization partners

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Activation of angiotensin type I receptor (AT1R) triggers a wide spectrum of signaling responses that mediate its physiological control of renal and cardiovascular function, including blood pressure. Upon activation by angiotensin II (Ang II), AT1R is internalized into early endosomes via regulation of Rab5, trafficked to late endosomes via regulation of Rab7 and to lysosomes. The occurrence of fluorescence resonance energy transfer (FRET) between AT1R and LAMP1 (a lysosome marker) confirms the trafficking of AT1R into lysosomes for eventual degradation. Latrunculin A but not nocodazole blocks the Ang II-induced FRET between AT1R and Rab5 or Rab7, indicating the requirement of intact actin but not microtubule cytoskeleton in the regulation of AT1R endocytic trafficking. However, upon activation of dopamine D5 receptor (D5R), the lifetime of AT1R is significantly shortened in the presence of ubiquitin as the acceptor fluorophore, suggesting that a fraction of AT1R is ubiquitinated and processed for proteasomal degradation. Some of the internalized AT1Rs escape degradation and coordinately via Rab4 and Rab11, recycle back to the plasma membrane. Both AT1R and D5R are expressed in the cholesterol-rich membrane lipid rafts, and portions of Rab4 (12.1±3.5%) and Rab11 (16.7±6.3%) in the same lipid rafts of sucrose gradient fractions in the AT1R/D5R HEK 293 cells. Therefore, the degradation of AT1R involves both lysosomes and proteasomes. The recognition of the diversity of AT1R intracellular trafficking and degradation may lead to a better understanding of AT1R-mediated regulation of blood pressure.

Biography

Hewang Lee completed in China his doctoral degree on medical science with a thesis on the signaling of adrenergic receptors. After receiving training in molecular and cellular biology in Germany, he moved to the National Institutes of Health at Bethesda, Maryland for his postdoctoral study on vehicle trafficking regulated by small GTPases. He subsequently worked on the intracellular trafficking of G protein-coupled receptors on the regulation of blood pressure in the kidney. He is now a Research Assistant Professor in the Department of Medicine, University of Maryland School of Medicine

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