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Engineering signaling-biased arrestins for targeted regulation of cell behavior

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Arrestins specifically bind active phopshorylated GPCRs, blocking further G protein activation and orchestrating G protein-independent signaling. Based on the elucidation of arrestin structure and key functional elements we constructed special arrestins to channel cell signaling in desired direction. We designed enhanced phosphorylation-independent arrestin-1 mutants and showed that they can compensate for the defects of rhodopsin phosphorylation in vivo. We identified the residues on the receptor-binding surface of non-visual arrestins that determine their preference for particular GPCRs. Based on this information we created arrestin-3 mutants with high receptor specificity by a few substitutions. We designed arrestin-3 mutant that suppresses JNK activation in the cell. We found that caspase-cleaved arrestin-2 facilitates apoptotic cell death, whereas its caspase-resistant mutant protects the cells. We also identified a small element of arrestin-3 that acts as a mini-scaffold, promoting JNK activation *in vitro*, in cells, and in the brain in vivo. Arrestins play a role in numerous signaling pathways and physiological processes. Therefore, targeted mutagenesis can yield arrestin-based molecular tools to tell the cell what to do in a language it cannot disobey.

Biography

Vsevolod V (Seva) Gurevich has completed his PhDin 1989 from Shemyakin Institute of Bioorganic Chemistry, Moscow, Russia, and postdoctoral training (1991-1995) in the laboratory of Dr. J.L. Benovic, Thomas Jefferson University, Philadelphia, PA. He is Professor of Pharmacology at Vanderbilt University. He has published more than 160 papers in reputed journals and has been serving as an editorial board member of several journals.

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