Universität Basel

Research Project

Structure, dynamics and function of CCR5-arrestin interactions

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Project title Structure, dynamics and function of CCR5-arrestin interactions
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The human CC chemokine receptor 5 (CCR5) is a G protein-coupled receptor (GPCR) that plays a major role in general inflammatory processes by recruiting and activating leukocytes. CCR5 is also the principal HIV coreceptor, is involved in the pathology of both cancer and neuroinflammation, and has been im plicated in the inflammatory complications of COVID-19. Binding of ligands to GPCRs results in the activation of G protein-, arrestin-mediated and other signaling pathways. The Grzesiek lab has recently solved the cryo-EM structure of an agonist chemokine CCL55protein complex, which delineates the G protein activation pathway triggered by chemokine agonists within CCR5. While meanwhile a number GPCRprotein complexes have been solved, much less is known on the structural basis of GPCR arrestin signaling. In particular, no structure of a chemokine receptorcomplex exists. The Shukla is one of the world leading labs in the structural and functional analysis of arrestins.

We propose here to combine the expertises and capabilities of these two groups to (A) solve the structure of a CCR5•ß arrestin 1 complex, (B) investigate the dynamics of interactions between CCR5-derived peptides and arrestin by NMR and other biophysical techniques, as well as (C) characterize the CCR5•ß arrestin 1 interactions by cell-based assays and develop new synthetic antibody fragments to stabilize the CCR5•ß arrestin 1 complex. The structural and functional insights from these combined experiments should decipher key elements of chemokine-induced CCR5-arrestin signaling and reveal differences to the G protein signaling pathway. This may pave the way for the development of directed therapeutics targeting either pathway. Due to the homology of CCR5 to a number of other chemokine receptors, the results obtained may serve as a paradigm for other chemokine receptor/ligand systems.

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