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Understanding differential selectivity of arrestins toward the phosphorylation state of G-protein-coupled receptors

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Arrestins (Arrs) are a family of four proteins (Arr1- 4) which mediate G-protein-coupled receptor (GPCR) desensitization and internalization by coupling to active and phosphorylated receptor. Recently, they have also been shown to mediate GPCR-independent signaling pathways. The specific functions of Arrs (desensitization vs. G-protein-independent signaling) can be regulated by differential phosphorylation of the receptor, which is known as the *phosphorylation barcode*. The molecular mechanism responsible for formation of a high-affinity complex between an Arr subtype and a GPCR having a certain phosphorylation pattern remains elusive but is crucial for directing the subtype towards a specific functional role, and hence paves the way for development of safer therapeutics with fewer side-effects. As a first step in that direction, we have started with elucidating the activation mechanism of Arr subtypes by carrying out comparative molecular dynamics (MD) studies of the two members of the family, namely Arr1 and Arr3, which exhibit the largest differences in terms of phosphorylation selectivity. In addition, we also modeled and simulated Arr1-R175E mutant, which is known to be constitutively active, and compared it to Arr1 and Arr3 to detect activation-related rearrangements. We found novel structural elements that had not been considered before as determinants for activation and can be targeted with drugs for functional modulation. The emerging model also proposes that activation of Arr1-R175E is connected to perturbation of the well-known region, namely, the polar-core, whereas no changes were observed in that region in Arr3 despite the presence of other activation-related changes. With that, we could propose a structural model to explain the molecular mechanism responsible for markedly reduced selectivity of Arr3 towards phosphorylated GPCRs. Finally, knowledge achieved in this study can also be utilized to modulate Arr binding to GPCRs under disease conditions such as otozomal dominant disorders and congestive heart failure.

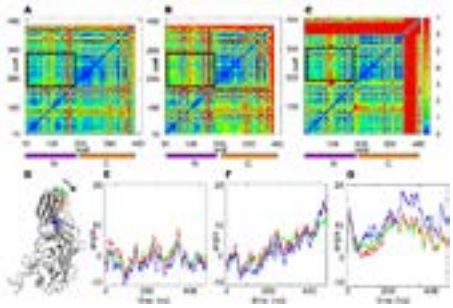

Figure1: *Top, Distance fluctuation maps calculated for Cα-Cα distances along the MD trajectories for (A) Arr1, (B) Arr1-R175E (B) and (C) Arr3. N and C-domains are identified by stripes. The dashed rectangles highlight the distance fluctuations in the N-C interface region. Bottom, Panel D: View of Arr3, with rotation axis perpendicular to the Picture plane and passing through Cα of I321, depicted in black (I306 in Arr1); rotation on this axis in the direction of the arrow corresponds to an increase in the rotation angle. Cα atoms used in quantifying the rotation along the MD trajectory are represented in blue, red, and green. Panels (E-G): Time dependent rotation of the selected residues in Arr1-WT (E), in Arr1R175E (F) and Arr3(G).*

Biography

Ozge Sensoy being a Computational Biophysicist, her research has focused on understanding molecular mechanisms of biologically important problems and providing mechanistic insight at the molecular level. In particular, she has been working with GPCRs and their interacting partners which are responsible for cellular signaling. She works in close collaboration with medicinal chemists to direct them for effective molecular designs. In addition, she is also responsible for testing the efficacy of these molecules *in silico* before transferring them to either *in vitro* or *in vivo* studies. Recently, she has been awarded an international COST (European Cooperation in Science and Technology) grant which is based on developing heterobivalent molecules capable of binding more than one target for treatment of symptoms of Parkinson's disease.

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