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Structural modeling of C5a receptor: Molecular insights into agonism and antagonism

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The complement component fragment 5a receptor (C5aR), also known as the anaphylatoxin receptor is one of the two major G-protein coupled receptor (GPCR) that demonstrates a high affinity interaction with C5a, the most potent proinflammatory polypeptide of the complement system, known for its pleiotropic effects in both immune and non-immune cells. No wonder, the C5a-C5aR interaction has been tagged druggable for discovery of targeted therapeutics.1 However, the molecular basis of agonism or antagonism in C5aR is yet to be established clearly, largely due to the unavailability of a structure of C5aR. In addition, while the role of allosterism in C5aR is discussed in the literature, it is completely unheard for C5a, a potential drug target that modulates the downstream signaling of C5aR. It not only hinders the discovery and development of new lead molecules, but also affects the rational optimization of the known lead molecules as potential therapeutics, targeting the C5a-C5aR signaling axes. In our quest toward better understanding of C5a-C5aR interaction, 2 we have recently generated the first set of atomistic model structures of inactive and meta-active C5aR in excellent agreement with the previously reported binding and signaling studies. 3 Further, we have also identified a pair of "allosteric switches"4 on C5a that potentially modulate the C5aR signaling. It is noteworthy that the peptide agonist, C5a and the small molecule antagonist5 NDT demonstrate binding at the exact same site on the meta-active structure of C5aR with distinctly different binding modes.6 In summary, the inactive, agonist and antagonist bound meta-active C5aR structures provide important structural insights, previously not known at an atomistic resolution, in regard to the ligand binding sites, selectivity and activation of C5aR, which will be discussed in detail.

Biography

Soumendra Rana has completed his PhD at the age of 29 years from IIT Bombay and postdoctoral studies from Washington University School of Medicine in St. Louis, including University of Arizona, Tucson. He is currently an assistant professor (Chemistry and Biosciences) at the IIT Bhubaneswar, one among the 14 premier technical institutes of the country. He has published more than 12 papers in reputed journals and has been serving as an editorial advisory board member in International Journal of Chemical and Pharmaceutical Review and Research.

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