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Identification of structural elements of MCP chemokines and their shared receptor CCR2

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Chemokine receptors are G-protein coupled receptors (GPCRs) that regulate the movement of leukocytes during inflammation. CCR2, a major chemokine receptor on monocytes and macrophages, binds to several CC chemokine ligands and plays a key role in atherosclerosis, obesity and type 2 diabetes.The major ligands of human CCR2 include monocyte chemoattractant protein 1 (CCL2) and MCP-3 (CCL7). Here we show that MCP-1 and -3 have distinct potencies and efficacies of signalling at CCR2 and we identify structural features of the chemokines and receptor contributing to the differences.First, using a series of chemokine chimeras, constructedby swapping the three main receptor recognition regions between MCP-1 and MCP-3,we have identified structural elements of MCP chemokines responsible for differences in receptor activation.We found that the chemokine N-terminus plays a major role towards full versus partial agonism.The affinities of the chemokine chimeras to the CCR2 also confirmed that the N-terminus makes a significant contribution to receptor binding by these two chemokines.Second, using a series of CCR2 mutants, we have identified elements of CCR2 that interact preferentially with the chemokines. The affinity of chemokine binding and the potency of ERK-1/2 phosphorylation by MCP-1 and MCP-3was determined for each receptor mutant. Four of the mutants, Y120F, R206A, I263A/N266A and Y259F displayed differential effects on the affinity of MCP-1 relative to MCP-3. These mutated residues are clustered together in the transmembrane region of the receptor.We conclude that this region of the receptor plays a major role in distinguishing between the two cognate chemokines, apparently by differential interactions with the N-terminal regions of the chemokines.Our investigation has yielded significant new information on chemokine receptor binding and signalling, which will guide future drug development.

Biography:

My name is Zil e Huma and I am a final year PhD scholar in the Department of Biochemistry and Molecular Biology at Monash University, Australia. In addition, I am also working as a teaching associate at the same department. My area of interest revolves around understanding the signalling mechanisms of GPCRs. Chemokines and their receptors have always been a target of interest because of their role in inflammatory diseases. I am interested to investigate different chemokines which cause differential signalling at the same receptor.This study will help understand the chemokine-receptor interactions to develop novel therapeutic agents.