Signaling of the fractalkine receptor CX3CR1 and its natural genetic variants: impact of receptor non-synonymous single nucleotide polymorphisms

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The chemokine receptor CX_3CR1 is a $G_{i/o}$ G protein-coupled receptor (GPCR) expressed in monocytes, NK cells, T lymphocytes, astrocytes and microglia, among other cells, and it plays an important role in inflammation and immunity as well as in neuron-microglia communication in the Central Nervous System [1]. Its known ligand is fractalkine (CX_3CL1), the sole member of the CX_3C chemokine subfamily. Genomic studies have identified non-synonymous single nucleotide polymorphisms (nsSNPs) in the *CX_3CR1* gene. Specifically, the common receptor genetic variant CX_3CR1-V249I/T280M has been associated with faster progression to disease in HIV-infected patients, cardiovascular atheroprotection, increased risk of age-related macular degeneration, and obesity [2]. We aimed to investigate the possible functional impact of the currently identified nsSNPs of CX_3CR1 on the pharmacology of this receptor.

Receptor interaction with G protein-coupled receptor kinase 2 (GRK2) and beta-arrestins were investigated in transfected HEK293 cells by bioluminescence resonance energy transfer (BRET)-based assays. Our results indicate that the CX_3CR1-V249I/T280M receptor variant interacts with more efficacy than the wild type receptor with beta-arrestins 1 and 2 (Emax 146% and 204% of wild type, respectively) and GRK2 (Emax 310% of wild type) in response to fractalkine. The functional impact of this observation on the dynamics and compartmentalization of the receptor signaling is being further investigated. Being GRKs and beta-arrestins crucial regulators of G protein-dependent and -independent signaling of GPCRs [3], our findings expand our current knowledge on the signaling pathways modulated by CX_3CR1 and their possible implications in physiological and pathological condition.

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