Integrating Structure-Based Modelling to Characterize Formyl Peptide Recognition by FPR1 and FPR2

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Formyl peptide receptors (FPRs) are part of the G protein-coupled receptor family involved in innate immune recognition of formyl peptides released by bacteria. Activation triggers inflammatory processes such as chemotaxis, phagocytosis, ROS and calcium release. There are three FPR subtypes in humans (FPR1, FPR2 and FPR3), with FPR1 and FPR2 exhibiting a high sequence similarity of 69%. Both receptors also show structural similarities and a common agonist portfolio with some differences and preferences in their interaction with formyl peptides. Here, we combine functional characterisation using calcium imaging with structure-based modelling to investigate structural determinants of ligand binding in FPR1 and FPR2. Internal, unpublished data have shown that the addition of a lysine group to f-MLFYLA and f-MGFFIS activates not only FPR1 but also FPR2 in calcium imaging experiments. To investigate the interactions between receptor and ligand, the two peptides with and without lysine were constructed using Avogadro and geometrically optimised prior to molecular docking. Comparative docking analyses were performed to evaluate variations in binding orientation and predicted interaction networks within the ligand binding pockets of FPR1 and FPR2, thereby explaining the functional differences of the tested peptides.