Identification of Structural Determinants for Amyloid Beta Sensing by Formyl Peptide Receptors

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Formyl peptide receptors (FPRs) are a small family of pattern recognition receptors that play a central role in the innate immune defense against invading pathogens such as bacteria and viruses. Beyond host defense, FPRs are increasingly implicated in neuroinflammatory disorders, including Alzheimer's disease, prion diseases, and multiple sclerosis. Notably, FPRs recognize a remarkably diverse spectrum of peptide ligands—including bacterial signal peptides, protein degradation products, inflammatory mediators, and neuropeptides such as amyloid beta (Aβ) and prion protein fragments—despite the absence of clear structural or sequential homology among these ligands. We recently identified human FPRs as novel detectors of non-canonical Aβ peptides and demonstrated that structurally related peptides can elicit differential cellular responses via FPR1 in a human glial model. In this study, we thus performed a detailed biochemical and functional characterization of FPR–Aβ interactions to further elucidate the molecular mechanisms governing FPR–ligand interactions and receptor activation

To this end, we employed physiological and modified Aβ variants to investigate their binding to and activation of human FPRs. Biochemical characterization included Thioflavin T aggregation assays, silver staining of PAGE gels, and bioinformatic analyses to assess the biochemical and biophysical properties of distinct Aβ variants. To map these properties to receptor activation, we next measured functional FPR responses in live-cell calcium imaging experiments using transfected HEK293T cells expressing individual FPRs. Based on these findings, we conducted initial structural modeling of receptor–peptide complexes and performed pilot docking experiments.

Our results identify distinct regions within the N- and C-termini of Aβ peptides that contribute to binding to FPR1 and FPR2, as well as FPR-subtype specific domains involved in receptor activation. Furthermore, we demonstrate that biochemical properties and structural conformation critically determine Aβ binding to FPRs and strongly influence downstream cellular responses. Taken together, these findings provide a mechanistic framework for differential FPR activation by Aβ peptides and offer new insight into the contribution of FPR signaling to the neuroinflammatory landscape of Alzheimer's disease and related neurodegenerative disorders.