Role of Formylpeptide Receptors in Host Defense

https://neurodegenerationresearch.eu/survey/role-of-formylpeptide-receptors-in-host-defense/

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Title of project or programme

Role of Formylpeptide Receptors in Host Defense

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

322431.1927

Start date of award
Total duration of award in years

11

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Cancer... Dementia... Immune System... Lung... Neurodegenerative... Neurosciences

Research Abstract
FPRL1 and mFPR2 are receptors on human and mouse myeloid cells that mediate cell chemotaxis to a pathogen and host derived peptides, including serum amyloid A (SAA) and amyloid beta peptides associated with Alzheimer’s disease (AD). We have found that upon binding to FPRL1 or mFPR2 on migcroglial cells, considered as brain macrophages, Amyloid beta42 and FPRL1 complexes were internalized into the cytoplasmic compartment of the cells and prolonged exposure to Amyloid(A) beta42 resulted in the retention of Amyloid beta42/FPRL1 complexes in the cells, followed by formation of Congo-red positive fibrils. In

contrast, brief exposure of macrophages/microglial cells to Abeta42 peptides also resulted in Abeta42 peptide ingestion, but without formation of fibrillary aggregation, suggesting a lower burden of Abeta42 peptides could be degraded. In microglial cells isolated from new born mice, treatment with a variety of proinflammatory agents such as the ligands for the Toll like receptors (TLRs), TNFalpha, IFNgamma and CD40 increases the expression of mFPR2, the mouse counterpart of human FPRL1. Activated mouse microglial cells exhibited potent chemotactic responses to Amyloid beta42 peptides and ingested the peptides through the receptor mFPR2. Our observations suggest that FPRL1 and its mouse counterpart may act as a sensor in the CNS for over produced Abeta42 peptides seen in AD. Abeta42-FPRL1(mFPR2) internalization results in production of proinflammatory mediators and the processing of Abeta42 peptides, which may determine the rate of the progression of AD pathology. To more precisely evaluate the role of FPRL1 (mFPR2) in innate host defense, inflammation and in the pathogenesis of AD, we have generated a mouse strain depleted of mFPR2. Our ongoing studies have revealed that in a mouse model of AD, depletion of mFPR2 reduced the number of activated microglial cells in the brain in association with increased level and more diffused distribution of Abata42 peptide deposition. Thus, FPRL1 (mFPR2) appears to play an important role in host defense favoring the accumulation of Abeta42 peptides in phagocytic microglial cells thus facilitating clearance and reducing damage in AD. The generation of mFPR2-/- mice also provides us with a unique tool to study the role of this receptor in other proinflammtory and immune diseases as well as in the development of cancer. We found that in an ovalbumin (OVA)-induced inflammatory and immune response model of lung disease, as compared with wild type mice, mFPR2-/- showed markedly reduced leukocyte infiltration in the lung tissue and in the bronchial lumen, in association with reduced antibody responses to OVA. Thus our studies suggest a key role of mFPR2 in inflammatory and immune responses to foreign antigen. Further studies are underway to determine the role of mFPR2 in inflammatory bowel disease-induced colon cancer and in the development of metastasis in mouse lung cancer and melanoma.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A