

Resolving the Mechanism of Neuroinflammation for the Innovative Therapy of Neurodegenerative Diseases

<https://www.neurodegenerationresearch.eu/survey/resolving-the-mechanism-of-neuroinflammation-for-the-innovative-therapy-of-neurodegenerative-diseases/>

Principal Investigators

Dr Iva Hafner Bratkovi?

Institution

Kemijski inštitut

Contact information of lead PI

Country

Slovenia

Title of project or programme

Resolving the Mechanism of Neuroinflammation for the Innovative Therapy of Neurodegenerative Diseases

Source of funding information

SLOVENIAN STATE RESEARCH AGENCY (ARRS)

Total sum awarded (Euro)

€ 59,216

Start date of award

01/08/2013

Total duration of award in years

3

Keywords

Research Abstract

Scientific background. Amyloid neurodegenerative diseases are characterized by accumulation of protein deposits and progressive neuronal cell loss. They are also accompanied by neuroinflammation. One of the leading roles in this inflammatory process is played by IL-1?. Inhibition of IL-1R activation demonstrated amelioration of neuroinflammation in the animal model of Alzheimer's disease. Pro-IL-1? is processed by protein complexes called

inflammasomes, which yield active IL-1 β . Recently it has been shown that NLRP3 inflammasome is activated by A β fibrils, the main component of plaques in Alzheimer's disease. We demonstrated that NLRP3 inflammasome is instigated by prion protein fibrils, which deposit in prion diseases (Hafner Bratkovi β et al., in review). We and others have shown that microglial cells activated by amyloids induce neuronal death, thus inhibition of inflammasome activation represents a promising therapy of neurodegenerative diseases.

Problem identification, goals and impact of the study. Transcription of NLRP3 is induced upon NF- κ B activation and the protein resides in the cytoplasm in an inactive form. Upon stimulation, NLRP3 is proposed to oligomerize and recruit adaptor ASC, which enables the proximal binding of pro-caspase-1 molecules, which self-activate, due to the formation of this multiprotein complex. The active caspase-1 cleaves pro-IL-1 β (and pro-IL-18) and mature IL-1 β (IL-18) is released from the cells. Several cellular processes and a variety of different molecular triggers have been linked to NLRP3 inflammasome activation, but the molecular mechanism of the inflammasome assembly as the critical step that leads to IL-1 β processing is unknown.

Goals of the proposed study:

1. To clarify the molecular mechanism of the NLRP3 inflammasome assembly. NLRP3 receptor is composed of three domains: N-terminal PYD, central NACHT and C-terminal LRR (Figures 1 and 2A). Upon activation, NLRP3 receptor oligomerizes via NACHT domain and via PYD recruits ASC, which further recruits pro-caspase-1 via CARD. We plan to investigate the early events in NLRP3 inflammasome assembly using NLRP3 mutagenesis. We will define the participation of the above mentioned domains and specific amino acid residues in the recognition of triggers and inflammasome assembly, which will allow us to prepare a molecular model of NLRP3 in inactive conformation and in the inflammasome.
2. To explore the potential of inhibitors of NLRP3 inflammasome pathway in the treatment of neurodegenerative disease. Currently, there are several inhibitors of IL-1 used in treatment of inflammatory disease. However, the IL-1 β is not the only product of the inflammasome, which is demonstrated by the fact that some patients (and some pathologies) with NLRP3 genetic diseases do not respond to anti-IL-1 therapy. Therefore, we propose that inhibition of early events in the inflammasome assembly might be more effective. We plan to investigate the possibilities of inhibition at several stages. We will use peptides, for which we predict they bind and abrogate PYD-PYD and CARD-CARD interactions. Based on our results from the first objective we will design peptides, which interrupt NACHT oligomerization. To improve the peptide transport over the blood-brain-barrier (BBB), peptides will be modified with cell-penetrating peptides and angiopeps. Peptides with highest inhibitory potential will be tested in a mouse model of AD.

The neurodegenerative diseases, which involve the NLRP3 inflammasome, represent a growing burden on the society and investigations of new therapeutic routes must have a high priority and impact. Based on the new knowledge on the NLRP3 inflammasome assembly mechanism we plan to test inhibitors which will not act on 'the products' of activation, but at earlier stages, interfering with the formation of the inflammasome. If proven effective, they will provide the alternative treatment of neurodegenerative disease with favorable safety profile.

Further information available at:

Types:

Investments < €500k

Member States:

Slovenia

Diseases:

N/A

Years:

2016

Database Categories:

N/A

Database Tags:

N/A