Microglial modulation, a potential therapeutic approach in neurodegenerative diseases

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Research Abstract

My research continues to focus on neurodegenerative disorders and understanding how inflammatory processes contribute to neuronal death. Here I have summarized my major research contributions from recent years. The research work published until 2002 was performed in Finland at University of Kuopio with Dr. Jari Koistinaho and thereafter in University of California, San Francisco as a post-doctoral fellow with Dr. Raymond Swanson and adjunct assistant professor 2006-2012.

1. Neuroprotective effects of minocycline.

Minocycline is considered one of the most promising treatments in ischemic stroke. My work today has described the two most central mechanisms explaining how minocycline provides its neuroprotection. As a graduate student I was a part of research group (lead by Dr. Koistinaho) describing for the first time the neuroprotective and anti-inflammatory effects of minocycline (Yrjänheikki, PNAS. 1999; 96:13496). My contribution (published in my maiden name, Tikka) to these studies was to describe the minocycline's ability to inhibit p38MAPK that may be a mechanism by which tetracycline derivatives exert a wide range of anti-inflammatory and anti-apoptotic effects (Tikka; JNeurosci. 2001; 21:2580, JImmunol. 2001; 166:7527, JNeurochem. 2001; 78:1409, Brain 2002; 125:722).

As a postdoctoral fellow I continued to study further minocycline's mechanism of action as a collaborative effort. In this project minocycline was found to directly inhibit poly(ADP-ribose)polymerase-1(PARP-1) activation, thus revealing PARP-1 as one of the inhibitory targets of minocycline (Alano, PNAS 2006; 103:9685). I also recently collaborated in hypoglycemia studies demonstrating that the low blood glucose levels (complication of diabetes) induced inflammatory hippocampal injury and cognitive impair, which can be reduced by minocycline (Won; JNeuroinflam. 2012; 9:182, JNeuroinflam. 2012; 9:225,). My contribution to these studies was to advise the experimental design regarding minocycline and inflammatory process evaluation, and mentor trainees.

2. Regulation of PARP-1 activity.

PARP-1 has been identified as a promising therapeutic target for various central nervous system(CNS) disorders due to its ability to target both neuronal death and inflammation. Similarly, MAPkinase signalling pathways have been considered to play key role in CNS pathology. The research initiated and run by me evaluated the potential cross-regulation between these proteins and revealed a novel function for ERK2 as a regulator of PARP-1 activity. ERK1/2 was demonstrated to directly phosphorylate PARP-1, and the phosphorylation of ERK2-specific putative residues was shown to be a requirement for PARP-1 activation (Kauppinen, PNAS 2006; 103:7136). During this project we generated phosphor-mutations of PARP-1 that allow modulation of PARP-1 activity. These mutants were utilized when addressing the conflicting issue regarding the requirement of enzymatic activity of PARP-1 or mere presence of protein in regulation of inflammation/NF-kB. I recently demonstrated the importance of PARP-1 enzymatic activity in NF-kB regulation, and further provided the underlining mechanistic explanation (Kauppinen, BBA-MolCellResearch 2013; 1833:1985*). In another study I explored the signaling pathway leading to PARP-1 activation upon inflammatory stimuli. I established the key enzymes and found that the PARP-1 signaling cascade differs depending on stimuli, though the requirement of ERK2-mediated phosphorylation of PARP-1 remains crucial. I am currently working to get these findings published.

I also significantly contributed to the study demonstrating that PARG (enzyme catabolizing poly-ADP-riboses produced by PARP) functions as an important negative feedback-system for PARP-1 activation (Burns, PLoS ONE. 2009; 4:e4896). My contribution to this study was to support the project development, optimize transfections and assays, and supervise trainees.

3. Mechanistic details of excitotoxic neuronal death.

Excitotoxicity is the central cell death mechanism in neurodegenerative disorders. Two of my projects significantly advanced the understanding of this mechanism.

1) Glutamate excitotoxicity is mediated by NMDA receptor activation and one of the key mediators in this neurotoxic cascade is production of superoxide. In this controversial collaborative study, we demonstrated that the primary source of this superoxide is not the mitochondria, but the NADPH oxidase (Brennan, NatNeurosci. 2009;12:857). My contributions included methodology related with detection of NADPH cellular translocation and activity, and mentoring.

2) PARP-1 is a key mediator of neuronal death in excitotoxicity, ischemia and oxidative stress. PARP activation is known to lead to energy depletion and mitochondrial release of AIF, but the details of the signaling pathways have remained uncertain. We establish in a collaboration project that NAD+ depletion is the central event in PARP-1 mediated cell death. NAD+ depletion and following glycolytic failure were shown to occur upstream of mitochondrial AIF release (Alano, JNeurosci. 2010;30:2967). My contribution was assisting with cell culture models, imaging and activity assays.

4. Role of PARP-1 in microglial regulation.

Microglia are brain immune cells driving inflammatory responses and potentially promoting disease progression. Understanding the regulation of this cell type will enhance development of therapeutic approaches. My cell culture studies have established that PARP-1 and its enzymatic activity have the key regulatory role in microglial responses due to ability to co-activate transcription factor NF-kB (Kauppinen; JImmunology 2005;174:2288, JNeurosci. 2008;28:5827*, JNeuroinflam. 2011;8:152*). In combined these studies demonstrated that PARP-1 inhibition/depletion reduces neurotoxic aspects of microglial activation, but preserves their ability to release trophic factors and provide controlled phagocytosis. These findings underline the potential of PARP-1 targeting in therapeutic approaches.

5. Therapeutic potential of PARP-1; an anti-inflammatory approach.

Acute brain injuries

Stroke; I have used transient forebrain ischemia in my in vivo studies to evaluate neuroprotective effects of PARP-1. In the first study, PARP inhibitor treatment started 8hrs post-ischemia reduced microglial activation and produced marked neuroprotection in CA1 area of hippocampi at day 7 post-ischemia (Hamby, Stroke 2007;38:632). In the second study, I attempted to target the post-stroke inflammation, instead of the acute neuronal death by delaying the treatment onset up to 48hr. PARP inhibition reduced microglial activation and astrogliosis, and promoted long term neuronal survival and neurogenesis in hippocampus; improved spatial memory was also observed in the Morris water maze tests (Kauppinen, JCBFM 2009;29:820*). While the neuroprotective ability of PARP-1 inhibition in stroke models has been well established, the novelty of my approaches was the attempt to target the post-ischemic inflammatory responses and evaluate the wideness of therapeutic window.

Traumatic brain injury; I supervised a postdoctoral fellow in a project where we demonstrated that PARP-1 inhibition reduces microglial activation after traumatic brain injury and thus could be useful approach in treating concussions and other brain traumas (d'Avila, JNeuroinflam. 2012;9:31).

Chronic conditions

Alzheimer's disease(AD); The in vivo study with AD mouse model cross bred with PARP-1ko mice showed reduced microglial activation throughout the brain, and improved synaptic integrity and cognitive functions (Kauppinen, JNeuroinflam. 2011;8:152*).While PARP-1 depletion is not exclusive in microglia in these studies, additional in vivo and in vitro data supported the notions that PARP-1 depletion reduces microglial activation induced by amyloid-? (A?) injection to hippocampi or added to culture medium. This was the first study to evaluate therapeutic potential of PARP-1 in AD, and findings were promising. As a collaborative effort with Dr. Li Gan we established the neuroprotective role of microglial CX3CR1, receptor facilitating leukocyte infiltration to the brain. This study revealed that AD patients have reduced expression of CX3CR1 and its depletion in microglia promotes AD pathology in mouse model (Cho, JBC 2011;286:32713).

Multiple Sclerosis(MS); Collaboration study with Dr. Chris Anderson demonstrated a significant role for PARP-2 in neuroinflammation and neurological dysfunction in EAE, animal model of MS (Kamboj, JNeuroinflam. 2013;10:49).

6. Methods to target microglia.

Based on the studies described above, PARP-1 inhibitor usage in clinical settings seems attractive, but might not be desirable, since the immersing evidence suggest that neuronal PARP-1 activation might be needed for long term memory formation. In addition, the lack of microglia specific inhibitors has lead me to study line discovering methods to directly and specifically target microglia in live animals. As a collaboration approach with Dr. Li Gan, we demonstrated that semiconductor quantum dots could be useful as a device to selectively deliver therapeutic agents to microglia (Minami, JNeuroinflam. 2012;9:22). Currently I have ongoing projects with lentiviral constructs allowing long lasting protein modifications specifically in microglia. I have also developed conditional PARP-1ko mouse model allowing cell type specific PARP-1 depletion. This model benefits PARP-1 research since it allows us to study the role of PARP-1 in individual cell types in vivo.

In all collaborations, my major contribution has been expertise in the field of neuroinflammation and related experimental designs, technology development and data analysis. In the studies where I am the first author, particularly after 2005, I have been the principal designer of the experiments, performed majority of experiments and data analysis, and wrote the publications. I am corresponding author in papers marked with *.

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