



INDO SWISS JOINT RESEARCH PROGRAMME (ISJRP)

JOINT RESEARCH PROJECT

ABSTRACT

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ROLE OF MICRORNAS AND NOX NADPH OXIDASES IN HIV INDUCED NEUROINFLAMMATION AND NEURODEGENERATION

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PROJECT ABSTRACT

Role of NOX NADPH oxidases in HIV associated neuropathologies

An important proportion (20-30%) of patients infected with human immunodeficiency virus (HIV-1) develops cognitive and motor dysfunction, a heterogeneous group of progressive neurological symptoms often referred as neuroAIDS. The underlying mechanisms of HIV associated neuropathologies (HAN) are only partly understood, but it is clear that the severity of the disease is strongly dependent of HIV-1 isoatypes (clades). Because neurons are probably not infected by HIV-1; it is thought that the predominant pathway leading to neuronal loss is indirect and depends on the glia, the non neuronal cells of the brain. Infection of glial cells by HIV-1 leads to neuroinflammation characterised by important neurochemical changes such as glial activation, release of neurotoxins and oxidative stress. Such neuroinflammatory processes are increasingly recognised as key aggravating factor in many neurodegenerative diseases like Parkinson, Alzheimer and amyotrophic lateral sclerosis. Common features of these neurodegenerative diseases are glutamate-mediated excitotoxicity, activation of microglia and the generation of large amount reactive oxygen species (ROS), i.e. oxidizing molecules. A broad range of studies using either brain or cerebrospinal fluid (CSF) tissues from well-characterized patients with HIV dementia, animal models, and in vitro studies using HIV-infected cells of HIV proteins provide overwhelming evidence for a role of oxidative stress in neuronal injury. One of the major sources of ROS in the brain is a family of enzymes, the NOX NADPH oxidases, whose main function is to generate large amount of ROS. Indeed, an increasing number of studies have shown increased NOX expression in neuropathological conditions and impressive neuroprotection in NOX-deficient mice. However, at this stage, the role of NOX enzymes in HAN has received little attention and the pathways controlled by NOX enzymes and/or leading to increased NOX activation are only poorly understood.



The aims of the proposed study are (i) to understand the impact of NOX enzymes in the control of neuroinflammation and oxidative stress observed in HAN, (ii) identify the expression profile of specific regulatory genes (microRNAs) and how they control NOX expression during the HIV-mediated neuroinflammatory process and (iii) to evaluate the feasibility of NOX inhibition as a novel approach for the treatment of HAN.

In order to achieve the above-mentioned objectives, we will use different specific approaches: (i) transgenic animal models of HAN cross-bred with NOX-deficient mice to identify the specific role of the different NOX isoforms (NOX1, NOX2 and NOX4) and how their deletion changes the severity and duration of HAN; (ii) cultures of human glial cells (astrocytes and microglia) treated with different HIV-1 clades in vitro in order to study the yet unexplored role of microRNAs in NOX regulation in HAN. Differential expression of microRNAs following treatment with HIV clades with either strong or low neuropathogenic effect will be studied and identified microRNAs will be tested for their effect on regulation on NOX enzymes and other key regulators of neuroinflammation; (iii) organotypic brain slices of transgenic models of HAN allowing pharmacological treatments using neuroprotective agents, NOX inhibitors and antioxidants as well as direct measures of NOX activity and other neuroinflammatory processes.

As of today, no therapy exists for HAN and targeting the ROS generating the NOX enzymes in the brain of HAN patients represents a novel promising approach. This project will generate original data regarding an unexplored pathway of HAN in the context of oxidative stress and NOX enzymes.