The role of the Fas/FasL pathway in neurodegeneration caused by herpes simplex type 1 (HSV-1) infection

Dementia is the loss of cognitive functioning—thinking, remembering, and reasoning—and behavioral abilities to such an extent that it interferes with a person's daily life and activities. Alzheimer's disease (AD) is the single biggest cause of dementia, accounting for 50%–75%, and is primarily a condition of later life. AD is an inflammatory brain disease associated with a combination of environmental agents and genetic influences leading to inflammation of the brain, neuronal cell death, and progressive dementia.

The cardinal features of Alzheimer pathology are amyloid plaques made up of amyloid-β (Aβ) and intracellular neurofibrillary tangles (NFTs) consisting of abnormally phosphorylated tau protein. In addition, neuroinflammation is a prominent feature in pathogenesis.

The AD pathogen hypothesis states that pathogens act as triggers, interacting with genetic factors to initiate the accumulation and/or formation of Aβ, hyperphosphorylated tau proteins, inflammation in the AD brain. Herpes simplex virus (HSV) causes a contagious infection that affects approximately 60% to 95% of adults worldwide. HSV-1 is associated mainly with infections of the mouth, pharynx, face, eye, and central nervous system (CNS). People infected with HSV can expect to have several (typically four or five) outbreaks (symptomatic recurrences) within a year. However, some people remain latently infected without symptoms. All conditions leading to suppression of immune functioning may lead to reactivation of herpes infections. Many studies have strongly supported the concept that proposes that HSV1 enters the brain in older age as the immune system declines and establishes latent residence there. During events such as immunosuppression, peripheral infection, and stress, the virus reactivates, causing localized damage and inflammation (in effect, a mild type of encephalitis). Repeated reactivations lead to the accumulation of damage, the formation of amyloid plaques and neurofibrillary tangles, and eventually to AD. Fas/CD95 is a member of the TNFR superfamily, which plays an important role in regulating cell life span but also proliferation, fibrosis and inflammation. Receptor-dependent Fas/FasL apoptotic pathway can participate both in direct elimination of HSV infection, but also in a complex regulation of the local neuroinflammatory response and mounting of the specific anti-viral response.

The aim of this study is to elucidate the role of Fas/FasL apoptotic and non-apoptotic pathways in HSV-1 induced neuroinflammation and its possible role in development of brain pathologies, such as Alzheimer's disease.

The study will use two models: (i) in vitro model of microglial cultures and (ii) the murine model of HSV-1 infection of the central nervous system with a highly neurotropic human HSV-1 strain applied to wild-type mice but also to mice strains lacking functional Fas or its ligand, FasL. We plan to use mice with (a) primary infection, (b) latently infected mice and latently infected mice subjected to reactivation with thermal stress (TS). *Additionally, we also plan to find correlation between lack of functional Fas/FasL pathway and cognitive impairments using behavioural tests.*

Economic costs of AD are significant for the health system given the resources used to prevent, diagnose, treat and manage dementia. The costs of dementia to society extend beyond these direct costs, as the disease impacts individuals, families and careers both economically and in terms of their quality of life. To date, no drug can successfully treat AD. Current approaches focus on helping people maintain mental function and slow down certain problems, such as memory loss. Therefore, there is a constant need to develop therapies targeting specific molecular and cellular mechanisms so that the actual underlying cause of the disease can be stopped or prevented.