Exploring the Role of Aging in Cerebral Ischemic Small Vessel Disease Using Notch3 Mutant Mice

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Exploring the Role of Aging in Cerebral Ischemic Small Vessel Disease Using Notch3 Mutant Mice

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Research Abstract

Cerebral small vessel disease (SVD) is one of the most prevalent neurological conditions of old age, and a leading cause of stroke and cognitive impairment. In this application, we propose to investigate the role of aging in the development of SVD in a mouse model of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), the most common genetic form of cerebral SVD. CADASIL is caused by dominant mutations involving cysteine residues in the extracellular domain of the Notch 3 receptor, and is characterized by progressive degeneration smooth muscle cells (SMCs) in the small penetrating arteries of the brain and accumulation of granular osmiophilic material (GOM) in vessel walls. CADASIL patients start suffering recurrent ischemic strokes in their thirties or forties, and progressive cognitive impairment and dementia starting in their fifties or sixties. Based on the observations that: 1) patients with loss-of-function Notch 3 mutations do not have overt vascular developmental abnormalities, and 2) heterozygous patients develop SVD much later in life than homozygous patients, we hypothesize that the requirements for Notch 3 signaling are higher in old age than during development or at younger ages. Therefore, it seems likely that aging will influence experimental outcomes related to Notch 3 signaling manipulation, and that older mice will be better models to study the molecular and cellular mechanisms linking Notch 3 signaling to SVD. In order to study this, we propose to test the hypothesis that the impact of manipulating Notch 3 signaling on SVD-relevant phenotypes in mice will change with age. In order to test our hypothesis, we will utilize mice that we generated and characterized in previous publications (Arboleda-Velasquez et al., 2008; Arboleda-Velasquez et al., 2011), including a Notch 3 knockout and two knockin models that allow inducible expression of either wild type human Notch 3 or human Notch 3 carrying the C455R CADASIL mutation, which lies in the Notch 3 ligand binding domain (LBD) (Arboleda- Velasquez et al., 2002). Our analyses of these model mice show that the C455R mutation impairs signaling in vitro and in vivo, leads to a robust SMC pathology, and (like other published CADASIL mutations located in the LBD, C428S) displays dominant-negative properties. In the UH2 phase of the project, we plan to: 1) breed mice carrying Notch 3 mutations and age them out to 24 months for use in the UH3 phase of the project and 2) determine feasibility by examining Notch 3 transgene expression in vessels of aged mice. During the UH3 phase of the project, we propose the following experimental goals: 1) to examine how age affects the impact of manipulating Notch 3 signaling on SVD by monitoring the progression of SVD phenotypes and changes in SMC gene expression in aged and young wildtype and Notch 3 mutant mice; and 2) to monitor the ability of an inducible wildtype human Notch 3 transgene to rescue SVD phenotypes as mice age. Ultimately, these studies are designed to establish whether old mice carrying mutations in Notch 3 are a more appropriate model to study SVD and whether the impact of manipulating Notch 3 signaling on SVD-relevant phenotypes in mice will change with age.

Lay Summary
Cerebral small vessel disease (SVD) is one of the most prevalent neurological conditions of old age, and a leading cause of stroke and cognitive impairment. We propose to investigate the role of aging in the development of SVD in a mouse model of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), the most common genetic form of cerebral SVD, that is caused by dominant mutations involving cysteine residues in the extracellular domain of the Notch 3 receptor and characterized by progressive degeneration smooth muscle cells (SMCs) in the small penetrating arteries of the brain and accumulation of granular osmiophilic material (GOM) in vessel walls. In order to test our

hypothesis that the requirements for Notch 3 signaling are higher in old age than during development or at younger ages, we will use aged Notch 3 mutant mice that we generated and characterized in previous publications (Arboleda- Velasquez et al., 2008; Arboleda-Velasquez et al., 2011). Ultimately, these studies may provide a new model in which to study the molecular and signaling mechanisms linking advanced age to SVD.

Further information available at:

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