Underlying Mechanisms of Vascular Disease

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Country

USA

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Underlying Mechanisms of Vascular Disease

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The project/programme is most relevant to:

Alzheimer's disease & other dementias

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CADASIL, Vascular Diseases, NOTCH1 gene, NOTCH4 gene, Tunica Media

Research Abstract

? DESCRIPTION (provided by applicant): Small vessel diseases are conditions characterized by the narrowing of small arteries leading to an imbalance of blood supply upon demand. This results in a progressive chronic hypoperfusion with detrimental outcomes for the affected organ system and for the patient. The affected vascular beds are not accessible to common percutaneous intervention or vascular grafting. Chronic hypoperfusion and subsequent ischemia

are refractory to many therapies with poor long-term outcome. Recent advances in genetic evaluation have identified several genetic variants causing cerebrovascular small vessel diseases. These have common clinical presentation including recurrent strokes, progressive white matter degeneration, and debilitating dementia. The link between these pathologies are defects in the tunica media of arteries, which is composed mainly of vascular smooth muscle cells (vSMC). The functional integrity of this muscular layer is essential for its function, thus alterations in the contractile properties or changes in the identity of vSMC can result in structurl anomalies that impair compliance. The objective of this U01 application is to expand and validate findings obtained from animal models into humans to promote translation. Our recent discoveries indicate that the identity, as well as the maintenance of vSMC fate and contractile properties requires constant signaling from NOTCH 1 and 3. It has been long recognized that mutations in NOTCH 3 result in a devastating neurological disease: CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). In this disease, NOTCH 3 mutations result in progressive degeneration of the tunica media that is first manifested in smaller arteries, particularly those in the brain but the disease is systemic in nature. Interestingly, our animal models indicate that while inactivating mutations in Notch3 are necessary, loss of function of this gene is not sufficient to trigger the disease; in addition reduction of Notch1 is also required. This new information provides the opportunity for therapeutic intervention in the treatment of CADASIL. While a clinical trial is the eventual goal o this application, validation of these findings using the NIH Clinical Center is a first step to tes the hypothesis that correction in NOTCH1 signaling will ameliorate the progressive degeneration of the tunica media typical of CADASIL patients. Thus, here we present three specific aims: (1) To inquire whether alterations of Notch signaling in CADASIL patients affect vascular homeostasis in non-cerebral vascular beds and establish a clinical baseline for a potential clinical trial; (2) To determine whether individuals with CADASIL exhibit lower levels of NOTCH1 expression and whether the clinical stage of the disease (or outcome) shows correlation with depressed activation of this pathway and (3) To determine if modulation of NOTCH1 signaling could be translated to a human clinical trial in CADASIL patients. Narrative: Vascular pathologies affecting small vessels underlie many hereditary multi-organ diseases. While most of the underlying genetic mutations have been identified, effective new treatments have been more difficult to develop. This application proposes to explore a novel therapy for one of those diseases: CADASIL that causes migranes, dementia and death.

Lay Summary
Relevance to Public Health Vascular pathologies affecting small vessels underlie many hereditary multi-organ diseases. While most of the underlying genetic mutations have been identified, effective new treatments have been more difficult to develop. This application proposes to explore a novel therapy for one of those diseases: CADASIL that causes migranes, dementia and death.

Further information available at:

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