Novel pathological features and potential therapeutic approaches for CADASIL: insights obtained from a mouse model of CADASIL

Xiao-Yun Liu 1, *, Maria E. Gonzalez-Toledo 1, *, Austin Fagan 2, Wei-Ming Duan 3, Yanying Liu 4, Siyuan Zhang 1, Bin Li 1, Chun-Shu Piao 1, Lila Nelson 1, Li-Ru Zhao 1,2,4,5

1Departments of Neurology, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, Louisiana 71130, USA
2Cellular Biology and Anatomy, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, Louisiana 71130, USA
3Department of Anatomy, Capital Medical University, Beijing 100069, China; Center of Parkinson’s Disease, Beijing Institute for Brain Disorders, Beijing 100069, China
4Department of Neurosurgery, State University of New York, Upstate Medical University, Syracuse, New York, 13210, USA
5Department of Neurobiology, Capital Medical University, Beijing 100069, China, Beijing 100069, China

*These authors contributed equally to this work.
Correspondence: Li-Ru Zhao
E-mail: ZHAOL@upstate.edu
Received: November 18, 2014
Published online: December 02, 2014

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common condition of hereditary stroke and vascular dementia. CADASIL is caused by Notch3 mutation, leading to progressive degeneration of vascular smooth muscle cells (vSMCs) of the small arteries in the brain. However, the pathogenesis of CADASIL remains largely unknown, and treatment that can stop or delay the progression of CADASIL is not yet available. Using both wild type mice and transgenic mice carrying the human mutant Notch3 gene (CADASIL mice), we have recently characterized the pathological features of CADASIL and determined the therapeutic efficacy of two hematopoietic growth factors, stem cell factor (SCF) and granulocyte colony-stimulating factor (G-CSF) in CADASIL. Our findings have revealed novel pathological changes in the endothelium of cerebral capillaries and in the neural stem cells (NSCs). We have also observed the impairment of cognitive function in CADASIL mice. Moreover, SCF+G-CSF treatment improves cognitive function, inhibits Notch3 mutation-induced vSMC degeneration, cerebral blood bed reduction, cerebral capillary damage, and NSC loss, and increases neurogenesis and angiogenesis. Here we compile an overview of our recently published studies, which provide new insights into understanding the pathogenesis of CADASIL and developing therapeutic strategies for this devastating neurological disease.

Keywords: CADASIL; SCF, G-CSF; vascular smooth muscle cell; bone marrow-derived cell; neurogenesis; angiogenesis; cognitive impairment; small vascular disease

To cite this article: Xiao-Yun Liu, et al. Novel pathological features and potential therapeutic approaches for CADASIL: insights obtained from a mouse model of CADASIL. Ther Targets Neurol Dis 2014; 1: e434. doi: 10.14800/ttnd.434.

CADASIL is a hereditary cerebral small vascular disease with specific damage in the vascular smooth muscle cells (vSMCs) of small arteries in the brain and in the pericytes of brain capillaries, resulting in poor blood circulation to the
brain especially to the deep brain regions [1]. The cause of CADASIL disease is dominant mutations in the Notch3 gene encoding the Notch3 receptor [2, 3]. Notch3 mutation in CADASIL patients was initially identified in 1996. [2] Since 2000, the genetic diagnosis for CADASIL by testing Notch3 gene mutation has become available [http://www.ninds.nih.gov/disorders/cadasil/cadasil.htm]. However, the pathogenesis for CADASIL has not yet been clarified.

Although Notch3 is not specifically expressed in the vSMCs of small arteries in the brain, the clinical symptoms and pathological changes of CADASIL patients are almost exclusively restricted to the brain. CADASIL occurs in young or middle-aged adults with no hypertension; most CADASIL patients have recurrent ischemic strokes, suffer cognitive decline with impaired motor function and die between the ages of 60-70 [1, 4, 5]. Clinical studies of postmortem brain tissue manifesting the late stage of CADASIL have revealed the pathological features of CADASIL including: 1) the Notch3 extracellular domain (Notch3EC) aggregation and granular osmiophilic material (GOM) deposition surrounding the vSMCs of the small arteries and brain pericytes [1, 6-12], 2) Notch3EC aggregation mixed with other aggregated extracellular matrix proteins, metalloproteinase 3 (TIMP3) and vitronectin (VTN) [13]; and 3) degeneration and loss of vSMCs in the small arteries of the brain [14-16] with impaired arteriolar dilation [17, 18]. CADASIL patients also show reduced cerebral blood flow (chronic hypoperfusion) in the cortex and white matter [4, 19, 20] and display white matter hyperintensities and subcortical infarcts on magnetic resonance imaging [1].

Mouse models of CADASIL have brought new insights into pathogenic understanding of CADASIL. During the past decade, Dr. Joutel’s group has developed several transgenic mouse models of CADASIL, including the model of TghNotch3R90C expressing a full-length human Notch3 with the Arg90Cys mutations under an SM22α promoter driven in vSMCs [21]. These Notch3 mutant mice have been characterized to show similar pathological features of CADASIL patients such as Notch3EC aggregation, Notch3EC-GOM-TIMP3-VTN aggregated complex formation and GOM deposits on vSMCs and/or brain pericytes, the impairments of cerebrovascular function, degenerative vSMCs in the cerebral small arteries, and reduction in cerebral blood flow [1, 13, 21-24].

Our recent research findings have further extended the current understanding on the pathology of CADASIL. Using TghNotch3R90C mice as a mouse model of CADASIL, we have revealed that mitochondrial damage and multiple large digestive lysosomes appear in the capillary pericytes of the brain, suggesting the involvement of autophagy in the degeneration of cerebral capillary pericytes in the CADASIL condition [25]. In addition, using the bone marrow transplantation approach to track bone marrow-derived cells, we have discovered that many cerebral capillaries in the brains of CADASIL mice are completely replaced by the bone marrow-derived endothelial cells, suggesting a progressive loss of cerebral capillary endothelial cells in CADASIL and the involvement of bone marrow-derived endothelial cells in the pathogenesis of CADASIL [26]. In support of this notion, a significant reduction in circulating endothelial progenitor cells (EPCs) has been found in the CADASIL patients with infarcts and dementia [27]. It is therefore plausible that the reduction of circulating EPCs in CADASIL may be due to the persistent consumption of EPCs to replace the damaged endothelium during the progressive degeneration of cerebral capillaries. Furthermore, the neural stem cells (NSCs) and neurogenesis in the neurogenic regions of TghNotch3R90C mice are remarkably decreased as compared to age-matched wildtype mice [26], indicating the impairments of NSC maintenance and differentiation in the condition of CADASIL. A large body of evidence has shown that microvascularature, blood flow and hemodynamics in the neurogenic regions play a crucial role in regulating NSC maintenance, proliferation and differentiation [28-38]. We therefore postulate that CADASIL-associated degeneration of cerebral capillaries provides an unfavorable microenvironment for NSC maintenance and differentiation. Finally, we have also found that TghNotch3R90C mice at ages of 11 and 19 months show the impairments of spatial learning and memory in a water maze test when compared with age-matched wildtype mice [26]. The impaired cognitive function may be associated with the cerebral vascular degeneration caused by the CADASIL-related Notch3 mutation, because vSMC degeneration and cerebral vascular dysfunction have previously been found in 10-month-old TghNotch3R90C mice [21, 23].

Currently, there is no treatment for CADASIL. Supportive interventions for controlling symptoms and decreasing stroke risk are used for affected individuals. However, treatment that can stop or delay the progression of CADASIL is not yet available. Our recent study has revealed that SCF+G-CSF treatment can restrict pathological progression in CADASIL.

SCF and G-CSF were initially discovered as hematopoietic growth factors based on their effectiveness to regulate bone marrow stem cell growth and blood cell production [39, 40]. Recently, considerable evidence has been accumulated to support the contribution of SCF and G-CSF in neuroprotection and brain repair in animal models of ischemic stroke. Systemic administration of SCF [41], G-CSF
or SCF in combination with G-CSF (SCF+G-CSF) in the acute or subacute phase of stroke reduces infarction size and improves functional outcome. Furthermore, in an animal model of chronic stroke we have demonstrated that SCF+G-CSF improves functional recovery in a stable and long-term manner as compared to SCF or G-CSF alone treatment [44]. Moreover, we have also revealed that SCF+G-CSF treatment in chronic stroke enhances neural network rewiring, increases synaptogenesis, angiogenesis, and neurogenesis in the peri-infarct cortex [46-48], and that SCF+G-CSF-induced neural network remodeling and blood vessel regeneration in the cortex surrounding the infarct cavities are required for functional restoration [48].

Using TghNotch3R90C mice as a mouse model of CADASIL, we have recently demonstrated the efficacy of SCF+G-CSF treatment in CADASIL [26]. In this study, SCF+G-CSF was subcutaneously administered for 5 days in 9 month-old CADASIL mice, before vSMC degeneration and cerebrovascular dysfunction occurs [21]. This treatment was repeated 4 times with 1-4 month intervals. We found that SCF+G-CSF treatment significantly improved spatial learning and memory one month after the second treatment as well as 4 months after the fourth treatment. In addition, SCF+G-CSF prevented small arterial vSMC degeneration in both the brain and peripheral tissue, inhibited periodic acid Schiff-positive GOM material deposition in the blood vessels of cerebral cortex, attenuated cerebral capillary degeneration, restricted NSC loss, prevented apoptosis in the cortex, enhanced neurogenesis, and increased blood vessel density in the brain of TghNotch3R90C mice. These findings suggest that SCF+G-CSF intervention restricts CADASIL-associated pathological progression.

Acknowledgments

This study was supported by the American CADASIL foundation and endowment of Daniel Nelson’s family.

References


