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Commentary

Notch–Rho–cGMP interaction: common point of convergence in microvascular aging-related disease

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Vascular smooth muscle biology is increasingly exploited as an interventional target in vascular disease. Vascular smooth muscle Notch3–Rho kinase–cGMP interaction has been implicated in brain and peripheral arteriopathy in CADASIL. In the present commentary, we discuss the potential implications for other, more common non-atherosclerotic microvascular diseases: INOCA and HFpEF. The relation to mechanotransduction, to cellular senescence and to sGC activators as potential intervention agents are described.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited disease, originating from a diversity of mutations in the Notch3 gene [1]. Notch3, a name derived from the inherited serration observed in drosophila wing tips over a century ago, is a family of genes involved in cell contact signaling and plays an important role in morphogenesis, during angiogenesis. CADASIL is a serious disease of the brain. At onset, on average at the age of 30 years, it is marked by migraine and from roughly a decade later it evolves into ischemia, infarctions, infarctions, depression and dementia [1]. CADASIL affects around 1:20,000 people and moderately decreases life expectancy (1–5 years). There is no treatment except for targeting classical cardiovascular risk factors [1].

CADASIL is a non-atherosclerotic microvascular disease. In the brain vasculature, the aberrant Notch3 signaling causes endothelial and non-endothelial cell dysfunction, which underlies a number of functional and histological anomalies. Importantly, white matter lesions are observed on diagnostic magnetic resonance imaging and are caused by granular osmiophilic material (GOM) accumulation and fibrosis around microvascular smooth muscle cells [1]. Such lesions are also associated with dementia in humans. The mutation Notch3R169C in mice mimics important CADASIL features in the brain microvasculature [2]. In the present study by Neves et al. in this model, as well as in human samples, it was shown that similar problems arise in the peripheral microvasculature [3]. Highlights are GOM deposition, increased vasoconstriction, and decreased eNOS–sGC signaling. Increased vasoconstriction involves Rho kinase and increased Ca2+ transients. Increased oxidation stress undermines sGC activity, which decreases NO–cGMP signaling, which could affect a number of vascular functions such as vasodilation, anti-thrombotic function and angiogenesis [4]. The present study suggests that in human samples sGC is oxidized [3]. In Notch3R169C mice; however, reduced H2O2 is identified as the mechanism that undermines vasodilations. Paradoxically, H2O2, like cGMP, can signal through protein kinase G (PKG), but this relates to oxidation of PKG and subsequent hyperpolarization of K+ channels [4]. Therefore, this finding in Notch3R169C mice versus human samples will need further exploration.

Many of the observations in the present study sound familiar, and are encountered in other conditions, such as hypertension and diabetes [5]. Yet, the present paper of Neves et al. should not be considered as a simple repetition of previous work. There is more to it than the meets the eye, as justly remarked upon at the very end of the Discussion section. This is because, in the broader sense, the findings might have important implications for non-atherosclerotic aging of the microvasculature, which is rapidly emerging as an understudied and crucial area. Clinically, microvascular aging is believed to lead to (M)INOCA
(myocardial infarction/ischemia due to non-obstructive coronary artery disease) and HFpEF (heart failure with preserved ejection fraction) [6]. These disorders are almost as frequently observed as obstructive coronary artery disease and are a massive burden on health care [7]. The vascular dysfunction observed in these diseases shows interesting parallels with CADASIL, being featured by microvascular dysfunction, inflammation, rarefaction and fibrosis. Increased oxidative stress, vasoconstriction and decreased vasorelaxation due to decreased NO–cGMP signaling are hallmarks of the dysfunction observed in HFpEF. Generally, the present data in Notch3R169C mice present a phenotype of accelerated (micro)vascular aging that is also observed in INOCA, HFpEF and models thereof [3,8]. Interesting in this regard is also the involvement of Notch in the contractile to synthetic phenotype switch in VSMC; a typical trait of aging [9]. A detailed exploration of cardiac function in Notch3R169C or related models is therefore warranted, especially in aged animals. The little work that has been performed thus far on Notch3 in cardiac disease shows compelling results. In humans, CADASIL with brain ischemia is associated with increased risk for myocardial infarction [10]. In patients with HFrEF (heart failure with reduced ejection fraction), Notch3 genetic variants correlate with the risk of developing atrial fibrillation [11]. Evidence for a causal relationship comes from mouse studies. Notch3tm1Grid mice, which are Notch3-deficient, develop dilated cardiomyopathy featured by inflammation. This is further marked by rarefaction, loss of coronary flow and flow reserve. Myocardial infarction induced by left coronary artery ligation is exaggerated in these mice, which might be an interesting link to the increased risk for AF in humans. Notch3tm1Grid mice display a decreased angiogenic response after myocardial infarction, further referring to rarefaction. This related evidence warrants a detailed exploration of Notch in relation to INOCA and HFpEF.

The present paper by Neves et al., and CADASIL research in general, revolves around microvascular smooth muscle cell function. The focus in the field of INOCA/HFpEF has been on microvascular endothelial cell function, but awareness of the role of vascular smooth muscle cells (VSMCs) has grown. The recognition of the relevance of disturbed NO–cGMP signaling in VSMCs for cardiovascular disease in general, with sGC stimulator and activators as interventional agents, has gained ground. The sGC stimulators only stimulate NO-activated sGC, whereas sGC activators also recruit oxidation-inactivated sGC [5]. The sGC stimulator vericiguat improved major adverse cardiac events in HFrEF [12]. In HFpEF patients, vericiguat improved quality of life but not cardiac damage markers [13]. In HFpEF cardiac oxidative stress due to microvascular aging is prominent, and sGC activators might be more effective. Are sGC activators a potential treatment in CADASIL? Chronic intervention in the Notch3R169C model might provide an important clue.

The role of microvascular VSMCs in non-atherosclerotic vascular disease might not only depend on vasomotor responses, the topic of the current paper by Neves et al. Changes in VSMC proliferation and cardiovascular fibrosis have also been linked to Notch3 signaling [14,15]. In the obese ZSF1 rat, HFpEF model increased cardiac pericyte proliferation and microvascular fibrosis suggest a similar phenotype [8]. The observations might point to a role of altered mechanotransduction leading to a derailed proliferative status of VSMCs. Notch is a well-documented mechanotransduction pathway, among others in vascular tissue, that determines cell fate with the transcription factor YAP1 (Yes-associated protein 1) signaling as an important intermediate [9,16]. Mechanosensing has been implicated in accelerated vascular aging in various ways. Interesting in the context of this commentary is the observation that in VSMCs incomplete maturation of lamin A, an important component of LINC (linker of cytoskeleton and nucleoskeleton complex) mechanosensing, leads to rapid development of (non-atherosclerotic) vascular aging and has also been implicated in aortic calcification [17,18]. Disturbed LINC signaling also leads to VSMC senescence due to increased DNA damage, a major causal factor in vascular aging, which might induce inflammation and fibrosis through the SASP (senescence-associated secretory phenotype) [19,20]. LINC signals either through matrix–cytoskeleton–nuclear envelope interaction or YAP1, which needs lamin A for proper transport into the nucleus [21]. YAP1 signaling has been implicated in senescence in response to DNA damage [22], but this role remains to be confirmed in vascular tissue. Interestingly, cGMP is a well-known inhibitor of RhoA/ROCK signaling, and the latter pathway importantly modulates both LINC and YAP [19]. It would therefore be interesting to examine if RhoA/ROCK signaling is a point of convergence in several models of accelerated vascular aging, in particular Notch3-, Lamin A-, DNA damage response-based mouse models and HFpEF models, not only in relation to impaired vasomotion but also in relation to mechanosensing, senescence and the SASP (Figure 1). In relation to clinical translation, the possibility to test the effect a single, clinically applicable, cGMP-augmenting drug, such as an sGC activator, in parallel in these models sounds very appealing. Thus, the current publication generates ideas for wider exploitation of the identified signaling pathways.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.
Disturbed Notch and LINC mechanosensing in fibrotic environments leads to transcriptional and DNA damage-mediated oxidation of sGC, inhibiting cGMP signaling. YAP1 is an important modulator of Notch-mediated transcription, and Lamin A, as a part of the LINC signaling pathway, controls YAP1 nuclear entrance. Decreased cGMP and Notch-mediated transcription of GEFs increase RhoA/ROCK kinase signaling, leading to further derailment of the mechanosensing pathways. Rho also creates a pro-contractile state of the myosin-actin complex. DNA damage leads to senescence and SASP, increasing inflammation and oxidation, and increasing fibrosis, further dysregulating mechanosensing. Treatment with sGC activator interrupts the pathological process by increasing cGMP under oxidative conditions, attenuating Rho, and decreasing contraction. Possibly, sGC activator could also beneficially modulate senescence, fibrosis and inflammation. Thus, sGC activators could be interesting for treatment of CADASIL, INOCA and HFpEF, in which microvascular plays a central role.

Abbreviations

GEF, guanine nucleotide-exchange factor; LINC, linker of nucleoskeleton and cytoskeleton; NICD, notch intracellular domain; NOX1, NADPH oxidase 1; SASP, senescence-associated secretory phenotype; sGC, soluble guanylyl cyclase; YAP1, Yes-associated protein 1.

References


