The Role of NRF2 in Cerebrovascular Protection: Implications for Vascular Cognitive Impairment and Dementia (VCID)

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BACKGROUND

- Vascular Cognitive Impairment and Dementia (VCID) represents a significant public health concern, with an increasing prevalence among the elderly.
- VCID is characterized by cognitive decline related to vascular pathologies, such as cerebral small vessel disease and atherosclerosis.
- The pathophysiology of VCID involves oxidative stress, inflammation, blood-brain barrier (BBB) dysfunction, and impaired cerebral blood flow regulation.
- Nuclear factor erythroid 2-related factor 2 (NRF2) is a master regulator of antioxidant responses and has garnered attention for its potential neuroprotective role in VCID.
- This article explores the effects of NRF2 on various components of the vasculature, including endothelial cells, vascular smooth muscle cells (VSMC), pericytes, and perivascular macrophages, with a focus on its potential as a therapeutic target.

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Results

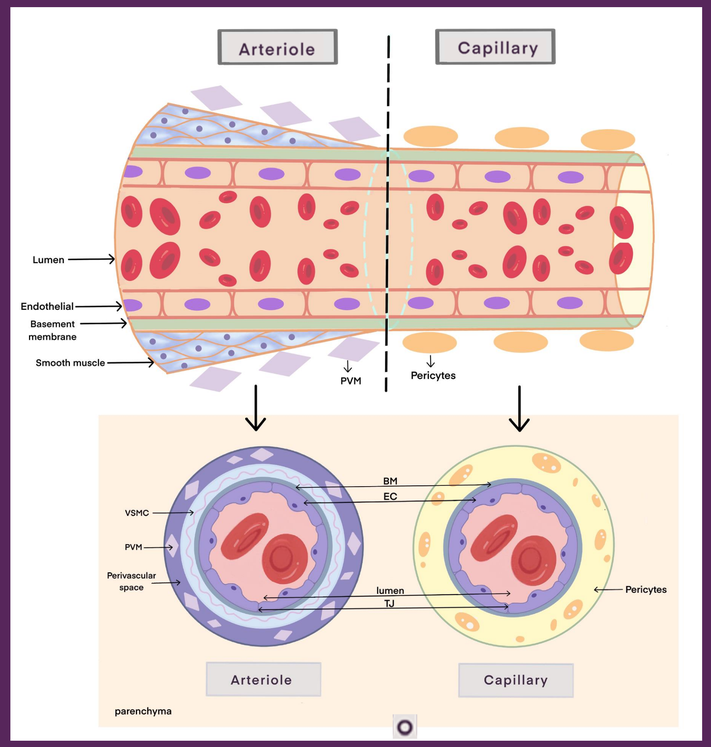

Figure 1: Overview of cerebral vasulature

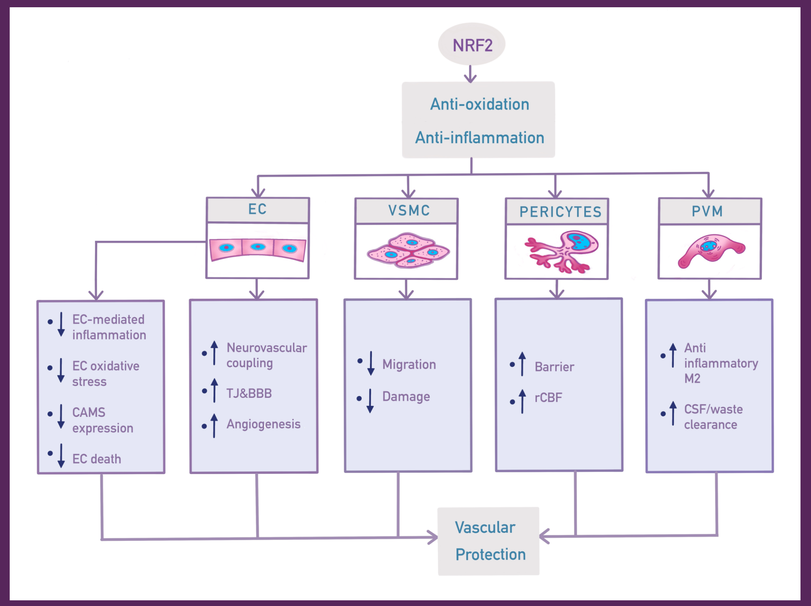

Figure 2: NRF2 exhibits different neuroprotective effects through different cells

Results

- • **Endothelial Cells (ECs)**:
- NRF2 exerts protective effects in ECs by reducing inflammation and oxidative stress, thereby preserving BBB integrity and regulating cerebral blood flow. It also plays a role in maintaining cell adhesion molecules (CAMs) and junction proteins critical for EC function.

- • **Vascular Smooth Muscle Cells (VSMC):**
- NRF2 modulates VSMC phenotype and function, with a potential role in preventing inflammation and oxidative stress-mediated VSMC dysfunction. It may contribute to cerebral blood flow regulation by influencing contractile and synthetic VSMC.

- • **Pericytes**:
- Although the precise role of NRF2 in pericytes is less clear, it is suggested that NRF2 may protect pericytes from oxidative stress, potentially contributing to BBB maintenance and cerebral blood flow regulation.

- • **Perivascular Macrophages**:
- NRF2 may mitigate oxidative stress and inflammation in perivascular macrophages, aiding in BBB integrity and clearance of metabolic waste products, such as amyloid beta.

Conclusion

- NRF2 emerges as a promising therapeutic target in the context of VCID due to its multifaceted protective effects within the vascular components of the brain.
- By alleviating oxidative stress and inflammation, NRF2 may help preserve BBB integrity, regulate cerebral blood flow, and facilitate the clearance of neurotoxic substances.
- VCID remains a complex and challenging condition, and NRF2 modulation offers a promising avenue for future research and therapeutic strategies aimed at ameliorating cognitive impairment associated with vascular pathologies.