HOT OFF THE PRESS: BASIC

Let's AIM2 find treatments for vascular dementia

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Vascular dementia is responsible for up to 30% of dementia cases, and is described as cognitive impairment arising from cerebrovascular disease leading to impaired blood flow to the brain¹. However, vascular complications are evident in other forms of dementia, and many patients are diagnosed with mixed dementia where they have both a neurodegenerative disorder such as Alzheimer's disease and cerebrovascular disease¹. At present, there are no disease-modifying therapies available for vascular dementia and current treatments can target symptoms only as the underlying mechanisms are not well understood.

Inflammation is emerging as a potential key player in the pathophysiology of dementia. Sustained inflammation appears to have detrimental effects in the brain and can promote cerebrovascular dysfunction, oxidative stress, white matter injury and blood brain barrier (BBB) breakdown – all processes currently thought to contribute to the pathophysiology of vascular dementia¹. Inflammatory responses are initiated through the inflammasome, a multiprotein complex that produces mature IL-1 β and/or IL-18. Inflammasome complexes comprise a pattern recognition receptor (PRR), an apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and caspase-1. Different inflammasomes are characterised by their PRR such as nucleotide-binding domain and leucine-rich repeat containing family pyrin domain containing 3 (NLRP3) and absent in melanoma 2 (AIM2)².

A recent paper by Poh L et al in *Molecular Psychiatry* has added to our understanding of the role of inflammation in vascular dementia. This elegant study demonstrated that the AIM2 inflammasome contributes to the pathophysiology of bilateral carotid artery stenosis (BCAS), a mouse model of vascular dementia². Chronic cerebral hypoperfusion – which is caused by experimental BCAS – is a major cause of vascular dementia due to chronic cerebral hypoperfusion-induced brain injury². Using this model, Poh et al found upregulation of the inflammasome receptors including AIM2 in the cerebral cortex and hippocampus – regions that play a critical role in cognitive function. The products of inflammasome activation, IL-1 β and IL-18, were also found to be increased in the cerebral cortex and hippocampus of BCAS mice specifically in a spatial and temporal manner. There was also evidence for brain injury including elevated apoptosis, pyroptosis, glial-cell activation, white matter lesions, myelin breakdown and hippocampal neuronal loss in BCAS mice. Interestingly, double stranded DNA – the only known agonist of the AIM2 inflammasome receptor – was increased in the serum of BCAS mice. Involvement of the AIM2 inflammasome in BCAS-induced brain injury was confirmed using AIM2-deficient mice in which there was blunted BCAS-induced inflammasome activation, IL-1 β and IL-18 levels and brain injury.

Importantly, AIM2-deficiency also reduced BCAS-induced cognitive decline.

Inflammasome activity has been implicated in the pathophysiology of major cardiovascular risk

factors for vascular dementia, such as hypertension and stroke. Specifically, the AIM2 inflammasome has been now also shown to contribute to brain injury and cognitive impairment following stroke³.

Many stroke patients go on to develop cognitive deficits, and approximately 30% of patients that survive a severe stroke develop dementia within 1 year¹. Hence, the study by Poh et al is consistent with the concept that AIM2 inflammasome antagonists may have therapeutic potential to reduce the risk of developing vascular dementia after stroke, or indeed to treat overt vascular dementia. Currently, there are no drugs available that specifically target the AIM2 inflammasome but there are commercially available drugs which target its inflammasome partner, caspase-1. Importantly, VX-765, a caspase-1 inhibitor, has been shown to reverse cognitive deficits and brain inflammation in a mouse model of Alzheimer's disease⁴. Alternatively, interleukin products of inflammasome activation in vascular dementia could be targeted with clinically available antagonists for IL-1 β and its receptor (IL-1 receptor) drugs which are currently used to treat several forms of arthritis⁵.

References

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The poster features a circular image of a city skyline at night with a large play button icon overlaid. A green speech bubble with the text 'the global hypertension hub' is positioned near the top right of the circle. To the right of the image, the text 'JOINT MEETING ESH-ISH 2021 ON-AIR' is displayed in large, bold, blue and green letters. Below this, the dates 'April 11-14, 2021' and the website 'www.hypertension2021.org' are listed. At the bottom, there are logos for the European Society of Hypertension (ESH), International Society of Hypertension (ISH), and British and Irish Hypertension Society (BIHS). A green banner at the very bottom contains social media handles for Twitter and Facebook, and the hashtag #hypertension2021.

the global hypertension hub

JOINT MEETING
ESH-ISH
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