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Editorial

Deficiency of TLR4 ameliorates hypoperfusion-induced brain pathology

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Abstract

Microglial inflammatory activation contributes to chronic cerebral hypoperfusion-induced brain pathology. This editorial highlights a study by Qin et al. (*Theranostics* 2018; 8(19):5434-5451. doi:10.7150/thno.27882) that deficiency of TLR4 attenuates cognitive dysfunction and white matter injury by reducing autophagy and pro-inflammatory activation in microglia.

Key words: chronic cerebral hypoperfusion, microglia, inflammation, autophagy, TLR4.

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Chronic cerebral hypoperfusion resulting from cerebral angiopathy or cardiac dysfunction is often associated with neurodegenerative diseases, especially Alzheimer's disease (AD) and subcortical ischemic vascular dementia [1, 2]. One prospective study based on a large population recently showed that cerebral hypoperfusion occurs in pre-symptomatic AD patients and predicts the future development of AD [3]. The chronically hypoperfused brain is pathologically characterized by white matter injury with demyelination and neuronal degeneration [2]. Chronic cerebral hypoperfusion in mice can be induced by installing microcoils around the common carotid arteries on both sides of the animal, creating bilateral common carotid artery stenosis (BCAS) [4]. Studies of the effects of chronic cerebral hypoperfusion using the BCAS animal model have shown that microglia are highly activated [4, 5]. In a recent study, inhibition of microglial inflammatory activation reduced white matter lesions and improved cognitive deficits in BCAS mice [6], suggesting that microglia-dominated neurotoxic inflammatory activation might be one of the pathogenic mechanisms. However, the mechanism by which microglial activation is initiated and regulated in the hypoperfused brain remains unclear.

In the recently published study [7], Dr. Wei Wang and colleagues established a BCAS model in wild-type C57BL/6J mice and CB57/10Scnj mice, which carry a spontaneous deletion of the gene encoding Toll-like receptor 4 (TLR4). They observed that deficiency of TLR4 significantly attenuates white matter lesions and improves cognitive function in BCAS mice. Interestingly, TLR4 deficiency shifts microglial activation from a pro-inflammatory to an anti-inflammatory profile in association with a decrease of autophagic activity in microglia. The authors further inhibited and activated autophagy in LPS- or interleukin 4 - treated cultured microglia with bafilomycin (or wortmannin) and rapamycin, respectively. They showed that activation of autophagy facilitates pro-inflammatory activation, while inhibition of autophagy displays contrary effects. Thus, they suggested that TLR4 deficiency induces anti-inflammatory polarization by inhibiting autophagy in microglia.

The findings are interesting. However, further studies are necessary in order to clarify a few

important issues on the pathogenic role of TLR4 in chronically hypoperfused brain:

- No causal link has yet been demonstrated between autophagic activation and TLR4-mediated inflammatory polarization in microglia. To test whether autophagy mediates TLR4 to regulate microglial inflammatory activation, autophagic activity in TLR4-deficient and wild-type microglia needs to be kept constant during inflammatory activation. Thus, some signaling molecules essential for autophagy, such as ATG5 or ATG7, can be deleted. When techniques to build genetic mouse or cell models are not available, microglia should be at least treated with autophagic inhibitors or enhancers.
- Oxygen-glucose deprivation (OGD), rather than lipopolysaccharide (LPS), should be used to activate cultured microglia [8]. LPS-activated microglia do not model activated microglia in the hypoperfused brain.
- In this study, a BCAS model was established in mice completely deficient in TLR4. The protective effects of TLR4 deficiency observed in this study might be attributed to its deficiency in microglia, but also to its deficiency in other cells, given that TLR4 may also be expressed on neurons [9], astrocytes [10] and endothelial cells [11]. The protective effect of TLR4-deficient microglia on chronic hypoperfusion-induced brain pathology needs to be investigated in a mouse model with a TLR4 deletion specifically in microglia; alternatively, TLR4-deficient bone marrow chimera mice might be used to create BCAS models [12].

Chronic cerebral hypoperfusion is manifested in a wide variety of neurodegenerative and cerebral vascular diseases with a common feature of cognitive impairment. The underlying pathophysiology is not well understood and needs further investigation. Dr. Wang's study demonstrates that TLR4 contributes to chronic cerebral hypoperfusion-induced pro-inflammation and subsequent demyelination and neurodegeneration. This study sheds light on the understanding of pathogenic mechanisms and may offer a novel therapeutic target for patients with dementia.

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Competing Interests

The authors have declared that no competing interest exists.

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