



## Editorial

## Sirtuin 5 promotes ischemia/reperfusion-induced blood-brain barrier damage after stroke



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Circulating inflammatory cells influence endothelial function, which is important for vascular homeostasis and diseases [1]. Endothelial dysfunction is induced by several cardiovascular risk factors (e.g. hypertension, diabetes, and dyslipidemia) and environmental factors (e.g. hypoxia, infection, smoking, and air pollution) [2]. Recently, we have demonstrated that endothelial AMP-activated protein kinase (AMPK) plays an important role in the regulation of microvascular tone and blood pressure in mice [3]. Additionally, AMPK plays an important role in pulmonary artery endothelial cells and protects against the development of pulmonary hypertension [4]. Mechanistically, endothelial AMPK is a metabolic sensor, which contributes to the activation of endothelial nitric oxide (NO) synthase (eNOS) [2]. Mammalian sirtuins (SIRT5) are a family of seven proteins that regulate cellular metabolism and functions [5]. It is known that they are distributed in the cytoplasm (SIRT1, 2), the mitochondria (SIRT3, 4, 5), and the nucleus (SIRT1, 2, 6, 7) [5]. Among them, SIRT1 has been extensively investigated in the cardiovascular system and plays a pivotal role in mediating cell death and survival [5]. However, the functions of SIRT5 in the cardiovascular system have been poorly investigated, particularly its function in vivo.

Stroke-induced damage of the blood-brain barrier (BBB) is induced by endothelial dysfunction and migrating inflammatory cells. It has been suggested that AMPK $\alpha$ 1 and AMPK $\alpha$ 2 may play different roles in endothelial function and inflammatory cell survival during hypoxia [2]. Recently, it has been shown that SIRT5 is under the control of both

PGC-1 $\alpha$ , a master regulatory of mitochondrial biogenesis, and AMPK. SIRT5 is involved in the regulation of mitochondrial energy metabolism [6]. Therefore, it is of great interest to develop novel strategies targeting AMPK and SIRT5 for the protection of BBB function and stroke-induced brain damage. In this issue of *International Journal of Cardiology*, Diaz-Cañestro et al. [7] assessed the role of SIRT5 in the regulation of ischemia/reperfusion-induced brain damage in vivo by using a mouse model of transient middle cerebral artery (MCA) occlusion. The authors demonstrated that SIRT5 is upregulated in both the peripheral blood monocytes (PBMCs) of patients with acute ischemic stroke and the MCA of mice after MCA occlusion. Additionally, they showed that SIRT5 promotes ischemia/reperfusion-induced brain damage by increasing BBB permeability through degradation of occludin. Finally, they concluded that SIRT5 may be a novel therapeutic target [7]. Why is this article so intriguing and important? First, to understand the specific role of the SIRT5 in ischemia/reperfusion-induced BBB damage, the authors performed an in vivo study using mice lacking SIRT5. Additionally, to elucidate the relationship of SIRT5 in brain endothelial cells with stroke size, the authors used an in vivo knockdown approach to target endothelial cells. Next, to investigate the mechanisms underlying the blunted BBB damage and to translate the in vivo murine data to human cells, the authors established an in vitro BBB model consisting of a monolayer of human brain microvascular endothelial cells. To elucidate the potential mechanisms for the effect of SIRT5 knockdown on BBB permeability, the authors assessed early responses on tight and adherens junctional proteins. Importantly, to assess the regulation of SIRT5 in patients with ischemic stroke, the authors measured the SIRT5 expression in PBMCs of patients. Altogether, the authors precisely demonstrate the molecular mechanism of endothelial cell SIRT5 function and its requirement for the development of ischemia/reperfusion-induced brain damage. Therefore, this study provides novel information about the role of SIRT5 in endothelial cells in the development of ischemia/reperfusion-induced brain damage. These data provide evidence towards the effectiveness of SIRT5 inhibitors in treating patients with acute ischemic stroke.

## 1. Clinical significance

As the authors noted, the only available treatment for ischemic stroke is early revascularization with thrombolysis and/or retrieval of the occluding thrombus. Thus, it is important to develop novel therapeutic strategies for stroke patients, including novel molecular targets

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that modulate BBB breakdown after reperfusion. As mentioned above, AMPK-mediated protection of endothelial function seems to be linked with its inhibitory effects on SIRT5 [6]. Several drugs such as metformin and statins activate AMPK and protect against the development of cardiovascular diseases [8,9]. Thus, the protection of vascular function by these drugs could be mediated by SIRT5. Indeed, it has been demonstrated that metformin protects against the development of brain damage after stroke in an AMPK-dependent manner [10]. Unfortunately, in the present study, the authors did not investigate AMPK function in the SIRT5 knockout mice. These reports, including the present study, suggest that novel therapeutic strategies could be developed for patients with acute ischemic stroke. Thus, SIRT5 may represent a novel therapeutic target against endothelial dysfunction and BBB damage after stroke. The present study also suggests that SIRT5 upregulation can be detected in the peripheral blood of patients with acute ischemic stroke [7]. Thus, we expect that SIRT5 may be useful as a biomarker for assessing therapeutic effects in patients with stroke.

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#### Disclosures

None.

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