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COMMENT

The E2F1-IREB2 axis regulates neuronal ferroptosis in cerebral ischemia

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Ferroptosis is a type of iron-dependent non-apoptotic regulated cell death characterized by excessive lipid peroxidation of cellular membranes caused by disruption of the antioxidant defense system and/or imbalanced cellular metabolism [1, 2]. Emerging evidence implicates ferroptosis in various disorders, including acute organ injury and neurodegenerative diseases, and in a cellular mechanism that promotes tumor suppression [1, 3]. The pathophysiologic importance of ferroptosis in cerebral ischemia–reperfusion damage, stroke, and post-traumatic brain injury has also been reported [4, 5]. Thus, a better understanding of the regulatory system of ferroptosis and the development of an effective intervention could lead to therapies for these disorders.

As the name "ferro"ptosis implies, iron is an important factor in the execution of ferroptosis. Intracellular labile iron (especially Fe^{2+}) promotes ferroptosis by the Fenton reaction catalyzing the formation of lipid radicals, which drives lipid peroxidation [6]. Consequently, many cellular processes related to the metabolism of cellular labile iron alter cell sensitivity to ferroptosis [1]. Iron regulatory protein 2 (IRP2), which is encoded by the *IREB2* gene, regulates cellular iron homeostasis through post-transcriptional regulation of iron metabolism-related proteins, such as transferrin receptor-1 and ferritin [7]. Normally, IRP2 is activated when cellular iron levels are low, initiating an iron-starvation response, which increases the available iron pool by modulating iron uptake, storage, and export. In the context of ferroptosis, accumulation of cellular iron by the activation of IRP2 has been reported to promote ferroptosis [8].

The transcription factor E2F family, including E2F1, plays a crucial role in the control of the cell cycle, metabolic activity, and cell death relevant to a wide range of disease settings, including cancer and neuronal injury [9, 10]. MicroRNAs are transcriptional targets of the E2F family and control the transcriptional network of the E2F family.

In the present work on this issue of *Hypertension Research*, Zheng et al. [11] examined the role of E2F1 in the regulation of neuronal ferroptosis using mouse cortical neurons treated with oxygen–glucose deprivation and reoxygenation (OGD/R), which is an in vitro model of cerebral ischemia–reperfusion damage. OGD/R caused lipid peroxidation and induced neuronal cell death that was prevented by ferrostatin-1, a ferroptosis inhibitor with lipid radical scavenging activity, indicating the involvement of ferroptosis in the mechanism of cell death. The authors found that OGD/R treatment markedly increased the mRNA expression of *E2F1* and *IREB2* and decreased miR-122-5p expression accompanied by increased cellular Fe^{2+} content. Subsequent assays and analysis demonstrated that the transcription factor E2F1 directly downregulates the expression of miR-122-5b, which upregulates *IREB2* transcription. Eventually, upregulated *IREB2* contributes to the promotion of oxidative stress and ferroptosis in OGD/R, possibly via increased cellular iron contents. According to this mechanism, gene silencing of E2F1 ameliorates the oxidative stress and ferroptosis induced by OGD/R. Taken together, the study showed the regulatory system of the E2F1-miR-122-5b-IREB2 axis in OGD/R-induced neuronal ferroptosis, which is relevant to cerebral ischemia (Fig. 1). Consistent with these findings, a previous study reported upregulated E2F1 and decreased miR-122 in subjects with ischemic stroke, which were in parallel with decreased cell viability, increased cerebral infarction and neuronal depletion [12]. Therefore, E2F1 might be a therapeutic target for the treatment of cerebral ischemic damage by preventing neuronal ferroptosis.

As a limitation of the present study, the role of E2F1 in ferroptosis was only examined in the neuronal OGD/R model. Future research is warranted to examine the role of E2F1 in commonly used ferroptosis settings, such as in pharmacological induction by erastin and RSL3 and in genetic *GPX4* depletion [1]. If the regulation of E2F1 is observed in global

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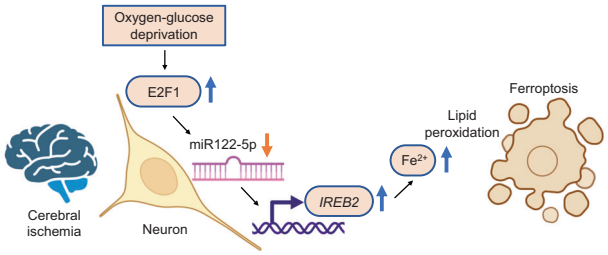

Fig. 1 The proposed model of neuronal regulation by the E2F1-miR-122-5b-IREB2 axis in cerebral ischemia. Increased E2F1 expression in oxygen-glucose deprivation and reperfusion inhibits miR-122-5p transcription to upregulate *IREB2*. Increased *IREB2* expression possibly increases cellular labile iron levels, contributing to the promotion of lipid peroxidation and ferroptosis

ferroptosis settings, as in OGD/R-induced neuronal ferroptosis, E2F1 would be a therapeutic target for diverse ferroptosis-related diseases not limited to cerebral ischemia.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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