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Nrdp1 increases ischemia induced primary rat cerebral cortical neurons and pheochromocytoma cells apoptosis via downregulation of HIF-1α protein

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Abstract: Objective Neuregulin receptor degradation protein-1 (Nrdp1) is an E3 ubiquitin ligase that regulates the proteasomal degradation and activity of proteins involved in cell growth, inflammation and apoptosis. In a previous study, we found that ischemia markedly upregulated Nrdp1 expression in cortical brain tissue and in cultured primary cortical neurons. The present study was aimed to investigate the role of Nrdp1 in ischemic neuronal injury on an in vitro ischemic of oxygen-glucose deprivation (OGD). Methods Primary rat cerebral cortical neurons and pheochromocytoma (PC12) cells were infected with adenoviral constructs expressing Nrdp1 gene or its siRNA before exposing to OGD treatment. Results Nrdp1 expression enhanced OGD-induced neuron apoptosis as compared with the green fluorescent protein (GFP) control; thus, these effects were attenuated by overexpression of Nrdp1-siRNA. Furthermore, the mechanisms underlying these effects were may be associated with the down-regulation of HIF-1α protein that may be secondary to accelerated USP8 degradation mediated by Nrdp1. Conclusion These data provide in vitro evidence for an important role for Nrdp1 in regulating OGD-induced ischemic neuronal death, which was accompanied by USP8
degradation and HIF-1α down-regulation. Nrdp1 may constitute a new therapeutic target for ameliorating early ischemic brain injury.

**Keywords:** ischemic stroke; neuronal injury; Nrdp1; apoptosis; HIF-1α; USP8