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Targeting Apoptosis-Inducing Factor as a Novel Therapeutic Strategy for Preventing Perinatal Brain Injury

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Karl Isaksson, Medicinaregatan 16A, Göteborg, den 6 februari 2020, klockan 13.00

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Avhandlingen baseras på följande delarbeten

I. Sun Y, Li T, Xie C, Xu Y, Zhou K, **Rodriguez J**, Han W, Wang X, Kroemer G, Modjtahedi N, Blomgren K, Zhu C. "Haploinsufficiency in the mitochondrial protein CHCHD4 reduces brain injury in a mouse model of neonatal hypoxia-ischemia." *Cell Death & Disease* 2017; doi:10.1038/cddis.2017.196

II. **Rodriguez J**, Zhang Y, Li T, Xie C, Sun Y, Xu Y, Zhou K, Huo K, Wang Y, Wang X, Andersson D, Ståhlberg A, Xing Q, Mallard C, Hagberg H, Modjtahedi N, Kroemer G, Blomgren K, Zhu C. "Lack of the brain-specific isoform of apoptosis-inducing factor aggravates cerebral damage in a model of neonatal hypoxia–ischemia." *Cell Death & Disease* 2018; doi:10.1038/s41419-018-1250-1

III. Li T, Li K, Zhang S, Wang Y, Xu Y, Cronin S, Sun Y, Zhang Y, Xie C, **Rodriguez J**, Zhou K, Hagberg H, Mallard C, Wang X, Penninger J, Kroemer G, Blomgren K, Zhu C. "Overexpression of apoptosis inducing factor aggravates hypoxic-ischemic brain injury in neonatal mice." Submitted 2019

IV. **Rodriguez J**, Xie C, Li T, Sun Y, Xu Y, Li K, Wang Y, Zhou K, Mallard C, Hagberg H, Doti N, Wang X, Zhu C. "Inhibiting the interaction between apoptosis inducing factor and cyclophilin A prevents brain injury in neonatal mice after hypoxia-ischemia." Submitted 2019

SAHLGRENSKA AKADEMIN
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Targeting Apoptosis-Inducing Factor as a Novel Therapeutic Strategy for Preventing Perinatal Brain Injury

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Abstract

Perinatal complications such as asphyxia can cause brain injuries that are often associated with subsequent neurological deficits. The mechanisms of perinatal brain injury are not fully understood, but mitochondria play a prominent role, not only due to their central function in metabolism, but also because many proteins with apoptosis-related functions are located in the mitochondrion. Among these proteins, CHCHD4 and apoptosis-inducing factor (AIF) have already been shown to make important contributions to neuronal cell death upon hypoxia-ischemia (HI), but a better understanding of the mechanisms behind these processes is required for the development of improved treatments. By inducing HI in 9-day-old mice, leading to moderate brain injury, we studied these mechanisms from multiple perspectives. First, we determined the effect of *chchd4* haploinsufficiency, and we showed that neonatal mice with this genotype experienced less brain damage due to reduced translocation of AIF and Cytochrome c from the mitochondrion. Second, we characterized the role of a newly discovered AIF isoform (AIF2), which is only expressed in the brain and the functions of which are unknown. By using *Aif2* knockout mice, we showed that under physiological conditions there is an increase in *Aif1* expression (the ubiquitously expressed isoform) due to a compensatory effect of loss of *Aif2* expression. As a result, these mice showed a higher degree of brain damage after HI and were more vulnerable to oxidative stress. Third, we used another transgenic mouse in which *Aif* was overexpressed by knocking in a proviral insertion of *Aif*, leading to an increased expression of *Aif1* without affecting the expression of *Aif2*. This mouse also showed a higher degree of brain damage and higher levels of oxidative stress. Finally, we used a peptide designed to block the apoptotic function of AIF. The results in young mice showed that the neuroprotective effect of the peptide was greater in male mice than in female mice. In summary, this PhD project has opened new perspectives in the comprehension of the mechanisms by which CHCHD4 and AIF are crucial proteins for brain damage after HI, and it has showed that AIF is a promising therapeutic target for improving outcome after perinatal brain injury.

Keywords: AIF, AIF/CypA complex, apoptosis, asphyxia, CHCHD4, hypoxia-ischemia, mouse, neonatal

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