Epigenetic regulation of apoptosis and inflammation in brain ischemia.

M. Pizzi, Dept. of Molecular and Translational Medicine University of Brescia, Brescia Italy
L. Faggi, Dept. of Molecular and Translational Medicine University of Brescia, Brescia Italy
A. Lanzillotta, Dept. of Molecular and Translational Medicine University of Brescia, Brescia Italy
M. Mota, Dept. of Molecular and Translational Medicine University of Brescia, Brescia Italy
G. Pignataro, Dept. of Neuroscience, Reproductive and Odontostomatological Sciences "Federico II" University of Naples, Naples Italy
E. Parrella, Dept. of Molecular and Translational Medicine University of Brescia, Brescia Italy
V. Porrini, Dept. of Molecular and Translational Medicine University of Brescia, Brescia Italy
M. Schwaninger, Institute of Experimental and Clinical Pharmacology and Toxicology, University of Là¼beck, Là¼beck Germany
L. Annunziato, Dept. of Neuroscience, Reproductive and Odontostomatological Sciences "Federico II" University of Naples, Naples Italy
PF. Spano, Dept. of Molecular and Translational Medicine University of Brescia, Brescia Italy

Ischemic stroke is a major cause of death and long-term disability worldwide. At the present time, effective therapies are still limited. Apoptosis and inflammation are key processes involved in the pathophysiology of stroke. We have shown that noxious ischemia is associated with an aberrant acetylation state of NF-κB/RelA, characterized by a reduced level of total acetylation despite an increase of K310 acetylation. The abnormal RelA acetylation is responsible for the pro-apoptotic transcription during lethal ischemia.

A single post-insult administration of the combination of an HDAC inhibitor, MS-275, and a SIRT1 activator, resveratrol, was shown to be neuroprotective in both transient and permanent models of ischemic stroke, synergistically reducing the infarct size and the associated neurological deficits. The epigenetic treatment was able to restore normal RelA acetylation, switching RelA binding from the pro-apoptotic Bim promoter to the anti-apoptotic Bcl-χL. Moreover, the treatment limited post-ischemic inflammation, decreasing both pro- and anti-inflammatory transcription and microglial/macrophage activation, and reducing the binding of RelA to the pro-inflammatory Nos2 promoter.

More recently, we replaced MS-275 with valproate, an antiepileptic drug also reported as a class I HDACs inhibitor. Valproate was neuroprotective per se at higher doses both in in vitro and in in vivo models of brain ischemia. Interestingly, in a transient model of ischemic stroke, the combination of valproate and resveratrol, at sub-threshold doses, significantly reduced the infarct volume as well as the neurological deficits. Moreover, this drugs combination reversed the insult-mediated increase in the RelA(K310) acetylation. Similarly to MS-275, valproate combined with resveratrol impaired the RelA binding at the pro-apoptotic Bim promoter and reduced the Bim promoter-specific histone acetylation, resulting in reduced Bim promoter activation. These data suggest valproate and resveratrol as a promising ready-to-use strategy for the therapy of post-ischemic brain damage.

In conclusion, the synergistic combination of an HDAC inhibitor and a SIRT1 activator, by reverting the aberrant acetylation of RelA, reduces post-ischemic brain injury. Our results support the use of epigenetic drugs as a potential treatment of acute ischemic stroke in humans.