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Mini Review



# Epigenetic Modifications Related to Oxidative Stress in Ischemic Stroke

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## Abstract

Epigenetic study of heritable modifications of genome without changes in DNA sequence. Recent investigations have documented the importance of these modifications in the regulation expression of genes involved in cell cycle, proliferation and differentiation. Imbalance of epigenetic modifications leads the development of several pathologies. In this review, we describe the relationship between epigenetic modifications and oxidative stress, pointed out the putative use of these changes as potential biomarkers or as therapeutic targets in ischemic stroke.

**Keywords:** Epigenetic, Oxidative Stress, Ischemic Stroke.

**Abbreviations:** DNMTs: DNA Methyltransferases; HATs: Histone Acetyltransferases; 5-mC: 5-Methylcytosine; 5-hmC: 5-Hidroxymethylcytosine; MBP: Methyl-CpG; H2O2: Hydrogen Peroxide; HDAC: Histones Deacetylases; NF: Factor Binding.

## Introduction

Epigenetic study of hereditable molecular mechanisms modulating the gene expression without DNA alterations in the DNA sequence, such as methylation, acetylation, phosphorylation, ubiquitination, and sumoylation, among others [1]. At molecular level, the most common epigenetic modification in DNA is methylation, a reaction catalyzed by DNA methyltransferases (DNMTs); while at protein level the main modification is the acetylation of histones catalyzed by histone acetyltransferases (HATs), allowing the activation or suppression of specific genes [2]. Usually, it modulates the expression patterns of genes involved in the normal development and differentiation of different specialized cells in the adult organism [3]; however, they can also mediate the pathophysiology of neurological diseases such as Huntington's, Alzheimer's, Parkinson's and ischemic stroke [4].

### Epigenetic, Oxidative Stress and Ischemic Stroke

Ischemic stroke occurs as a focal, sudden-onset, and non-convulsive neurological deficit; it is defined by the World Health Organization like a clinic syndrome consisting of rapidly progressive neurological focal, or global signs, in the case of coma, lasting more than 24 hours or leading to death without any other apparent cause besides vascular alteration [5,6]. The ischemic component tends to enhance cerebral infarction defined like death by ischemic of the encephalic tissue due to artery occlusion that nourishes it [7]. Evidence from preclinical and clinical studies has linked the

oxidative stress with ischemic stroke, suggesting that epigenetics also plays an important role in the pathogenesis.

Oxidative stress besides the direct disturbances produced in the macromolecules such as proteins, lipids, and the DNA, it also impact in the methylation profile of DNA. Reactive oxygen and nitrogen species such as hydrogen peroxide (H2O2) and nitric oxide, generate the oxidation of 5-methylcytosine (5-mC) to 5-hidroxymethylcytosine (5-hmC), inhibiting the interaction of DNMTs to methyl-CpG (MBP) binding domains in DNA, provoking changes in the methylation profile; some reports have showed that the 5-hmC increment has been associated with the increase infarct volume in patients with ischemic stroke [8]. Furthermore, peroxides also produce modification of nitrogen base such as 5-chlorocytosine, which mimics the 5-mC, inducing an inadequate binding of DNMTs to the CpG sequences, producing gene silencing. Drugs like 5-aza-2´- deoxycytidine and zebularine that inhibit DNMTs, also decrease the ischemic injuries [9]. Although the exact mechanism has not been revealed yet, in vitro studies have described that H2O2 promotes the binding of NF- κB and SP1/3 nuclear factors to DNA [10].

Oxidative stress progression in ischemic stroke, also promotes the participation of histone deacetylases (HDACs), decreasing the DNA binding of some transcription factors, such as SP1 and NRF2, that favors the regulation of redox profile. SP1 has been associated with increased expression of catalase, MnSOD and p21 waf1/cip1 genes [11]. The HDACs inhibition decreased the Keap1 expression, promoting dissociation of Keap1/Nrf2 complex. Thus, NRF2 is translocated to the nucleus to promote the expression of antioxidant heme oxygenase enzyme, glutamate-cysteine catalytic ligase and NAD(P)H: quinone oxidoreductase, counteracting oxidative stress in ischemic stroke [12].

## Conclusion

Ischemic stroke is a multifactorial pathology in which several, not fully understood, molecular mechanisms are involved. In this context, the epigenetic studies can open new insights for drug treatment and/or for the identification of biological markers of disease. Epigenetics changes caused by oxidative stress during ischemic stroke can promote DNMTs and HDACs expression which allow changes in DNA methylation and histone acetylation, respectively, modulating gene expression of transcription factors such as SP1 and NRF2, to regulate the redox profile. These findings provide new insights to find therapeutics opportunities to improve neuronal survival during ischemic stroke.

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## Conflict of Interest

None.

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