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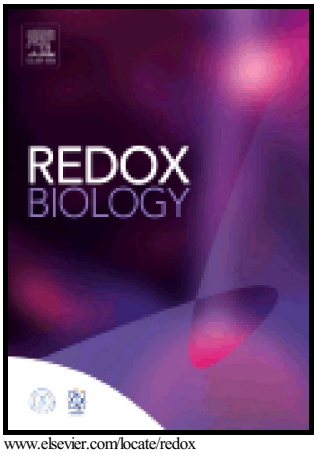

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The Enzyme Activity of Histone Deacetylase 8 is Modulated by a Redox-Switch

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ABSTRACT:

Enzymes from the histone deacetylase (HDAC) family are highly regulated by different mechanisms. However, only very limited knowledge exists about the regulation of HDAC8, an established target in multiple types of cancer. A previous dedicated study of HDAC class I enzymes identified no redox-sensitive cysteinyl thiol in HDAC8. This is in contrast to the observation that HDAC8 preparations show different enzyme activities depending on the addition of reducing agents. In the light of the importance of HDAC8 in tumorigenesis a possible regulation by redox signaling was investigated using biochemical and biophysical methods combined with site directed mutagenesis. The occurrence of a characteristic disulfide bond under oxidizing conditions is associated with a complete but reversible loss of enzyme activity. Cysteines 102 and 153 are the integral components of the redox-switch. A possible regulation of HDAC8 by redox signal transduction is suggested by the observed relationship between inhibition of reactive oxygen species generating NOX and concomitant increased HDAC8 activity in neuroblastoma tumor cells. The slow kinetics for direct oxidation of HDAC8 by hydrogen peroxide suggests that transmitters of oxidative equivalents are required to transfer the H_2O_2 signal to HDAC8.

Graphical abstract: