

PEROXYNITRITE INACTIVATES HUMAN-TISSUE INHIBITOR OF METALLOPROTEINASE-4 (TIMP-4) FAVOURING CORONARY ENDOTHELIAL CELL MOTILITY

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Peroxynitrite (ONOO⁻) is involved in the pathogenesis of cardiovascular diseases. The activity of tissue inhibitor of metalloproteinase-4 (TIMP-4), involved in cardiovascular remodeling, is impaired in response to vascular injury. Since TIMP-4 has several residues, including tyrosine and cysteine, which are susceptible to ONOO⁻, we investigated its role as a potential target of ONOO⁻. Human TIMP-4 (hTIMP-4) was nitrated by ONOO⁻, as indicated by Western blot, and mass spectrometry analysis. ONOO⁻ induced a concentration-dependent nitration and oligomerization of hTIMP-4. hTIMP-4 inhibited basal- and growth-factor-induced microvascular coronary endothelial cell (CVEC) invasion. ONOO⁻-treated hTIMP-4 resulted in the inactivation of its inhibitory activity both toward the gelatinase activity of matrix metalloproteinase-2, and toward the invasiveness of CVEC. In consideration of the key role of TIMP-4 in protecting the heart from ischemic or inflammatory stress, our data highlight the notion that nitration of TIMP-4 is a potential mechanism contributing to ischemic heart disease.

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