

Signaling by nonreceptor surface-mediated redox-active biomolecules.

J D Crapo, J S Stamler

J Clin Invest. 1994;**93**(6):2304-2304. <https://doi.org/10.1172/JCI117233>.

Editorial

Find the latest version:

<https://jci.me/117233/pdf>



In this issue of *The Journal* Clerch et al. (1) show that hyperoxia regulates lung manganese superoxide dismutase (MnSOD) through a nonreceptor-mediated pathway involving G proteins. These observations suggest a number of possibilities regarding the cell involved and signaling mechanism used. Regulation of MnSOD expression is a critical element in the lung's response to multiple forms of oxidant stress. It is likely that the location of MnSOD in mitochondria imparts protection to electron transport chain components enabling maintenance of cell energy sources under conditions of metabolic stress. Exposure to hyperoxia leads to a specific upregulation of MnSOD in the mitochondria of alveolar epithelial type II cells (2). Selective over-expression of MnSOD in the mitochondria of type II cells protects mice against hyperoxic stress (3). Indeed, the enhanced whole lung expression of MnSOD identified by Clerch et al. (1) is likely to have occurred in type II cells. These cells have a number of specialized functions designed to protect the host against inflammatory stimuli, microbes, and pollutants. In particular, they express extracellular (EC)-SOD and produce the bioactive radicals superoxide ($O_2^{\cdot-}$) and nitric oxide ($NO\cdot$) (4). Selected biological functions of these radicals may derive from their rapid interaction to form peroxynitrite ($OONO^-$). Which species predominates at the cell surface will depend on the rates and sites of production of the primary radicals and the local concentrations of antioxidant enzymes such as EC-SOD. In this context one wonders if EC-SOD is not also regulated in the model of Clerch et al. (1).

Two important questions are raised by this study. First, what is the molecular mechanism by which small diffusible ligands are recognized (i.e., what is the molecular sensor)? Second, how are these redox signals transduced into changes in gene expression? It has become increasingly clear that redox-active species such as $O_2^{\cdot-}$ and $NO\cdot$ play important servoregulatory roles through activation of cytosolic enzymes and transcription factors. Signaling by these redox species may be initiated in or at the plasma membrane (1, 5). Indeed, $NO\cdot$ and H_2O_2 have been shown to activate G proteins (6). A distinctive feature shared by redox-active biomolecules is that they exert biological activity by virtue of their chemical reactivity, as opposed to the traditional noncovalent interactions of ligands with receptors. Metal- or sulfur-containing proteins are molecular targets for these diffusible signals. Critical thiols on the G protein are, therefore, candidate regulatory sites. Such activation of G proteins by *S*-nitrosylation (7) would be consistent with reports that $NO\cdot$ opposes pertussis toxin-mediated ADP-ribosylation of cysteinyl residues (6). Analogous covalent interactions of $O_2^{\cdot-}$ with protein thiols should be entertained. Con-

formational changes induced in the protein likely serve as a switching mechanism to transduce the chemical signal into a physiological response.

It is possible that redox-active biomolecules ($O_2^{\cdot-}$ and $NO\cdot$) act as chemical sensors for one another and, as such, are one component of the molecular basis of redox recognition. While the reaction of $NO\cdot$ with thiols is relatively unfavorable, the product of its reaction with $O_2^{\cdot-}$ ($OONO^-$) is highly reactive. Thus, production of $OONO^-$ at the cell membrane may channel $O_2^{\cdot-}/NO\cdot$ metabolism towards reactions with thiols, and thereby serve as a genetic switch leading to upregulation of MnSOD. This notion is supported by other findings in the study by Clerch et al. (1). Oxidant stress was associated with depletion of reduced glutathione without concomitant disulfide formation. This may be explained by the formation of *S*-nitroso-glutathione (GS-NO) which has been previously identified in airways, and is not detected in standard thiol assays. GS-NO could react with thiols on the G protein to transduce the induction of MnSOD (5, 7).

The concept of nonreceptor surface-mediated covalent interactions of redox-active biomolecules integrates their biological chemistry into more traditional signaling paradigms; and offers new insights into metabolic pathways which may regulate diverse cellular responses. In this context, the challenge is now to demonstrate the specific roles of individual redox molecules ($O_2^{\cdot-}$, $NO\cdot$, GS-NO, and $OONO^-$) in the signaling pathways of type II alveolar cells in response to redox perturbations.

James D. Crapo and Jonathan S. Stamler
Division of Pulmonary and Critical Care Medicine
Duke University Medical Center

References

1. Clerch, L. B., G. Neithardt, U. Spencer, J. A. Melendez, G. D. Massaro, and D. Massaro. 1994. Pertussis toxin treatment alters manganese superoxide dismutase activity in lung: evidence for lung oxygen toxicity in air-breathing rats. *J. Clin. Invest.* 93:2482-2489.
2. Vincent, R., L. Chang, J. W. Slot, and J. D. Crapo. 1994. Quantitative immunocytochemical analysis of manganese superoxide dismutase in alveolar type II cells of the hyperoxic rat. *Am. J. Physiol.: Lung Cell & Mol. Physiol.* In Press.
3. Wispé, J. R., B. B. Warner, J. C. Clark, C. R. Dey, J. Neuman, S. W. Glasser, J. D. Crapo, L. Y. Chang, and J. A. Whitsett. 1992. Human Mn superoxide dismutase in pulmonary epithelial cells of transgenic mice confers protection from oxygen injury. *J. Biol. Chem.* 267:23937-23941.
4. Kobzik, L., D. S. Bredt, C. J. Lowenstein, J. Drazen, B. Gaston, D. Sugarbaker, and J. S. Stamler. 1993. Nitric oxide synthase in human and rat lung: Immunocytochemical and histochemical localization. *Am. J. Respir. Cell Mol. Biol.* 9:371-377.
5. Lipton, S. A., Y. B. Choi, Z. H. Pan, S. Z. Lei, H. V. Chen, N. J. Sucher, J. Loscalzo, D. J. Singel, and J. S. Stamler. 1993. A redox-based mechanism for the neuroprotective and neurodestructive effects of nitric oxide and related nitroso-compounds. *Nature (Lond.)* 364:626-632.
6. Lander, H. M., P. K. Sehajpal, and A. Novogrodsky. 1993. Nitric oxide signaling: a possible role for G. Proteins. *J. Immunol.* 151:7192-7187.
7. Stamler, J. S., D. I. Simon, J. A. Osborne, M. E. Mullins, O. Jaraki, T. Michel, D. J. Singel, and J. Loscalzo. 1992. *S*-nitrosylation of proteins with nitric oxide: Synthesis and characterization of biologically active compounds. *Proc. Natl. Acad. Sci. USA.* 89:444-448.

J. Clin. Invest.

© The American Society for Clinical Investigation, Inc.

0021-9738/94/06/2304/01 \$2.00

Volume 93, June 1994, 2304