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Forum Editorial

Redox Control of Protein Tyrosine Phosphorylation

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EVERY CELL generates reactive oxygen species (ROS) such as the superoxide radical, the hydroxyl radical, and H_2O_2 through multiple mechanisms, including the respiratory redox chain in mitochondria, the respiratory burst of phagocytes, and the activation of various oxidases. On the other hand, cells contain several ROS-scavenging enzymes such as catalase, glutathione peroxidase, and superoxide dismutase. Oxidative stress can result from increased exposure to reactive oxidants or from a decrease in the protection against these oxidants. Recently, convincing evidence has been presented to show that intracellular ROS are generated in a variety of cells stimulated with cytokines, growth factors, and agonists of heptahelical receptors, and can act as a signaling molecule or as a second messenger.

Oxidative stress has been shown to stimulate a variety of intracellular signaling pathways related to cell activation, proliferation, and apoptosis. One of the earliest important events in cells exposed to ROS is the increased tyrosine phosphorylation of intracellular proteins, which results from the activation of protein-tyrosine kinases (PTKs). The catalytic activity of PTKs is regulated by protein-tyrosine phosphatases (PTPases), which are a well known target of oxidative chemical reaction. Oxidative modification of PTPases by ROS impairs the catalytic activity of PTKs, suggesting that the mechanism of PTK activation by oxidative stress is through inactivation of regulatory PTPases. However, a number of recent reports have shown that the mechanism of PTK activation by oxidative stress is very complex, including ROS-induced crosslinkage of cell-surface receptors and structural modification of PTK proteins by ROS. About this issue, a review by Nakashima *et al.* describes new mechanisms for oxidative stress-mediated PTK activation (3). In their review, involvement of "raft" on oxidative stress-induced PTK activation is particularly noteworthy.

ROS have been shown to activate a variety of PTKs, such as Src, Lck, Fyn, Syk, ZAP-70, Btk, c-Abl, Ltk, Jak, focal adhesion kinase (FAK), epidermal growth factor receptor, insulin receptor kinase, and RET in many types of cells. The activation of PTKs by oxidative stress induces the activation of several pathways including calcium mobilization, the cascade of mitogen-activated protein kinases (MAP kinases), phosphatidylinositol 3-kinase–Akt survival pathway, and transcription factors. This forum highlights intracellular signal transduction in hematopoietic cells exposed to oxidative stress. Hematopoietic cells including lymphocytes are highly sensitive to oxidative stress. A review by Takano *et al.* describes the role of Syk in oxidative stress signaling in B cells (6). Syk has an important role in calcium mobilization, the activation of MAP kinases, and Akt survival pathway. They suggest that the activation of Akt survival pathway by Syk enhances cellular resistance to oxidative stress-induced apoptosis. Moreover, He *et al.* describe the role of Syk in the regulation of cell-cycle progression upon oxidative stress (1). Also, Qin *et al.* describe the role of CD45 in B cells exposed to oxidative stress (4). CD45 is one of the PTPases and has bidirectional roles in oxidative stress signaling: a negative regulatory role for tyrosine phosphorylation of cellular proteins and c-Jun N-terminal kinase activation and a positive regulatory role for calcium mobilization upon oxidative stress.

Oxidative stress-induced cellular responses follow different patterns such as necrosis, apoptosis, and mitotic arrest according to the intensity of oxidants. The dosage and duration of oxidative stress are important aspects in the regulation of cell function. A review by Verweij and Gringhuis describes the effects of chronic oxidative stress on T-cell antigen receptor (TCR) signaling (7). Treatment with agents that lead to a decrease in the intracellular glutathione concentrations mimicks chronic oxidative stress. Exposure of T cells to chronic oxidative stress for an extended period suppresses TCR-induced tyrosine phosphorylation of cellular proteins and calcium mobilization. They suggest that redox signal influences the functional status of cells at the sites of inflammation through the regulation of PTK activity. On the other hand, lymphocytes normally encounter the oxidizing agents produced at sites of inflammation. Hypochlorous acid is one of the important oxidizing agents and leads to acute oxidative stress. Schieven *et*

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al. describe the effect of hypochlorous acid on tyrosine phosphorylation signal pathways and calcium mobilization in T and B cells and on TNFα production in mononuclear cells (5).

It is intersting how redox-controlled protein-tyrosine phosphorylation determines the fate of a cell exposed to oxidative stress. Kasahara *et al.* describe the role of FAK on antiapoptotic action against the ionizing radiation (2). As described above, Takano *et al.* report that oxidative stress-induced Syk activation triggers the responses of both proapoptotic and survival pathways (6). On the other hand, a recent report shows that ROS-induced activation and localization of c-Abl to mitochondria mediate mitochondrial dysfunction and cell death. Oxidative stress activates various PTKs, and the balance among PTK-mediated signal transduction may determine the fate of a cell exposed to oxidative stress. Further investigation is warranted to clarify the regulation of redox-mediated signal pathways.

Further, three-dimensional structural changes of PTKs mediated by redox has become clear, although this issue is not taken up in this forum. Determination of redox-mediated structural change of PTKs may provide invaluable insight into the molecular basis of redox-regulated processes in PTK activation and its subsequent downstream signal transduction.

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ABBREVIATIONS

FAK, focal adhesion kinase; MAP kinase, mitogen-activated protein kinase; PTK, protein-tyrosine kinase; PTPase, protein-tyrosine phosphatase; ROS, reactive oxygen species; TCR, T-cell antigen receptor.

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