NADPH-Oxidase Might Also Act as an Antithrombotic

To the Editor:

Herkert et al. recently showed that thrombin stimulates tissue factor (TF) mRNA expression in human vascular smooth muscle cells. In the thrombin-signaling pathway, reactive oxygen species (ROS), which are generated by NADPH-oxidase, seem to be involved. Apart from the intracellular, however, there is also an extracellular generation or release of ROS, depending on the cellular localization of the NADPH-oxidase. This enzyme is found in all 3 layers of aorta, for example. Extracellular ROS, and in particular singlet oxygen, is a powerful antithrombotic. Therefore, cell activation by thrombin or fibrin could also result in a physiological defense mechanism against a pathological coagulation. polymorphonuclear neutrophils, in contrast to TF-rich monocytes, seem to be the main effector cells of physiological cellular fibrinolysis, and singlet oxygen, generated by NADPH-oxidase/myeloperoxidase, might act here as an important intercellular signal.

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Response

We appreciate the critical reflection on our article “NADPH Oxidase Mediates Tissue Factor-Dependent Surface Procoagulant Activity by Thrombin in Human Vascular Smooth Muscle Cells.”

On the basis of a plethora of studies performed during the last decade, many data support the major role of reactive oxygen species (ROS) in the pathogenesis of a multitude of cardiovascular diseases. In addition to leukocytes, many, if not all, non-phagocytic cells have now been shown to be able to generate ROS, although at lower levels and with different kinetics than with leukocytes. These findings suggest a substantially different role of non-phagocytic ROS, namely to act as signaling molecules. This assumption is further supported by the identification of cell-type specific isoforms of NADPH oxidase in many tissues, including vascular smooth muscle cells (SMCs). These cells contain NADPH oxidases that share the p22phox subunit with the leukocyte enzyme, but which express, other than leukocytes, Nox1 and/or Nox4. Moreover, SMCs do not express a myeloperoxidase like leukocytes do. Myeloperoxidase activation is a prerequisite for the formation of hypochlorous acid, which then will allow the formation of singlet oxygen. These findings support the concept that NADPH oxidases in SMCs may be involved in signaling processes, and they make it very unlikely that SMC are a major source of singlet oxygen.

Furthermore, numerous studies of phagocytes and other cell types have demonstrated a role for ROS in the upregulation and activation of tissue factor. Tissue factor is a key determinant of hemostatic and thrombotic responses of the vascular wall, and the importance of ROS in controlling coagulation by promoting a thrombogenic state of the vessel wall has now been supported in both in vitro and in vivo studies.

Although one has to clearly distinguish the situation at the vessel wall from the situation in the blood stream, a myeloperoxidase/NADPH oxidase-dependent interaction between neutrophils and platelets resulting in the release of platelet constituents was reported more than 20 years ago. Conflicting data with regard to the role of ROS in platelet aggregation seem to be related to the dose and type of ROS, in that at high doses of ROS, which can only be released by leukocytes or generated artificially, the toxic properties may augment the signaling properties of ROS.

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4. Herkert O, Görlach A. Redox control of tissue factor expression in leukocytes and thrombocytes resulting in the release of platelet constituents was reported more than 20 years ago. Conflicting data with regard to the role of ROS in platelet aggregation seem to be related to the dose and type of ROS, in that at high doses of ROS, which can only be released by leukocytes or generated artificially, the toxic properties may augment the signaling properties of ROS.
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