ANTIOXIDANTS & REDOX SIGNALING
Volume 4, Number 5, 2002

Forum Editorial

Redox Regulation of Vascular Angiogenesis

NILANJANA MAULIK

ENDOTHELIAL CELLS are the building blocks of blood vessels. For a new blood vessel to be formed, endothelial cells must respond to biochemical signaling and begin to migrate toward one another to form microtubules that eventually become new blood vessels. The process governing the new blood vessel development is angiogenesis. Angiogenesis is regulated and controlled by several known and as yet unknown factors. It is an important process in inflammation, solid tumor growth, and several other pathologic phenomena. Some diseases are enhanced during pathologic situations by excessive vascular growth (*e.g.,* tumors), whereas in others inadequate vascular growth contributes to morbidity and mortality (*e.g.,* ischemic heart disease).

Angiogenesis is thought to be regulated by several growth factors [epidermal growth factor, transforming growth factor-α, basic fibroblast growth factor, and vascular endothelial growth factor (VEGF)]. Induction of angiogenic factors is triggered by various stresses. For instance, tissue hypoxia exerts its proangiogenic action through various angiogenic factors, the most notable being VEGF, which has been associated mainly with initiating the process of angiogenesis through the recruitment and proliferation of endothelial cells. Recently, reactive oxygen species (ROS) have been found to stimulate angiogenic response in ischemic reperfused hearts. Short exposure to hypoxia/reoxygenation, either directly or indirectly, produces oxidative stress that is associated with angiogenesis or neovascularization. A recent study demonstrated that vessel wall thickening after in-stent restenosis was accompanied by extensive neovascularization, VEGF and platelet-derived growth factor expression, iron deposits, and epitopes characteristic of oxidative stress (1). This would tend to indicate that ROS cause tissue injury on the one hand and promote tissue repair on the other hand by promoting angiogenesis. The ROS-mediated angiogenic response was observed in several studies. The administration of EGB-761, an antioxidant derived from *Ginkgo biloba* leaves, was found to inhibit lymphocyte-induced angiogenesis, suggesting a role of ROS in angiogenesis (9). The evidence that T-cell response requires the action of oxygen free radicals (3) further supports the role of ROS in angiogenesis. Another related study showed that thiol-containing compounds could inhibit the production of macrophage-mediated angiogenic activity (4). Monocyte- or macrophage-derived angiogenesis was inhibited by oxygen free radical scavengers (5). Recent study demonstrated that hydrogen peroxide is directly involved in lymphocyte activation of angiogenic response (10).

It thus appears that after causing injury to the cells, ROS promptly initiate the tissue repair process by triggering angiogenic response. Dichotomy in ROS behavior can be explained in the light of recent findings that ROS can function as signaling molecules. Evidence is rapidly accumulating to indicate that ROS can initiate a cascade of signal transduction processes. Nitric oxide (NO) is a typical example: it is a highly reactive radical that functions as a signaling molecule. It has been reported that during myocardial adaptation to ischemia, NO plays a crucial role by initiating a cascade of signal transduction processes (7).

Significant efforts in this area of research have led to the discovery of a growing number of pro- and antiangiogenic molecules, some of which are already in clinical trials. However, there are several outstanding questions that must be addressed for successful translation of discoveries from the bench to the bedside. With advances in molecular genetics and the availability of molecular probes, imaging technologies, and therapeutic opportunities, we are now beginning to answer these questions.

This forum issue consists of four review articles and three original articles. The first review article surveys the role of ROS that play a crucial role in vascular angiogenesis, especially in heart (6). This angiogenic response in vascular tissue is triggered by ROS signaling in a highly coordinated manner. It appears that massive amounts of ROS produced during ischemia and reperfusion in the vascular tissue, especially in heart, cause significant injury to the cardiomyocytes and endothelial cells. However, during the reperfusion, the same ROS potentiate the repair process and trigger a signal transduction cascade leading to angiogenesis. The review by Donnini and Ziche (2) addresses the molecular mechanism of NO signaling in angiogenesis in general, whereas Murohara and Asahara (11) summarize the NO-mediated regulation of post-

Molecular Cardiology Laboratory, Cardiovascular Research Center, Department of Surgery, University of Connecticut School of Medicine, Farmington, CT 06030-1110, U.S.A.

natal angiogenesis during ischemic cardiovascular disease. The remaining review, by Tuder and Voelkel (14), discusses the components of endothelial cell proliferation present in the pulmonary arteries during severe pulmonary vascular hypertension.

The three original research articles are very timely and varied in their topics. Mirsky *et al.* (8) report low energy laser irradiation mediated angiogenesis. Murohara *et al.* (12) showed lysophosphatidylcholine-mediated activation of angiogenesis is prevented due to the inhibition of the protein kinase C-dependent signal transduction pathway by vitamin E. Sood *et al.* (13) report the induction of oxidative stress and increased nitrotyrosine formation that lead to the activation of matrix metalloproteinase in the presence of homocysteine.

The editor hopes that this forum will serve as an up-to-date source of information regarding the molecular mechanism of vascular angiogenesis for scientists as well as clinicians. The editor would like to thank the contributing authors for their excellent contributions and cooperation.

ABBREVIATIONS

NO, nitric oxide; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

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Address reprint requests to:
Nilanjana Maulik, Ph.D.
Molecular Cardiology Laboratory
Cardiovascular Research Center
Department of Surgery
University of Connecticut School of Medicine
Farmington, CT 06030-1110, U.S.A.

E-mail: nmaulik@neuron.uchc.edu

Received for publication April 10, 2002; accepted April 10, 2002.

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