Lipid Rafts Take Center Stage in Endothelial Cell Redox Signaling by Death Receptors

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Reactive oxygen species are important signaling molecules mediating diverse biological effects in vascular cells ranging from cell growth to cell death. The primary enzymatic source of vascular reactive species is the multisubunit NAD(P)H oxidase, expressed and functionally active in endothelial, vascular smooth muscle, and adventitial cells. Activation of G protein-coupled receptors by vasoactive agents, such as angiotensin II (Ang II), and receptor tyrosine kinases by growth factors, such as epidermal growth factor (EGF), stimulate NAD(P)H oxidase–derived generation of superoxide and hydrogen peroxide in vascular smooth muscle cells, which activate mitogen-activated protein kinase growth signaling pathways and promote cell cycle progression. In pathological conditions associated with vascular injury and remodeling, increased oxidative stress is now considered a fundamental factor underlying proliferation and hypertrophy of vascular smooth muscle cells. Paradoxically in endothelial cells, death receptor ligands and proapoptotic agonists, including tumor necrosis factor (TNF) α, Fas ligand (FasL), and endostatin, also stimulate NAD(P)H oxidase–mediated production of reactive oxygen species. These processes trigger endothelial cell apoptosis, anoikis, and impaired dilation. How then can agonists that promote cell growth and cell death trigger the same redox-sensitive pathways to elicit divergent cellular responses, and what are the mechanisms that link growth/death receptors to NAD(P)H oxidase in vascular cells?

Emerging evidence indicates that lipid microenvironments on the cell surface, known as lipid rafts, may be critically involved in distal redox-sensitive signaling events and ultimate cell fate. In vascular smooth muscle cells, Ang II–induced cell growth involves epidermal growth factor receptor (EGFR) transactivation, mediated through redox-sensitive c-Src, which is dependent on angiotensin I type 1 receptor trafficking through caveolin 1–enriched lipid rafts. Zhang et al demonstrate that lipid raft clustering is coupled to gp91phox, the catalytic subunit of NAD(P)H oxidase, and that on FasL stimulation, p47phox and the small G-protein Rac translocate into membrane rafts to assemble the activated oxidase complex that generates superoxide (Figure). These novel findings in endothelial cells, together with those described in vascular smooth muscle cells and neutrophils where NAD(P)H oxidase subunits have been detected in lipid raft fractions, strongly suggest that in addition to the classical raft-associated proteins (mentioned above), NAD(P)H oxidase subunits (at least gp91phox and p47phox) can be classified as lipid raft–associated proteins. However, it still remains unclear how these proteins align spatially and temporally within rafts, how they physically interact with death receptor domains on lipid raft aggregation and how cytoplasmic NAD(P)H oxidase subunits are site-directed to specific cholesterol-rich microdomains. The actin cytoskeleton may play an important role in these events, as we recently reported in vascular smooth muscle cells.

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The functional significance of death receptor signaling in endothelial cells seems to extend beyond apoptosis. FasL and TNFα impair endothelium-dependent vasodilation and promote endothelial injury. These processes occur through lipid raft clustering, activation of NAD(P)H oxidase, and formation of reactive oxygen species, since lipid raft disruption with nystatin and inhibition of NAD(P)H oxidase with apocynin improved vasodilatory responses and endothelial function. Such events may represent early functional responses to death receptor signaling, whereas apoptosis may be the consequence of long-term signaling.

The novel findings of Zhang et al. certainly contribute to the further understanding of signaling mechanisms mediating the early response of death receptors in endothelial cells and highlight the importance of lipid rafts as central players linking death receptor domains to NAD(P)H oxidase and reactive oxygen species. However, there are some limitations that warrant attention. First, the relative importance of lipid rafts versus non-lipid rafts (caveolae) is not fully addressed. This is particularly important in the context of endothelial function, because caveolae are richly endowed with endothelial NOS, the major source of nitric oxide, a potent vasodilator. Second, studies were performed in cultured coronary endothelial cells. Whether findings are particular to coronary endothelial cells or to all endothelial cells, whether effects are cell-type specific, and whether similar responses occur in vivo conditions remain unknown. Third, the experimental paradigm was designed to mimic pathological conditions where death receptors are stimulated. The physiological significance of lipid raft clustering and redox signaling platform formation in endothelial cells still awaits clarification. It is now becoming clear that lipid microdomains on the cell surface participate in signal transduction and that they may constitute a missing link between death receptor domains and NAD(P)H oxidase in endothelial cells. Findings that NAD(P)H oxidase subunits are raft-associated proteins and dependency of intact lipid rafts in efficient death receptor and redox signaling highlights the importance of these cholesterol-rich domains in endothelial cells. Future challenges will be to identify the significance of lipid rafts as key players in redox signaling in the physiological regulation of vascular function and in the pathophysiological effects of oxidative stress in vascular disease.

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