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Forum Editorial

Redox Control of Growth Factor Signaling in Heart, Lung, and Circulation

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GROWTH FACTORS play important roles in the pathophysiology of the heart, lung, and circulation. In the heart, factors such as angiotensin II and endothelin-1 have been shown to induce cardiac muscle cell hypertrophy, which may result in heart failure (23). These factors, as well as others, also induce hypertrophy of the vessel wall, which may be important in the development of hypertension and atherosclerosis (2). Growth factors also play essential roles in lung diseases such as pulmonary hypertension, chronic obstructive pulmonary disease, and asthma by increasing the mass of pulmonary artery and airway smooth muscle (12, 14). At the cellular level, growth factors promote hyperplasia, hypertrophy and survival of cardiac muscle, smooth muscle, endothelial, and epithelial cells. Understanding the signal transduction mechanisms utilized by growth factors should help to identify therapeutic targets for various cardiovascular and pulmonary diseases.

Regulation by reactive oxygen species (ROS) is a common element in the growth of cardiac and smooth muscle cells (18). One of the earliest demonstrations of a role for ROS in cardiovascular signaling was the observation that ROS are required for angiotensin II-mediated vascular smooth muscle cell hypertrophy (9). Since then, various growth factors have been shown to generate ROS which then serve as signaling molecules in systemic and pulmonary vascular and airway smooth muscle cells. This mechanism has been implicated in the development of systemic and pulmonary hypertension, atherosclerosis, and asthma (10, 11, 22). Furthermore, more recent experiments have provided evidence for a role of ROS in cardiac muscle cells, suggesting a role for redox regulation in the development of cardiac hypertrophy and failure (15, 20).

The sources and targets of ROS have been under intense investigation. NAD(P)H oxidases appear to be promising sources of ROS during growth factor signaling (4, 10, 11). Various signaling molecules have been shown to be activated by ROS (19); however, it is not yet clear how specific signaling events can be elicited. Potentially important targets of ROS may include protein kinases and phosphatases (1, 8, 13, 21). In addition, ROS may induce cell growth signaling by modulating the levels of cellular glutathione (7).

In addition to the regulation of growth factor signal transduction by oxidants, growth factors may in turn affect oxidant-induced biological responses. For example, some growth factors can serve as cell survival mediators and protect cells against oxidative stress-induced apoptosis (17). Cardioprotective mechanisms may involve redox regulatory molecules such as thioredoxin (16). Boveris *et al.* (3) demonstrated that the angiotensin-converting enzyme inhibitor enalapril increases mitochondrial nitric oxide synthase activity, indicating that angiotensin II may regulate localized nitric oxide production. Estrogen, whose deficiency is associated with hypertension and angiotensin II-induced vasoconstriction, inhibits the hypoxia-induced increase in xanthine dehydrogenase/xanthine oxidase, a major reactive oxygen-producing enzyme (5).

Understanding the interactions between growth factor signaling and redox regulatory components is an important research area in cardiovascular/pulmonary physiology and pathology. The Forum on redox control of growth factor signaling in heart, lung, and circulation includes both review articles and original contributions that significantly expand our current understanding of the roles of ROS and redox reactions in growth factor signaling, as well as the regulation of redox biology by growth factors.

ABBREVIATION

ROS, reactive oxygen species.

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