INTRODUCTION

There is an increasing body of evidence suggesting an important role of apoptosis for cardiac development and diseases. This is based on the observation that in animals and humans the ontogenesis of the normal heart is characterized by the appearance of apoptosis peaking in the perinatal period (1) and in specific regions of the heart (2). Furthermore, myocardial infarction has been shown to be associated with apoptosis in rats (3) and humans (4). Additionally, apoptosis is evident in the heart of patients suffering from certain conductance disturbances (2) as well as in human cardiomyopathies, including the arrhythmogenic right ventricular dysplasia (5) and dilated cardiomyopathy (6). Those studies are important not only because of their proof of apoptotic cell death in yet another organ, but particularly because they let us understand that the capacity for apoptotic cell death exists in both mitotic cells and in post-mitotic cells. However, only little information exists regarding the identification of stimuli responsible for the induction of apoptosis in the heart.

Interestingly, apoptosis could be proven to occur during reperfusion following ischemia in several organs, including the heart (7). However, it is not known how reperfusion triggers apoptosis in this event. Experimental studies employing isolated organ preparations or in vivo animal models have demonstrated the generation of reactive oxygen species (ROS) during ischemia and reperfusion (8). Also, there are several clinical procedures which frequently are associated with ischemia and reperfusion injury on one side and production and release of ROS on the other, including clinical bypass surgery (9), thrombosis (10), and coronary balloon angioplasty (11). The threat being imminent in ROS even for the ontogenesis of the normal heart was demonstrated recently by the induction of
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cardiomyopathies and early lethality in knockout-mice lacking the manganese superoxide dismutase, which acts as an intracellular ROS-scavenger (12). However, in all these cases it remains unclear how ROS induce the pathological phenotype.

Vascular remodeling represents the pathophysiological basis of many diseases, including atherosclerosis, hypertension and restenosis. It is referring to the modulation of the phenotype of vascular smooth muscle cells (VSMCs) which is characterized not only by cell migration and synthesis of extracellular matrix, but also by such contrasting phenomenon as cell proliferation on one hand, and cell death on the other.

Recently, ROS have been found to be related to VSMC proliferation. In vivo studies show that balloon-injured arteries produce increased amounts of ROS (13). Vitamin E, an antioxidant, can attenuate intimal response to balloon injury (14). In vitro studies also demonstrate that ROS can stimulate DNA synthesis in VSMCs (15,16). Since ROS comprise a group of different molecules, including hydrogen peroxide (H$_2$O$_2$), superoxide anion (O$_2^-$) and hydroxyl radical (•OH), it would be important to understand the specific role of each of these species for VSMC proliferation.

There is an increasing body of evidence showing that apoptosis of VSMCs participates in the pathogenesis of atherosclerosis, restenosis and hypertension (17-20), and plays a role in intimal thickening induced by endothelial denudation (21). Furthermore, inflammatory components are important for the induction of apoptosis as indicated by the observation that simultaneous treatment with interferon-γ and TNF-α and/or IL-1-β can trigger apoptosis in cultured human and rat VSMCs (22). While cultured human VSMCs derived from normal vessels undergo apoptosis only upon serum withdrawal, VSMCs from coronary atherosclerotic plaques are much more susceptible to apoptotic stimuli resulting in a significantly elevated rate of apoptosis after serum deprivation (23). Eukaryotic cells continuously produce ROS in physiological levels. The imbalance between their generation and decomposition has been shown to be implicated in many kinds of clinical disorders (24,25). It is therefore conceivable that ROS might participate in inducing apoptosis of VSMCs. However, whether ROS can trigger VSMC apoptosis remains unknown.

The following chapters address the importance of ROS for the induction of apoptosis in the cardiovascular system and summarize our studies performed with cardiomyocytes (26), cardiac fibroblasts (27) and vascular smooth muscle cells (28-30).

WHAT ARE REACTIVE OXYGEN SPECIES (ROS)?

ROS are extremely unstable and highly reactive oxygen compounds with atoms carrying one or more unpaired electrons. The family of molecules to which the specification of ROS applies includes superoxide anion (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), hydroxyl radicals (OH•), and nitrogen oxides (NO, ONOO•). These ROS are produced either by the mitochondrial respiratory chain (cytochrome-oxidase complex containing ubiquinone and NADH-dehydrogenase), or by metabolism of arachidonic acid (COX), membrane bound oxidases (NADPH), xanthine oxidase, or phospholipases.