INTRODUCTION

Apoptosis was first introduced into biology in a seminal paper by a group of pathologists studying cell population regulation (1). In this paper, the authors described a form of cell death marked by its singularity, a unique morphology and resolution without apparent "traces" (e.g., inflammation) in the tissue of origin. These features of cell death were contrasted to various forms of cell death by necrosis, due to noxious stimuli leading to cell membrane disruption, swelling, disintegration, cell-content leakage and local inflammation. Featuring prominently in the apoptotic process are the "apoptotic bodies" (fragments of dense DNA surrounded by an apparently intact plasma membrane), DNA condensation and fragmentation (the latter noted as "ladder" when separated on DNA-gel electrophoresis). The apoptosis phenotype has been later on associated with "programmed cell death" (PCD) described first in the nematode, C. elegans, where genetically specified deletions of cells during development followed a highly timed activation of specific genes (ced-3/4) (2). It is now quite common to use apoptosis and PCD interchangeably; in this review, apoptosis represents the cellular phenotype resulting from activation of genomic programs that lead to DNA damage and cell death. The objectives of this review are: a. to highlight the key evidence on apoptosis in human cardiac myocytes; b. review the key stimuli and signal transduction pathways identified in cardiac myocytes; c. discuss the significance of apoptosis in cardiac function and disease; d. suggest potential novel therapeutic strategies for cardiac diseases based on modulation of selected molecular targets in cardiomyocyte apoptosis.
APOPTOSIS IN CARDIAC BIOLOGY

APOPTOSIS IN CARDIAC DISEASE - THE EVIDENCE

Reports on cardiomyocyte apoptosis in human cardiac disease were only recently published (3,4). Using the key markers: 1. DNA "ladder" and 2. Markers of doublestranded DNA damage by TUNEL (Terminal deoxy-Uridine-Nick-End-Labeling) histochemistry, apoptosis of cardiomyocytes and non-myocytes were identified in the following cardiac diseases: 1. Ischemic and idiopathic dilated cardiomyopathy, associated with clinical heart failure; 2. Acute myocardial infarction; 3. Congenital arrhythmogenic dysplasias; 4. Myocarditis; 5. Arrhythmias. The incidence of cardiac myocyte apoptosis in these conditions varies considerably with estimates of 0.1 % to 30%, depending on the disease specimen, methodology, and area of sampling. However, the rate of cardiac cell deletion (myocytes and non-myocytes) by apoptosis is difficult to assess in vivo especially in the human situation; however, in vitro, the resolution of the apoptotic process from initiation to complete engulfment is quite rapid: hours or few days and, therefore, even a low prevalence, e.g., 0.1 %, recycled over years, may lead to substantial depletion of cardiac cells. At the present time, the contribution of cardiac myocyte apoptosis to initiation and progression of the above-cited heart diseases cannot be accurately estimated.

STIMULI THAT ELICIT CARDIOMYOCYTE APOPTOSIS

Significant research has been launched over the past 5 years to identify stimuli that elicit cardiomyocyte apoptosis and to decipher their signal transduction pathways (5). It is important to note that much of the information is derived from 1. in vitro studies; 2. Nonhuman (and often non-adult) cardiomyocytes; 3. Highly controlled (artificial) conditions.

Circumstantial evidence supports the existence of many of these stimuli also in human cardiac disease, including: 1. Stress conditions such as ischemia (especially when followed by reperfusion) and oxygen radicals (H₂O₂, O₂⁻, OH⁻). The capacity of oxygen radicals to elicit cardiomyocytes apoptosis has been demonstrated in both cell cultures and isolated cardiac perfusion studies (6,7). In the former condition, deprivation of growth factors, energy sources (glucose), and endogenous antioxidants are usually present; 2. Cytokines, such as TNFα have been shown to produce cardiomyocyte apoptosis in culture. Cytokines may figure prominently, especially in the advanced heart failure where very high levels of circulating TNFα (and other cytokines) are present. Endogenous synthesis of TNFα in the heart (where its receptors are present) may be equally important; 3. Nitric oxide (NO) produced primarily by the Type II iNOS (inducible nitric oxide synthase) elicits cardiomyocyte apoptosis possibly in association with peroxinitrite iNOS (ONOO⁻) production. Activation of iNOS in heart failure has been established; 4. Neurohormonal factors such as angiotensin II (ATII) acting via the AT-receptors have been shown to produce cardiomyocyte apoptosis (8). Elevated circulating levels of ATII, correlating to disease stage, and in situ cardiac ATII production, (possibly by a non-ACE pathway) may play an important role in this respect. It remains to be shown whether drugs that effectively block ATII production (ACE