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The dilemma of the strive for apoptosis in oncology: mind the heart

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Contents

Abstract

In recent years, apoptosis has increasingly drawn the attention of both oncologists and cardiologists alike. Anticancer treatment is possible by induction of apoptosis in cancer cells, and targeted anticancer drugs are being developed to promote this. However, since these drugs usually are not selective for malignant cells, side effects on non-cancerous tissue, such as the myocardium must be anticipated. Since apoptosis is a pathophysiological mechanism in cardiac diseases leading to heart failure, cardiologists in contrast to oncologists, aim at preventing apoptosis in the heart. The purpose of this review is to describe new insights in mechanisms of cardiomyocyte apoptosis. In addition to the mitochondrial and death receptor apoptotic pathways, apoptosis through lack or inhibition of growth factor receptor-mediated signalling is discussed. Exploration of the apoptotic pathways in the heart can contribute to the safer use of new anticancer drugs and to the development of new therapies for heart failure.

Keywords: Anti-tumour treatment; Heart; Apoptosis; Epidermal growth factor receptor; Cytokines; Cytokine receptor

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1. Introduction

Cardiac toxicity is a serious adverse effect that can accompany the use of several chemotherapeutic agents. Anthracyclines in particular are related to an increased risk of cardiac dysfunction, which is mostly due to cardiomyopathic changes, causing impaired myocardial contractile function. Impaired myocardial contractile function can reflect a reduction of the number of functional myocytes, decreased contractility of viable myocytes or both. Myocyte loss can be caused by autophagic cell death [1], necrosis and apoptosis. Autophagy consists of sequestration of cellular material into double membrane vacuoles that fuse with lysosomes, which are subsequently degraded by lysosomal proteases [2]. Necrosis, or better oncosis, is a passive process of cell death that occurs when a cell is deprived of oxygen. In contrast, apoptosis is an active, energy consuming process of controlled cellular and organellular destruction and has been described as an important pathophysiological factor in chronic heart failure (CHF) [3–5]. Apoptotic pathways are extensively studied to develop new strategies for inducing cell death in cancer cells. New drugs are being developed that specifically target key components involved in tumour cell apoptosis. However, a major concern is that these new compounds increase apoptosis in organs, such as the heart. Although the role of apoptosis in the pathophysiology of CHF is still controversial, the discovery of previously unknown apoptotic pathways in cancer research may place cardiac apoptosis in another perspective. The aim of this paper is to describe new insights in the molecular pathways underlying cardiomyocyte apoptosis. Inhibition of growth factor receptor signalling, which is currently widely investigated in anti-tumour treatment, may also induce apoptosis in the heart. Growth factor receptor signalling pathways will, therefore, be emphasised here. In addition, the relevance of these apoptotic pathways for clinical practice will be reviewed.

2. Mechanisms of apoptosis

Apoptosis can be induced by stimuli activating the intrinsic pathway (mitochondrial pathway), the extrinsic pathway (death receptor pathway), or both (Fig. 1). In addition, growth factors and their receptors, e.g., the epidermal growth factor receptor family (EGFR family), promote cell growth and survival, thereby inhibiting apoptosis. Absence, deficiency or inhibition of growth factor receptor signalling causes apoptosis to increase, for instance by the monoclonal antibody against human epidermal growth factor receptor 2 (HER2), trastuzumab. Apoptosis can be initiated by intracellular and extracellular triggers, including DNA damage, a defective cell cycle, hypoxia, detachment of cells from their surrounding tissue and loss of trophic signalling. Caspases play an important downstream role in the intracellular apoptotic signalling cascade. These proteases form a family, consisting of three functional groups based on their substrate specificities [6]. Caspase 2, 3 and 7 cleave specific structural proteins and key intracellular DNA repair enzymes (e.g., actin, Poly ADP ribose polymerase). These proteins function as executors of apoptosis and are activated by initiator caspases (Fig. 1). The remaining group of caspases, caspase 1, 4, 5, 11, 12 and 13, are merely involved in transduction of apoptotic signals.

Oxidative cardiac stress primarily induces “mitochondrial apoptosis” [7,8]. Activation of receptors belonging to the tumour necrosis factor receptor (TNFR) superfamily, can also induce apoptosis. However, mitochondrial apoptosis is considered to be the main pathway for cardiac apoptosis, since inhibitors of the death receptor pathways in the heart are relatively overexpressed [9]. Deficient growth factor receptor signalling can also lead to apoptosis via the intrinsic and extrinsic pathway (Figs. 1 and 5).

2.1. Intrinsic apoptosis

The mitochondrion is the pivotal site for the intrinsic apoptotic pathway. The common activator for this route is cytochrome *c*, which is released from the intermitochondrial space (Fig. 1). Once released in the cytosol, cytochrome *c* promotes pro-caspase 9 cleavage into its active form [10]. Intrinsic apoptosis is regulated by the *Bcl-2* gene family of pro- and anti-apoptotic factors, which consists of at least 18 proteins [11]. In cardiomyocytes, *Bcl-2* inhibits mitochondrion-related apoptosis in isolated neonatal ventricular muscle cells [12]. However, *Bcl-2* knock-out mice show no increased cardiomyocyte apoptosis, suggesting that *Bcl-2* is not indispensable for cardiomyocyte apoptosis inhibition

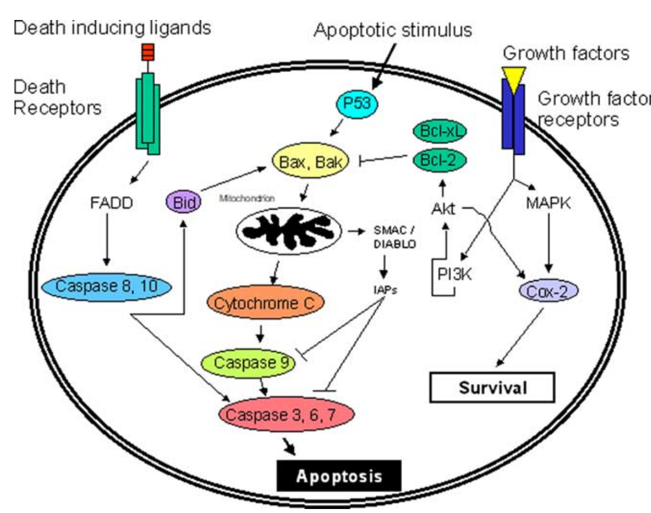

Fig. 1. Schematic overview of cardiomyocyte apoptotic pathways. Death receptors pathway: intracellular signalling cascade upon ligand binding. Death receptors are: TNFR-I and II, Fas, DR 4 and 5. Death-inducing ligands are: TNFα, Fas ligand and TRAIL. Mitochondrial pathway is activated following an apoptotic stimulus mediated by p53. Growth factor receptor signalling occurs upon binding of a growth factor to the specific growth factor receptor. HER1/EGFR can bind EGF, transforming growth factor-α, β-cellulin, HB-EGF, amphiregulin and epiregulin. No cognate ligand has been discovered for HER2. Neuregulins can activate both HER3 and HER4 subtypes. HGF binds to HGFR.