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Apoptosis in Anthracycline Cardiomyopathy

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Abstract

Apoptosis is a tightly regulated physiologic process of *programmed cell death* that occurs in both normal and pathologic tissues. Numerous *in vitro* or *in vivo* studies have indicated that cardiomyocyte death through apoptosis and necrosis is a primary contributor to the progression of anthracycline-induced cardiomyopathy. There are now several pieces of evidence to suggest that activation of intrinsic and extrinsic apoptotic pathways contribute to anthracycline-induced apoptosis in the heart. Novel strategies were developed to address a wide variety of cardiotoxic mechanisms and apoptotic pathways by which anthracycline influences cardiac structure and function. Anthracycline-induced apoptosis provides a very valid representation of cardiotoxicity in the heart, an argument which has implications for the most appropriate animal models of damaged heart plus diverse pharmacological effects. In this review we describe various aspects of the current understanding of apoptotic cell death triggered by anthracycline. Differences in the sensitivity to anthracycline-induced apoptosis between young and adult hearts are also discussed.

Keywords

pediatric; cardiomyopathy; anthracycline; apoptosis

Introduction

Heart failure in childhood causes significant morbidity and mortality. The etiologies are diverse [1-3]. One of the most common causes is chemotherapy, such as anthracycline-induced cardiotoxicity. The anthracyclines, primarily doxorubicin, also including daunomycin, epirubicin and idarubicin, are among the most widely used and successful chemotherapeutics for childhood cancers, but their cumulative and dose-dependent cardiac toxicity has been the major concern of oncologists for decades [4, 5]. With the increasing population of cancer survivors, there is a growing need to develop preventive strategies and effective therapies against anthracycline-induced cardiotoxicity, in particular, the late onset cardiomyopathy.

Apoptosis, a Greek word that means falling of leaves from trees in autumn in response to the impending threat of freezing and damage in winter [6], is a genetically programmed cell death which proceeds through distinct morphological changes such as nuclear condensation, DNA fragmentation, shrinkage of the cell body, membrane blebbing and cellular fragmentation into apoptotic bodies. These apoptotic bodies are then engulfed by

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neighboring healthy cells or macrophages [7]. Apoptosis deletes cells with little tissue disruption and no inflammatory response. Two major apoptotic signaling cascades have been described and are generally referred to as the extrinsic (or receptor-mediated) and intrinsic (or mitochondrial) pathways. Apoptotic cell death is an essential process in normal and diseased pediatric heart. Recent *in vitro* and *in vivo* studies provided compelling evidence that terminally differentiated cardiomyocytes, can and do undergo programmed cell death. Apoptosis has been shown to be involved in numerous pathophysiological consequences, contributing to many diseases including cancer, immunity disorders, and cardiovascular disorders. Cardiomyocyte death has been found in major heart diseases, including cardiomyopathies, myocardial infarction (MI), end-stage heart failure, arrhythmogenic right ventricular dysplasia, etc [8-10]. Besides adult cardiac problems, numerous human and animal studies have shown distinct roles of apoptosis in normal and abnormal aspects of the pediatric heart. These studies have been instrumental in demonstrating the importance of cardiomyocyte apoptosis and in the characterization of the distinct apoptotic pathways.

Although intensive investigations on anthracycline-induced cardiotoxicity have continued for decades, the underlying mechanisms responsible for anthracycline-induced cardiotoxicity remain incompletely understood. The mechanism for anthracycline-induced cadiotoxicity has been suggested to be attributable, at least in part, to the generation of free reactive oxygen species (ROS), which then activate mitochondrial-mediated apoptotic signaling pathway leading to caspase 3 activation and cardiomyocyte apoptosis [11-16] (Fig. 1). In this review, we will focus on the current understanding of molecular mechanisms underlying anthracycline-induced apoptosis and on the differences in the sensitivity to anthracycline-induced apoptotic signals between adult and young cardiomyocytes.

Pediatric cardiomyopathy

The etiologies of heart failure in childhood are strikingly different from adults and can result from 1) congenital structural defects; 2) inherited cardiomyopathies (i.e. abnormalities of sarcomeric or cytoskeletal proteins); 3) acquired disease (i.e. infection such as viral myocarditis [17] or exposure to cardiotoxic agents such as anthracycline chemotherapy for cancer [18, 19]); 4) ischemia-reperfusion injury during open-heart surgery to repair structural defects [20, 21]. Among the diverse causes, congenital heart defects are the leading cause of heart failure in children and represent approximately 1% of all live birth, making this the most common birth defect in humans [22]. As a result of abnormal heart morphogenesis, they present most commonly during infancy between birth and one year of age. Dilated or hypertrophic cardiomyopathies are most common in children over one year of age and remain the principal indication for cardiac transplantation in children throughout childhood [23]. The prognosis of dilated cardiomyopathy in children is poor, with a 5-year survival rate of only 60% [24].

Despite the importance of heart failure in infants and children, this disease is still under-studied during these ages. On the contrary, there are rich literature and a relatively better understanding of the cellular molecular aspects of heart failure in adults. As a result, most new concepts for management of heart failure in children today are based on translation of adult treatment strategies with little preclinical evidence supporting their use in children [1, 3].

Anthracycline cardiotoxicity

The anthracyclines are among the most widely used and successful anticancer drugs ever developed. Despite extensive and long-standing clinical use (more than 40 years), they still play a major role in the treatment of a wide spectrum of hematologic malignancies and solid

tumors. Anthracycline chemotherapy, together with other improvements to treatment, has significantly improved cancer survival, particularly among children, with an increase in the 5-year survival rates from less than 50% in the 1970s to about 80% currently [25-27]. Unfortunately, the therapeutic potential of anthracycline is limited by their cumulative and dose-dependent cardiac toxicity [4, 5]. Three types of anthracycline-induced cardiotoxicity have been described: acute (within the first week of treatment), early-onset (within a year) and late-onset (more than one year after completion of treatment). Most patients who develop significant cardiotoxicity have a late-onset dilated cardiomyopathy.

Children and adolescents are particularly susceptible to the cardiotoxic effects of anthracycline chemotherapy [19, 28, 29]. About half of the young adult survivors of childhood cancer have received anthracyclines at some time points in their treatment. The frequency of cardiotoxic effects has been reported to be more than 50% among the survivors of childhood cancer and there is no safe dose in this population [18, 28-33]. At 30 years after diagnosis, cardiac complications are the leading noncancerous cause of chronic health condition in childhood cancer survivors. The standardized mortality rate for cardiac death in long-term survivors of childhood cancer is 8 times higher than expected [34]. There are currently more than 300,000 long-term survivors of childhood cancer in the United States, and this number is increasing [35]. Hence, the development of novel therapeutic strategies to improve the survivor outcome is of high clinical importance.

Apoptosis in anthracycline-induced cardiotoxicity

Because anthracyclines are such effective anticancer drugs, their mechanisms of action have been under intense investigation for many years. Cardiomyocyte death, which occurs within hours after anthracycline exposure and during the late process of ventricular remodeling, is one of the most studied mechanisms for anthracycline-induced cardiomyopathy [11-15]. Cell death is classified by the morphology of the affected cells: apoptosis, necrosis and autophagy. Most experimental studies and histopathology of endomyocardial biopsies from human patients have provided evidence that anthrocycline-induced cardiac toxicity is associated with cardiomyocyte apoptosis and necrosis [11, 12]. Recent evidence indicates that autophagy and senescence can also be related to anthracycline-induced cardiomyopathy [36-39].

Oxidative stress generated by anthracyclines has been the most studied cause of cardiotoxicity and is believed acting as a major trigger for cardiomyocyte death [40-42]. ROS such as superoxide and hydroxyl radical are formed when the quinine moiety of anthracyclines is reduced to semiquinone [40-42]. These drugs are also able to combine with iron, generating toxic and highly charged ROS. Also, mitochondrial damage induced by ROS or directly by anthracyclines can further lead to respiratory chain failure and ROS liberation [43, 44]. Endothelial nitric oxide synthase (eNOS) reductase domain converts anthracycline to an unstable semiquinone intermediate that favors ROS generation [45]. Oxidative stress can also occur via induction of NOS, leading to nitric oxide and peroxynitrite formation [46]. Oxidative stress leads to many deleterious effects on cell membrane (lipid peroxidation) [47] and subcellular apparatuses, specifically cardiac mitochondria [48]. Ultimately these changes can lead to cell death by apoptosis and necrosis, and organ damage.

Cardiac mitochondria are the key mediators of anthracycline-induced cardiomyocyte death [48] (Fig.1). Mitochondrial damage induced by ROS or directly by anthracyclines include, but are not limited to, mitochondrial membrane damage due to lipid peroxidation, impaired mitochondrial oxidative phosphorylation and adenosine triphosphate synthesis, impaired mitochondrial calcium homeostasis resulting in loss of membrane stability [48], increased

mitochondrial DNA mutations [49], impaired mitochondrial creatine kinase activity and function [50], disruption of cardiac mitochondrial biogenesis [51], and mitochondrial fragmentation [52]. All these events can trigger cardiomyocyte death by activating mitochondrial intrinsic apoptotic pathway or necrosis. For example, mitochondrial calcium overload triggers mitochondrial permeability transition (MPT), resulting in a loss of mitochondrial membrane potential, mitochondrial swelling, and outer membrane rupture, consequently release of cytochrome *c*, apoptosis inducing factor (AIF), and endonuclease G (EndoG) from mitochondria. Following mitochondrial release, cytochrome *c* forms a complex with the adaptor protein Apaf-1, dATP, and caspase 9, resulting in the formation of apoptosome. Apoptosome formation leads to the proteolytic cleavage and concomitant activation of caspase 9. Active caspase 9 directly cleaves and activates caspase 3. When a critical amount of activated caspase 3 is present within a cell, apoptosis is elicited. In addition, MPT can also trigger necrosis through inducing inner membrane rupture. Multiple studies have shown that anthracyclines induce cardiomyocyte apoptosis via the mitochondrial intrinsic pathway [16, 53-57].

In addition to mitochondrial damage, numerous signaling pathways are activated by ROS or by anthracyclines leading to the activation of the intrinsic apoptotic pathway. Cytochrome *c* release from mitochondria is regulated by the members of the Bcl-2 family, which includes three groups: anti-apoptotic members Bcl-2, Bcl-X_L, and Mcl-1, pro-apoptotic members Bax and Bak, and BH3 only proteins such as Bad, Bid, Nix and BNip3 that enhance apoptosis via inhibition of anti-apoptotic Bcl-2 proteins or activation of pro-apoptotic Bax and Bak. Activation of BH3-only proteins by stress stimuli promotes Bax/Bak translocation from the cytosol to the outer membrane of mitochondria, resulting in increased mitochondrial outer membrane permeabilization (MOMP), leading to protein release from the intermembrane space to the cytoplasm, particularly the apoptogenic molecule cytochrome *c*. Anthracycline-induced cardiomyocyte apoptosis is associated with increased Bax/Bcl-2 ratio and down-regulations of anti-apoptotic factors, which can result from multiple mechanisms which include, but are not limited to, 1) activation of p53 tumor suppressor protein leading to increased Bax expression [58, 59]; 2) down-regulation of transcriptional factor GATA-4 leading to decreased Bcl-X_L expression [57, 60]; 3) activation of the stress-activated protein kinase c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) [56, 61, 62]; 4) down-regulation of apoptosis repressor with a caspase recruitment domain (ARC) (mediated by ubiquitin-proteasome system mediated degradation) leading to increased Bax translocation to mitochondria [63, 64]; 5) inactivation of PI-3K/Akt survival pathway which has multiple impacts on apoptotic signaling [51, 65-68]; 6) dysregulation of a phosphodiesterase 3A/inducible cAMP early repressor feedback loop resulting in decreased Bcl-2 expression [69].

In addition to the activation of the intrinsic mitochondrial apoptotic pathway, activation of extrinsic apoptotic pathway also contributes to anthracycline-induced cardiomyocyte apoptosis [70-73]. In the extrinsic pathway, death ligands, such as FasL and TNFα, bind their receptors and stimulate recruitment of the adaptor proteins Fas-associated via death domain (FADD) and TNFR associated death domain (TRADD). FADD and TRADD recruit caspase 8 into a complex named death-inducing signaling complex (DISC), where it undergoes dimerization and concomitant activation. Activated caspase 8 then activates caspase 3 directly or indirectly through the mitochondria via activation of Bid which translocates to mitochondria and activates Bax and Bak to trigger the release of cytochrome *c*. Anthracyclines activate the extrinsic apoptotic pathway by several mechanisms which include 1) activation of nuclear factor-activated T cell-4 (NFAT4) by increased mitochondrial ROS production and activation of the calcium/calcineurin signaling pathway, leading to up-regulation of Fas/FasL [74]; 2) activation of transcription factor NF-κB by ROS leading to increased Fas/FasL and p53 [75-77]; 3) down-regulated expression of FLIP,

a FLICE/caspase-8 inhibitory protein, by ROS thereby sensitizing Fas-mediated apoptosis [72]; 4) down-regulation of ARC, an endogenous inhibitor of extrinsic pathway through interaction with Fas, FADD, and caspase 8 to prevent the formation of DISC [63, 64].

Additional mechanisms for anthracycline-induced apoptosis include endoplasmic/sarcoplasmic reticulum (ER/SR)-mediated apoptotic pathway leading to the activation of caspase 12 [78], and caspase-independent but AIF- and/or EndoG-dependent apoptosis [79-82]. Although a majority of the studies documented the involvement of apoptosis in anthracycline-induced cardiotoxocity, other reports have challenged the induction of apoptosis in these pathologies [83-85]. This controversy may be explained by the low prevalence of cardiomyocyte apoptosis in these hearts (typically <1%) and a wide variety of experimental conditions used in the studies including differences in dosage and frequency of anthracycline administration, in timing of assays, and in animal species and so on [86].

Potential therapeutic targets in anthracycline-induced apoptosis

Several approaches have been used to reduce the incidence of anthracycline-induced cardiotoxicity [11, 12, 87]. These strategies includes 1) dose limitation; 2) close cardiac monitoring; 3) alteration of dosage schedule such as using low-dose prolonged continuous infusion; 4) development of new anthracycline analogs that retain chemotherapeutic potential but with reduced cardiotoxicity; 5) liposome-encapsulation which limits the drugs to escape the tight capillary junctions of the heart, but not the discontinuous capillary system in tumors; 6) the administration of protective agents such as antioxidants, iron chelators and free radical scavengers. Although many efforts have been focused on reducing anthracycline-associated cardiotoxicity, it continues to have a high incidence.

Therapeutic blockage of cardiomyocyte programmed death is obviously a challenge that might require identification of numerous players in the apoptotic cascade and the right time-point to begin treatment without compromising anthracycline toxicity to tumor cells. Inhibition of the propagation and execution stages of anthracycline-induced apoptosis, e.g. inhibition of caspases may delay or block cell death and could be used to recover cardiac function. Therefore, a combination of an antiapoptotic therapy together with other cardioprotective therapies may be more effective. In addition, models of anthracycline-induced cardiotoxicity will probably help clarify the significance of combined therapies. Future novel cardioprotective therapeutic strategies might be tested in both the intrinsic and extrinsic apoptotic pathways using genetic and biochemical approaches. In keeping with this view, unraveling the sequence of key apoptotic factors recruited during anthracycline-induced apoptosis should enable us to identify regulatory molecules to be targeted for producing an optimal effect.

Caspase inhibitors has been shown to be effective in reducing myocardial reperfusion injury, which could at least be partially attributed to the attenuation of cardiomyocyte apoptosis [88, 89]. Inhibition of apoptotic DNA fragmentation and nuclear cleavage may block programmed cell death, however, blockage of earlier signaling steps required for anthracycline-induced apoptotic nuclear fragmentation might work better to ensure cell survival. For instance, blocking MOMP is likely to maintain long-term survival by abolishing the killing functions of downstream molecules including caspases. In fact MOMP inhibition can also block caspase-independent cell death found in autophagic or necrotic death. Therefore, inhibition of MOMP may have a wider range of cardioprotective actions than inhibition of caspases. MOMP can be blocked by the antiapoptotic proteins of the Bcl-2 family and is proven to have very effective cytoprotective effects in various tissues including the heart [90-93]. However, inhibition of mitochondrial permeabilization may not block cell death in conditions in which caspase activation is activated via the external

pathway or, for instance, by of IAP (Inhibitor of Apoptosis Protein) antagonists, where cell death can occur without of MOMP.

Differences in anthracycline-induced cardiotoxicity in neonatal, young and adult, and old hearts

As suggested by clinical studies, children and adolescents are particularly susceptible to the cardiotoxic effects of anthracycline chemotherapy [19, 28, 29]. Children treated before the age of 4 years are especially vulnerable [29]. Potential underlying mechanisms include, but are not limited to, 1) increased cardiomyocyte apoptosis as neonatal cardiomyocytes appear to be more susceptible to doxorubicin-induced apoptosis compared to adult cardiomyocytes [94]; 2) impaired cardiac growth resulting in inadequate left ventricular mass and cardiomyopathy in younger patients whose hearts are less developed [28]; 3) increased proportion of fat in younger children (also in female sex) resulting in more sustained exposure and resultant cardiotoxicity due to the lipophilic nature of anthracyclines [95]; 4) cardiomyocyte atrophy and myofiber disarray which is observed in anthracycline treated juvenile mice [96]; 5) increased anthracycline-sensitive cardiac transcription factors in younger hearts including cardiac ankyrin repeat protein (CARP) which is present at a higher level in neonatal hearts than in adult hearts [97, 98]; 6) increased number of cardiac progenitor cells in younger hearts which can be more sensitive to anthracycline-induced cytotoxicity resulting in impaired cardiac regenerative capacity [99, 100]. It is possible that anthracycline-induced loss of cardiomyocytes, together with early damage of cardiac stem cells in pediatric patients, can cause permanent cardiotoxicity among long-term cancer survivors. Another effect of age is increased sensitivity in the old age group (more than 65 years) [101], possibly due to the alteration of doxorubicin pharmacokinetics [102, 103].

Decreased apoptotic potential has been demonstrated in postmitotic cells such as cardiomyocytes [104], skeletal muscle cells [105], and neuronal cells [106]. Reduced expression levels of Apaf-1, caspases, and some pro-apoptotic members of the Bcl-2 family, may contribute to the reduced apoptotic potential in postmitotic cells [82, 104-107]. Rapid down-regulation of key apoptotic regulatory proteins including Bim, Apaf-1 and caspase 3 was observed in mouse heart, from neonate to adult [82, 107]. Recent *in vitro* studies also support increased anthracycline-induced apoptotic signaling in neonatal cardiomyocytes compared with adult cardiomyocytes, associated with significant down-regulation of pro-apoptotic molecules [94]. The research in our laboratory has indicated that neonatal mouse cardiomyocytes exhibit increased anthracycline-induced apoptosis compared to the frequency in adult cardiomyocyte *in vivo* (Shi et al, unpublished observations). Given the unique properties of cardiomyocytes during postnatal development, it is therefore important to understand the molecular events involved in cardiomyocyte apoptosis in this age group.

Conclusion and future directions

A large body of experimental evidence indicates that cardiomyocyte death through apoptosis and necrosis is a primary contributor to the progression of anthracycline-induced cardiomyopathy. Excessive oxidative stress, DNA damage, changes in calcium handling and cellular contractility, suppression of transcription factors that regulate cell survival and sarcomere protein synthesis, and disruption of sarcomere stability are identified as contributors to the mechanisms of cardiomyocyte death. These experimental results are supported by clinical data. Dexrazoxane, the only cardioprotective drug currently available clinically, is an intracellular iron chelator which has been proven to reduce cardiotoxicity including cardiomyocyte death induced by anthracyclines, via removing iron from its complex with anthracyclines, thereby reducing ROS formation [108-110]. Carvedilol, an adrenergic blocking agent with potent anti-oxidant activity, has been found to be protective

against anthracycline-induced ROS generation and apoptosis in experimental studies [111, 112] and in clincial trials with adult patients undergoing anthracycline therapy [113]. Combined treatment of antharcyclines and trastuzumab, an antibody targeting the erbB2, shows synergistic cardiotoxic potential in metastatic breast cancer patients [114]; the increased cardiotoxicity is attributable to the inhibition of PI-3K/Akt-mediated survival signaling through inhibiting neuregulin/erbB2 interaction by trastuzumab resulting in increased apoptosis and necrosis in response to anthracycline treatment [65, 115].

Numerous studies evaluating anthracycline-induced cardiomyocyte death were performed *in vitro* or *in vivo* with a time window of hours or days after exposure to anthracyclines at high concentrations. Future studies using long-term animal models should be performed to evaluate the contribution of different types of cardiomyocyte death to the chronic and delayed anthracycline-induced cardiotoxicity associated with clinically relevant doses of the drugs. In addition to apoptosis and necrosis, future research should determine the contribution of other forms of cell death such as autophagy and senescence as well as the relative importance of each form of cell death in anthracycline-induced cardiotoxicity, especially the late-onset cardiotoxicity. As mentioned above, the mechanisms for the late-onset anthracycline cardiac toxicity in children remain under-explored. Future research should continually validate the essential mechanisms and develop therapeutic strategies to prevent premature cardiomyocyte death in pediatric patients who need anthracycline treatment.

Although considerable efforts to prevent cardiotoxicity have been made, a significant portion of patients, especially children, are still threatened by heart failure. At present, there is no general accepted method to provide selective protection of the heart from damage induced by anthracyclines. Knowledge derived from basic research has provided an increasing number of potential therapeutic targets for developing new strategies of cardioprotection against anthracycline-induced cardiotoxicity. Continuous efforts in elucidating the pathogenic mechanisms and identifying new therapeutic targets will certainly be helpful for the development of more effective therapies to minimize the most serious adverse effect of this broadly used anticancer agent in order to increase cancer cure rate and improve the life quality and expectancy of cancer survivors.

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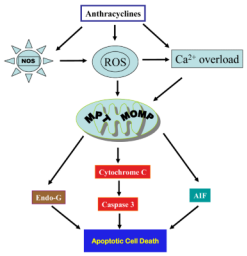

Figure 1.
Simplified mitochondrial pathway of anthracycline-induced cardiotoxicity via activation of distinct apoptotic mechanisms following mitochondrial outer membrane permeabilization (MOMP) and/or mitochondrial permeability transition (MPT).