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Pathophysiology of anthracycline cardiotoxicity

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Anthracyclines (ANTs) are powerful drugs that have reduced the mortality of cancer patients. However, their use is limited by the development of cardiotoxicity (CTX), which is dose dependent and may lead to left ventricular dysfunction and heart failure. Although various strategies have been suggested to reduce the negative effects of ANTs, CTX is still an important unresolved clinical issue. This may be due at least partly to the incomplete characterization of the molecular and cellular mechanisms of ANT-induced CTX. In addition, although various forms of cardiac damage have been demonstrated with the use of these drugs in experimental studies, it is not yet clear how these translate to the clinical setting. Appropriate characterization of potential candidates for ANT-based therapies is essential to decide whether to administer these drugs. Hopefully, new information from genetic profiling will help to identify patients who are at high risk of developing CTX.

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Introduction

Anthracyclines (ANTs) are widely used and effective chemotherapeutic agents. They are currently utilized for the treatment of many malignancies including lymphomas, leukemias, and sarcomas, and for both early and advanced breast cancer. Unfortunately, these drugs also induce cardiotoxic effects, which have been recognized since the 1960s.[1] ANT-related cardiotoxicity (CTX) may lead to the development of cardiomyopathy (CMP) and heart failure,[2] which limits the administration of the drugs, and consequently limits the treatment of malignant disease.

Several efforts have been made to understand the mechanisms underlying ANT-related CTX, to generate molecules to decrease the CTX, to set up strategies to reduce the development of cardiac dysfunction and for the early recognition of myocardial damage due to CTX. However, CTX remains a relevant problem for all of the ANTs.

General characteristics of anthracyclines

The ANTs (or anthracycline antibiotics) are a class of drugs composed of an aglycone and a sugar.[3] The aglycone is a tetracyclic ring structure containing an anthraquinone chromophore and a short side-chain with a carbonyl group at C-13. The sugar, called daunosamine, is attached by a glycosidic bond to C-7 of the tetracyclic ring (Fig. 1).

Daunorubicin, the first ANT compound to be characterized, was isolated from *Streptomyces peucetius*, a soil bacterium. Doxorubicin (also known as Adriamycin) is a hydroxyl derivative of daunorubicin. Various chemical modifications have been introduced in these two molecules to obtain new ANTs. Idarubicin is a semisynthetic derivative of daunorubicin, characterized by the absence of a methoxy group at C-4 in ring D of the tetracyclic structure (Fig. 2); this gives the compound a high lipophilicity, which results in an increased rate of cellular uptake compared with other ANTs. Epirubicin is a semisynthetic derivative of doxorubicin obtained by an axial-to-equatorial epimerization of the hydroxyl group at C-4 in daunosamine (Fig. 2). Valrubicin is a semisynthetic analog, and mitoxantrone is a synthetic analog, of doxorubicin. Notably, mitoxantrone is a substituted aglyconic anthraquinone, with no daunosamine (Fig. 2).

In an effort to reduce CTX, specific formulations of ANTs have been generated with the encapsulation of these drugs by nonpegylated or pegylated liposomes (in the latter case with an additional polyethylene glycol layer). A lower proportion of ANTs administered in the liposomal form (especially in the pegylated liposomes) is delivered to the cardiomyocytes compared with the nonliposomal form.

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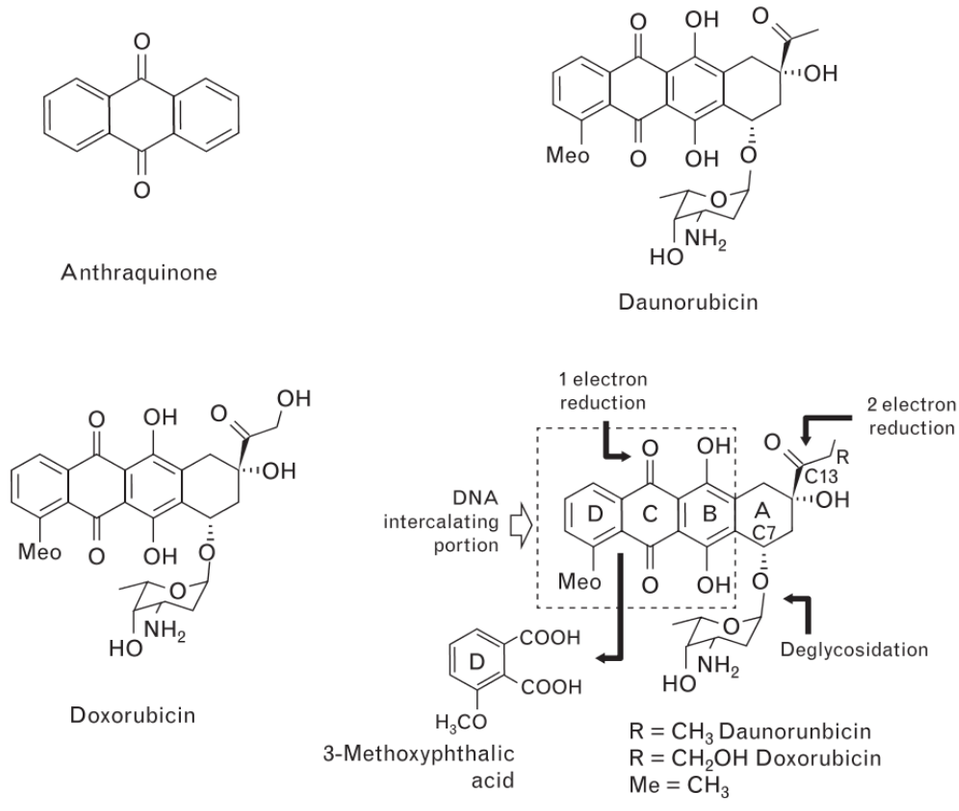
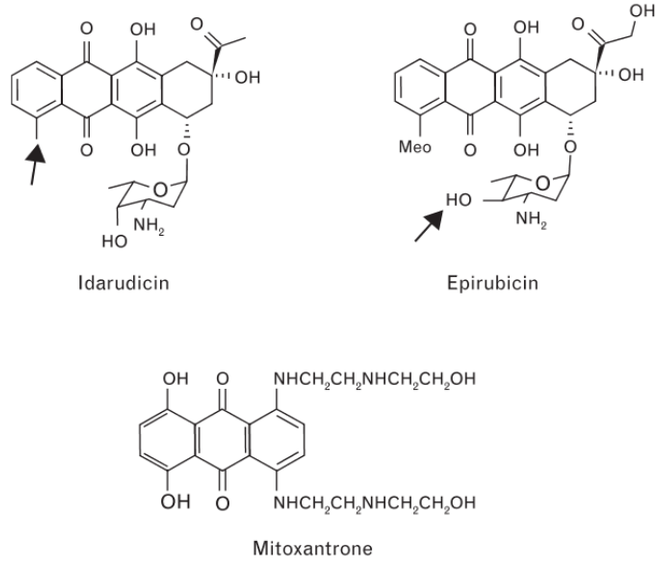
Fig. 1



The chemical structures of anthraquinone and the main anthracyclines. The portion of the anthracycline molecule involved in the interaction with DNA and the sites involved in anthracycline metabolism are indicated.

Fig. 2



The chemical structures of idarubicin, epirubicin and mitoxantrone. The arrows indicate the differences between idarubicin and epirubicin and daunorubicin and doxorubicin, respectively.

The mechanisms of action of ANTs in tumor cells are based on interactions with the nucleus, mitochondria, and biological membranes[3] (Table 1). Specific portions of the ANT molecules may be involved with specific mechanisms (Fig. 1).

ANTs are generally administered intravenously. Valrubicin and epirubicin can be given by intravesical instillation for the treatment of bladder cancer. Idarubicin can also be administered orally. ANTs are excreted mostly through the bile.

Anthracyclines metabolism

Knowledge of the metabolism of ANTs is important to understand the mechanisms of CTX induced by these drugs. ANTs can undergo metabolism via three

Table 1 Main mechanisms of action suggested for the antitumor effect of anthracyclines

Intercalation of the planar ring structure between adjacent DNA base pairs, leading to inhibition of protein synthesis and DNA replication
Generation of ROS, leading to DNA damage and/or lipid peroxidation
Inhibition of the topoisomerase II enzyme, initiating DNA damage
DNA cross-linking, binding, and alkylation
Interference with DNA unwinding or DNA strand separation helicase activity
Direct membrane effect with disruption of the bilayer structure

DNA, deoxyribonucleic acid; ROS, reactive oxygen species.

different routes: two-electron reduction, one-electron reduction, and deglycosidation.[4] However, approximately half of the dose of doxorubicin is eliminated from the body unchanged.

Two-electron reduction

The two-electron reduction of the side-chain C-13 carbonyl group of ANTs (Fig. 1) results in the formation of active secondary alcohol metabolites (like doxorubicinol, daunorubicinol, epirubicinol, and idarubicinol).[4] This is considered the primary metabolic pathway. The enzymes involved with this pathway are cytoplasmic reductases, specifically the carbonyl reductases 1 and 3 and aldo-keto reductases (especially AKR1A). Doxorubicinol, which is more polarized than doxorubicin, accumulates at higher levels and for longer times in the heart, leading to a long-lived cardiac ANT reservoir. This may favor cytotoxicity.[3,5]

One-electron reduction

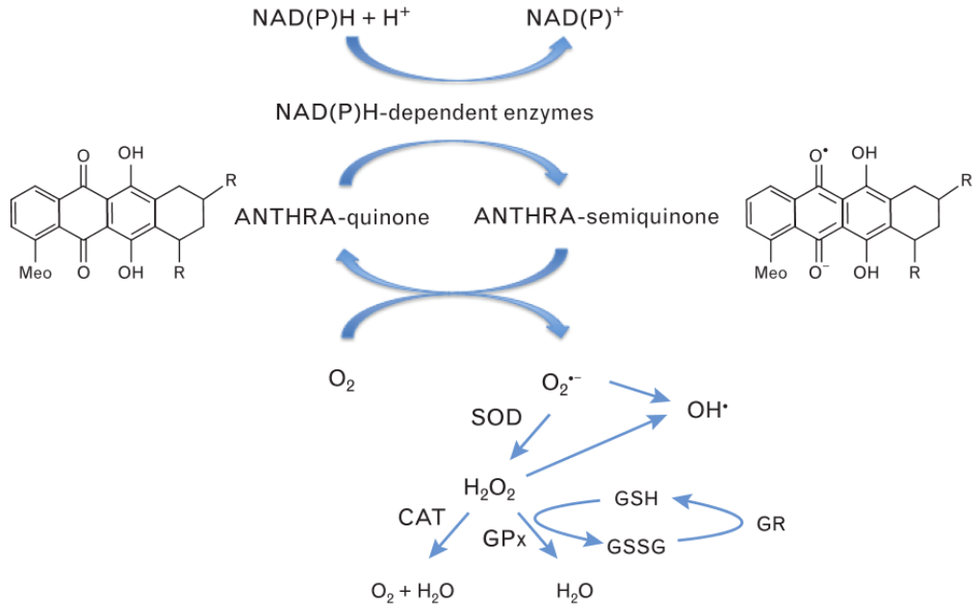
In this type of reduction, the nicotinamide adenine dinucleotides, NADH and NADPH, which act as coenzymes, play a role as electron donors[4] (Fig. 3). The ANT in its quinone form accepts the electron. A one-electron addition to the quinone moiety in ring C of ANTs induces the formation of a semiquinone free radical, which is an unstable metabolite under aerobic conditions. It therefore regenerates its original quinone by reducing molecular oxygen, also leading to the formation of the superoxide radical ($O_2^{\bullet -}$). This sequence of reactions is an example of 'redox cycling.'

In the mitochondria, NADH is a coenzyme of NADH-dehydrogenase (or complex I) of the electron transport chain, which normally transfers an electron to the quinone form of ubiquinone to generate a semiubiquinone. NADPH is a coenzyme of NADPH-oxidase (NOX), which is a multimeric enzyme located in the plasma membrane (the NOX2 isoform is present at high levels in cardiomyocytes); it is also a coenzyme of the NADPH-dependent cytochrome P450 reductases of the endoplasmic reticulum and soluble oxidoreductases of the cytoplasm, such as the xanthine oxidase. Therefore, the one-electron reduction of ANTs can occur at the mitochondrial, endoplasmic reticulum, and/or cytoplasmic level, although most of the free oxygen radical generation seems to take place in the mitochondria.

Deglycosidation

This is a minor metabolic pathway (1–2% of the dose undergoes metabolism via this pathway)[4] (Fig. 1). The resultant metabolite of deglycosidation is generally the doxorubicin deoxyaglycone, obtained by a reduction process. The deoxyaglycone is more lipophilic, has improved membrane diffusion, and accumulates more in the mitochondrial membrane compared with the parent compound. There are various enzymes involved in this metabolic pathway, which include the NADPH-cytochrome P450 reductase.

Fig. 3



The enzymatic pathway leading to the generation of reactive oxygen species. DOX = doxorubicin, NADPH = nicotinamide adenine dinucleotide phosphate, SOD = superoxide dismutase, CAT = catalase, GPx = glutathione peroxidase, GR = glutathione reductase, GSH = monomeric glutathione, GSSG = glutathione disulfide.

Peculiarities of the different anthracyclines

It is important to emphasize that differences exist in the intracellular metabolism of different ANT molecules. This is particularly important for epirubicin. Although this molecule differs from doxorubicin in a limited modification of the daunosamine (Fig. 2), it is sequestered in cytoplasmic acidic organelles such as recycling endosomes, lysosomes, and the vesicles of the trans-Golgi network; hence, epirubicin fails to reach the mitochondria and forms no free oxygen radicals, in contrast to doxorubicin.[6] In addition, the two-electron reduction of the epirubicin side-chain C-14 carbonyl group is impaired, so considerably less alcohol metabolite (epirubicinol) is formed compared with the doxorubicinol derived from doxorubicin.[6] Finally, epirubicin shows a unique metabolic pathway wherein it is converted to doxorubicinolone (the product of epirubicin carbonyl reduction and deglycosidation) which causes plasma membrane permeation to augment epirubicin elimination.[7] These metabolic differences lead to defective conversion of epirubicin to toxic species and to augmented elimination and are counterbalanced by the fact that epirubicin exhibits a higher uptake and reaches higher myocardial levels than doxorubicin.[7] Moreover, at high doses, epirubicin may cause CTX by direct interactions with cardiomyocytes. Therefore, some metabolic peculiarities would, in theory, predict that epirubicin would be less toxic than doxorubicin; however, it exhibits other factors that would lead to greater toxicity. This means that the real impact of epirubicin on the CTX in patients should be derived from clinical studies.

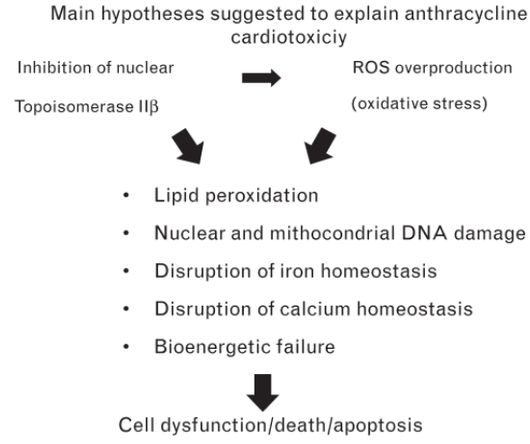
Oxidative degradation

Recently, it was observed that, in addition to the reductive metabolism described earlier, doxorubicin can undergo oxidative degradation catalyzed by peroxidases. The H_2O_2-activated myoglobin is the catalyst of this reaction, and the 3-methoxyphthalic acid is the final product[8] (Fig. 1). Because the 3-methoxyphthalic acid seems to be considerably less toxic than doxorubicin, it has been speculated that the oxidative degradation may represent a salvage pathway that diminishes ANT-related CTX.[8]

Molecular mechanisms of cardiotoxicity

The mechanisms underlying ANT-induced CTX at the molecular level remain controversial and are not fully understood[3,9–13] (Fig. 4). Generally, ANT-induced CTX is considered to be independent of the anticancer activity. This is based on the concept that cardiomyocytes, as terminally differentiated cells, should not be sensitive to the primary antineoplastic activity, which is related to blocking cell proliferation. However, some similarities exist between the anticancer and CTX effects of ANTs (Table 1 and Fig. 4), although the CTX to cardiomyocytes seems to have its own peculiarities. It is clear that ANTs must enter cardiomyocytes to generate their toxic effects.

Fig. 4



DNA = deoxyribonucleic acid, ROS = reactive oxygen species.

Overproduction of free radicals

In the past, the most widely accepted hypothesis for ANT-induced CTX was the overproduction of reactive oxygen species (ROS), that is, free radicals derived from oxygen. ANTs can generate free radicals by enzymatic and nonenzymatic mechanisms. In the enzymatic mechanism, various enzymes can be involved (as previously explained) in redox cycling pathways in the mitochondria, sarcoplasmic reticulum and cytoplasm, leading to the formation of the superoxide radical, $O_2^{\bullet -}$. These redox cycling pathways can be highly damaging because a relatively small amount of ANTs is sufficient for the formation of numerous superoxide radicals. The $O_2^{\bullet -}$ can be converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD)[3] (Fig. 3). H_2O_2 is a relatively stable molecule, which under physiological conditions is eliminated by catalase (which favors the decomposition of H_2O_2 to water and oxygen) and glutathione peroxidase (GPx, which also generates water from H_2O_2) (Fig. 3). However, H_2O_2 and $O_2^{\bullet -}$ may also originate highly reactive and toxic hydroxyl radicals ($OH^{\bullet}$) (Fig. 3). In addition, ROS can react with nitric oxide to generate reactive nitrogen species, thus amplifying the production of oxidant compounds. In the nonenzymatic mechanism, ANTs form a complex with ferric iron (ANT-Fe^{3+}) because of their strong affinity for iron. The ANT-Fe^{3+} may originate a free radical (ANT-$Fe^{2+}\bullet$) capable of reducing molecular oxygen to generate the superoxide radical $O_2^{\bullet -}$.[13]

High levels of free radical production that overwhelm the cellular antioxidant defense systems (leading to so-called 'oxidative stress') may damage biomolecules and deregulate cellular signaling pathways. In particular, ROS can lead to lipid peroxidation (i.e. oxidative degradation of

lipids) with consequent membrane damage. They can also lead to deoxyribonucleic acid (DNA) damage, and may trigger apoptotic cell death (described below). In addition, doxorubicin inactivates GPx and SOD, eliminating important defenses against ROS.[3]

These mechanisms based on ROS generation provided the rationale for using SOD mimetics,[14] drugs with antioxidant properties (such as probucol, carvedilol, and telmisartan)[15–18] and iron-chelating agents (such as dexrazoxane)[19] in an effort to protect patients against ANT-induced damage. In human studies, however, negative results have been reported with some of these agents.[14] Therefore, further investigations are needed to ascertain the exact biological interaction of ANTs with the cellular redox balance.

Topoisomerase inhibition

More recently, the primary event in the pathogenesis of the ANT-induced CTX has been attributed to the inhibition of nuclear topoisomerase (Top) IIβ activity.[20] In humans, there are two types of Top II enzymes: Top IIα and Top IIβ.[21] Top IIα, found predominantly in proliferating cells, is necessary for unwinding DNA strands during DNA replication and transcription; it is considered a target for the anticancer effects of ANTs (Table 1). Conversely, Top IIβ is present in all quiescent cells, including cardiomyocytes. Top IIβ inhibition by ANTs causes DNA double-strand breaks and transcriptome changes, which are responsible for defective mitochondrial biogenesis and ROS formation.[20] Ultimately, this would result in cell dysfunction and death (Fig. 4).

Interestingly, dexrazoxane changes the Top II configuration through tight binding to Top II ATP-binding sites, thus preventing ANTs from binding to the Top II complex.[10] This observation supports the inhibition of the nuclear Top IIβ as the major mechanism underlying ANT-related CTX.

Role of alcohol metabolites

ANT alcohol metabolites can induce CTX through iron-dependent and -independent mechanisms, which disrupt iron and calcium homeostasis, respectively.

Iron-dependent mechanism

It has been shown that doxorubicin interacts with cellular iron in a more complex way than by simply producing ROS. In particular, it interacts with aconitase/iron regulatory protein 1 (IRP 1).[22] This is a bifunctional protein that, when it contains a [4Fe–4S] cluster (i.e. in iron-rich cells), converts citrate to isocitrate as part of the tricarboxylic acid (Krebs) cycle. On the other hand, when the intracellular iron levels are low and the cluster is not formed, IRP-1 becomes an RNA-binding protein, which regulates the expression of genes involved in iron metabolism to optimize cellular iron availability. Doxorubicinol leads to an irreversible conversion of aconitase/IRP-1 into a 'null protein,' that is, a protein devoid of RNA-binding activity and that is unable to recover aconitase activity, to sense iron levels or to regulate iron uptake or sequestration within cells. Cells also contain IRP-2, but doxorubicinol does not seem to have any effect on IRP-2, which is instead highly sensitive to ROS-dependent oxidative modifications.[22]

Iron-independent mechanism

Doxorubicinol is a strong inhibitor of a number of ATPases including the Ca^{2+}-Mg^{2+} ATPase of the sarcoplasmic reticulum, the F0-F1 ATPase (proton pump) of the mitochondria, and the Na^{+}-K^{+} ATPase and Na^{+}-Ca^{2+} exchanger of the sarcolemma.[3] It also suppresses the expression of ryanodine receptor 2 of the sarcoplasmic reticulum.[3] As a consequence of these actions, calcium homeostasis is disrupted and intracellular calcium overload occurs.

Sarcomere disruption and 'sarcopenia'

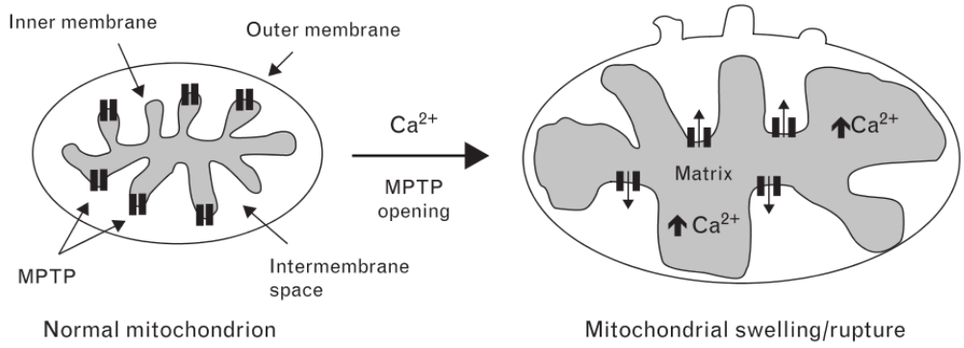
An effect of ANT exposure is a disarray and loss of myofibrils (sarcopenia), which is the consequence of multiple mechanisms. The first mechanism is an increase in the proteolytic activity of calpain (probably due to intracellular calcium overload) which accelerates the degradation of titin, a giant myofilament protein of the sarcomere in striated muscle.[23] Titin integrity is critical for normal contractile function and its degradation leads to sarcomere disorganization and contractile dysfunction.

In addition to titin degradation, ANTs may suppress sarcomere protein synthesis through interactions with critical signaling pathways and transcription factors, such as GATA-4, the cardiac ankyrin repeat protein (ankyrin repeat domain 1, ANKRP1), and the transcriptional coactivator, p300. Cardiac ankyrin repeat protein is also called 'cardiac Adriamycin-responsive protein' because of the sensitivity of its mRNA to ANT exposure. These three transcription factors regulate the expression of cardiac genes involved in sarcomere synthesis and are essential for normal sarcomere organization.[24] Therefore, their downregulation or degradation in myocytes after ANT treatment may contribute to myofibrillar disarray, sarcopenia, and cell dysfunction.[24]

Effects on mitochondria

ANT-induced CTX has a strong mitochondrial component. Doxorubicin has a high affinity for cardiolipin, a negatively charged phospholipid located in the mitochondrial inner membrane.[3] The interaction of doxorubicin with cardiolipin leads to a high concentration of the drug in this organelle. Once accumulated in the mitochondrion, doxorubicin may exert its deleterious effects, which mainly include stimulation of ROS production, inhibition of oxidative phosphorylation (OXPHOS), and interaction with the mitochondrial DNA (mtDNA).[25]

Fig. 5



Left. A schematic of a normal mitochondrion with the mitochondrial permeability transition pores (MPTPs) on the inner membrane. The MPTPs are closed. *Right.* The model shows the mitochondrion undergoing MPTP opening in response to a Ca^{2+} increase. This causes the mitochondrial inner membrane to dissipate its electromechanical gradient, leading to swelling. The process may proceed to rupture of the outer mitochondrial membrane.

As explained earlier, doxorubicin can divert electrons from mitochondrial complex I as well as from several other dehydrogenases, being converted into a semiquinone radical that generates ROS (Fig. 3). The ROS can directly inhibit the respiratory complexes of OXPHOS and increase mitochondrial calcium accumulation.[25] This latter effect results in opening of the nonselective mitochondrial permeability transition pores (MPTPs) located in the inner mitochondrial membrane. The opening of the MPTPs, via cyclophilin D (CypD), allows the free passage of low molecular weight solutes (<1.5 kDalton) but not of larger proteins in the intermembrane space, affecting the colloidal osmotic pressure and leading to mitochondrial swelling (Fig. 5). If the MPTPs remain open, the inner membrane expands and mechanically disrupts the outer membrane, which has a smaller area (Fig. 5). Damage of the mitochondrial membranes with a consequent release of cytochrome c into the cytosol can activate the apoptotic cascade (described later).

Compared with nuclear DNA, mtDNA is more susceptible to oxidative damage because of its proximity to the site of ROS generation, its lack of introns and histones, and the limited DNA repair capacities in the mitochondria.[26] Upon accumulation of insults to mtDNA, the cellular capacity for energy production is progressively reduced and cell dysfunction occurs.[27,28]

Role of apoptosis

Until a few years ago, apoptosis was not considered to be a mechanism of ANT-induced CTX, but this view has now changed. ANTs can induce apoptosis, especially through the mitochondrial (intrinsic) pathway, which involves proteins of the outer mitochondrial membrane (Bax and Bak, among others), cytochrome *c*, and caspase activation. In particular, ANTs may favor cytochrome c release into the cytosol through the activation or induction of Bax and Bak proteins, which increase mitochondrial outer membrane permeability.[3] When cytochrome c is introduced into the cytosol, it binds to the apoptotic protease activating factor (Apaf) 1 and leads to the formation of the apoptosome complex, which in turn, activates the caspases, a group of proteases that cleave several hundred cellular proteins to coordinate the destruction of the cell.

The induction of several apoptotic pathways by doxorubicin has been demonstrated including the activation of the tumor suppressor protein, p53; the activation of the p38 mitogen-activated protein kinase; the downregulation of the GATA-4 transcription factor (an effect coupled with downregulation of antiapoptotic proteins); the activation of the nuclear factor-kappaB transcription factors; and the activation of sphingomyelinases (favoring the accumulation of ceramide with the opening of the MPTPs).[3] The activation of all of these apoptotic pathways occurs via the induction of oxidative stress, determined by the redox cycling of ANTs.

However, despite solid evidence for ANT-induced apoptosis in cardiomyocytes *in vitro*, there is little evidence regarding the contribution of apoptosis to ANT-related CTX *in vivo*.[3] Therefore, the precise role of apoptosis in the pathogenesis of the ANT-induced CMP in patients requires further elucidation.[3]

Why is the heart the most affected organ?

Many hypotheses have been formulated to explain the selective induction of CTX by ANTs, but there is currently no conclusive evidence. One hypothesis relies on specific ANT accumulation in cardiomyocytes compared with other tissues.[29] A second hypothesis is that because antioxidant resources (like catalase) are lower in the cardiac tissue compared with other organs (like the liver), this can make the heart potentially more vulnerable to free radical damage.[3] A third hypothesis is based on the primary role of mitochondria in cardiomyocytes. The

heart is rich in mitochondria, which occupy approximately 40% of the cardiomyocyte volume and produce approximately 90% of the cellular energy.[30] Therefore, impairment of the mitochondrial function could be particularly critical in cardiomyocytes. It cannot be excluded that all of these mechanisms are concurrently active in determining the selective ANT-related CTX. Conversely, it is unlikely that the CTX relies on the postmitotic nature of cardiomyocytes because skeletal muscle is also a postmitotic tissue, but it is not selectively affected by ANT toxicity.

Additional mechanisms underlying cardiotoxicity

Progenitor cells

ANT-induced CTX involves not only the population of terminally differentiated cardiomyocytes but also the pool of cardiac progenitor cells, which play a role in cardiac repair.[31–33] Therefore, ANT-related depletion of these cells may hinder the capability of cardiac tissue to regenerate following minor injuries.[34,35]

Stress vs. survival pathways

ANTs, while activating cardiomyocyte 'stress pathways,' also activate 'survival pathways,' the most important of which is the neuregulin/human epidermal growth factor receptor 2 (HER2) system.[36] The activation of this survival pathway often overwhelms the toxic effects of ANTs, and cardiac dysfunction might not appear for several years. Although, should a patient be treated with anti-HER2 drugs, such as trastuzumab, this will create an imbalance in favor of the toxic effects, with a significantly increased risk of inducing left ventricle dysfunction.[36]

The multiple mechanisms and multiple hits hypotheses

It is possible that the development of ANT-related CTX is the consequence of multiple mechanisms. In this view, Minotti *et al.*[3] proposed a mechanism of chronic CMP linking ROS and iron-dependent apoptosis with the iron-dependent and independent actions of alcohol metabolites of ANTs. According to these authors, the loss of iron and calcium homeostasis due to the alcohol metabolites, along with the negative influence on the energy and redox balance of the cell, would be sufficient to induce chronic CMP, but the damage could be enhanced by the loss of viable cardiomyocytes due to ROS and iron-dependent apoptosis.[3] It should also be considered that progenitor cell impairment may play a role, as well as concomitant or subsequent treatments with other antineoplastic drugs, and genetic predisposition.

Finally, it should be kept in mind that the ability of the heart to adapt to stress is impaired after exposure to ANTs. Therefore, late-onset CTX could be a consequence of pharmacological and nonpharmacological sequential injuries (*the multiple hit hypothesis*).[37]

Morphological characteristics of chronic anthracyclines-related damage

The morphological changes of the myocardium observed following ANT treatment include myocardial cell loss (by necrosis or apoptosis), which is accompanied by interstitial fibrosis.[38] There is generally no evidence of inflammation in chronic CMP.[39,40] In electron microscopy studies, the typical early morphological changes included cytoplasmic vacuolization and myofibrillar loss caused by dilatation of the sarcoplasmic reticulum and mitochondrial swelling. Nuclear crenation or deformation, an increased number of mitochondria (mitochondriosis), and some intracellular edema have also been described.[40]

It has been reported that the myocardial damage due to ANT therapy is more prominent in the subendocardial layer of the left ventricle myocardial walls.[40] This is consistent with the knowledge that the subendocardium is more vulnerable than the subepicardial layer of the left ventricle walls to a variety of diseases ranging from ischemic heart disease to hypertension and diabetes. As a consequence, because the inner luminal part of the myocardium is dominated by longitudinal myocardial fibres,[41] any early damage will result in a deterioration of the longitudinal left ventricle function. This may explain the value of assessing the longitudinal myocardial deformation for the early diagnosis of ANT-induced CTX, as reported in recent guidelines.[42]

In some patients treated with ANTs, extensive endocardial fibrous thickening leading to restrictive (rather than dilated) CMP has been described.[40]

The issue of genetic predisposition

There are emerging data in the literature about the genetic predisposition to ANT-related CTX.[43–50] This is an important issue because it may explain the large inter-individual variability in developing CTX after ANTs, even at very low doses of these drugs.[46] Many gene polymorphisms associated with an increased risk of ANT-induced CTX have been documented.[4] Generally, the involved genes have been shown to encode proteins affecting the pharmacokinetics of ANTs;[43–47] in other cases, they are involved in free radical deactivation[48] or of repair of the myocardial damage induced by ANTs.[49] Large prospective clinical studies are needed to establish the value of predictive models for ANT-induced CTX based on genetic variants.

Conclusion

ANTs have reduced the mortality rates of many cancers. However, their use is limited by CTX, which is dose dependent. Although several strategies have been proposed to reduce ANT-related CTX (e.g. limited dose exposure, the encapsulation of ANTs in liposomes, concurrent administration of the iron chelator dexrazoxane, and modifications of the ANT structure), left ventricle systolic dysfunction and heart failure still occur in treated

patients. Unfortunately, the molecular and cellular mechanisms underlying the ANT-induced CTX are still not fully characterized. In addition, although several forms of cardiac injury (e.g. accelerated myofilament degradation, defective mitochondrial biogenesis, death of cardiomyocytes and resident stem cells, sarcopenia, etc.) have been demonstrated in experimental studies, it remains unclear how they translate to the clinical setting. A thorough clinical, laboratory, and echocardiographic characterization of potential candidate to ANT-based therapies is fundamental to decide whether to administer these drugs. The addition of genetic profiling to clinical risk factors is expected to improve the future identification of patients at high risk of developing ANT-induced CTX.

Acknowledgement

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