Understanding Doxorubicin-induced cardiotoxicity

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Abstract

Doxorubicin (DOX) is a highly effective anthracycline chemotherapeutic agent used to treat a wide range of cancers. However, its clinical use is significantly limited by the development of dose-dependent cardiotoxicity, manifesting as acute, early-onset, or late-onset chronic progressive cardiomyopathy, often leading to heart failure. Understanding the complex mechanisms underlying DOX-induced cardiotoxicity is crucial for developing effective preventative and treatment strategies. DOX's cardiotoxic effects are multifaceted, involving several interconnected pathways. A primary mechanism involves the generation of reactive oxygen species (ROS) through redox cycling of DOX's quinone moiety. This oxidative stress damages cellular components, including lipids, proteins, and DNA, leading to mitochondrial dysfunction and ultimately cardiomyocyte apoptosis. Iron plays a crucial role in this ROS generation, exacerbating oxidative damage. DOX also interferes with topoisomerase IIβ, an enzyme crucial for DNA replication and repair, leading to DNA damage and genomic instability in cardiomyocytes. Furthermore, DOX disrupts calcium homeostasis within cardiomyocytes, contributing to contractile dysfunction and cell death. Recent research has highlighted the role of endoplasmic reticulum stress, autophagy dysregulation, and immune system activation in DOX-induced cardiotoxicity. Beyond these cellular mechanisms, genetic predispositions and patient-specific factors, such as age, pre-existing cardiovascular disease, and concomitant medications, can influence the susceptibility to DOX-induced cardiotoxicity. Current research focuses on identifying biomarkers for early detection of cardiotoxicity and developing cardioprotective strategies. These strategies include the use of antioxidants, iron chelators, and targeted therapies aimed at mitigating ROS generation, preserving mitochondrial function, and inhibiting specific signaling pathways involved in DOX-induced cardiomyocyte damage. Further research is needed to fully elucidate the intricate mechanisms involved and develop effective clinical strategies to minimize the risk of this debilitating side effect, ultimately improving the quality of life for cancer survivors.

Keywords: Doxorubicin, cardiotoxicity

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Introduction

Doxorubicin-induced cardiotoxicity

Cancer is one of the most common causes of death worldwide and the number of cancer deaths continues to increase globally. According to World Cancer Research Fund International, about 10 million people died from cancer in 2020, and nearly 29 million cancer-related deaths are expected in 2040 **(Gordon-Dseagu and Vlad, 2023)**.

Advances in clinical research have increased the range of effective anti-cancer therapies in clinical practice, but their adverse effects are often a major challenge. Many patients experience serious side effects from anti-cancer drugs including the non-selective effects of chemotherapeutics. Among the most commonly reported side effects, due to the unselective action of antineoplastic agents, are chronic fatigue, alopecia, nausea, vomiting, oral mucositis, diarrhea, hematologic disturbances such as anemia or neutropenia, and lymphedema, as well as thromboembolic events **(Chunarkar-Patil et al., 2024).**

In today's oncology practice, anthracycline-based chemotherapeutic agents, notably doxorubicin (DOX), remain a cornerstone for treating a variety of adult and pediatric cancers **(Peter et al., 2022)**. It was isolated in the early 1960s from the pigment-producing bacterium Streptomyces peucetius var. caesiusand. DOX is widely used to treat various types of cancers such as breast cancer, sarcomas, hematologic malignancies, and carcinomas **(van der Zanden et al., 2021)**.

The tumoricidal properties of DOX are based on its ability to to diffuse across the cell membrane and intercalate into DNA, inhibit topoisomerase II (Top2), disrupt mitochondrial function, and increase free radical formation, which in turn leads to oxidative damage **(Kciuk et al., 2023)**. However, it is important to note that the precise mechanisms of DOX action are still not fully understood and are currently a topic of debate **(Avagimyan et al., 2024)**.

In normal conditions, Top2 makes nicks in DNA strands during replication to relieve the stress of supercoiled DNA and re-ligates the strands **(Pommier et al., 2016)**. However, binding of Dox inhibits the enzyme and prevents it from being able to rejoin the nicked ends. This results in “unrepaired” DNA double-strand breaks, that lead to a cascade of signaling as part of the DNA damage repair response, leading to cell death **(Jekimovs et al., 2014)**.

This is thought to be the primary mechanism of action by which Dox exerts its anti-cancer activity. As a result, this can also lead to apoptosis in non-cancerous cells, including cardiomyocytes. Since topoisomerase II β is present in cardiomyocytes, the inhibition of its isoform has been shown to induce long-term side effects in cardiac muscle, resulting in cardiomyopathy **(Vejpongsa and Yeh, 2014)**..

The incidence of cardiotoxicity has been rapidly growing, extending to younger demographics and those without prior health concerns **(Hedayati et al., 2020)**. Patients attaining stable and prolonged remission from oncological conditions are confronting a wide spectrum of cardiovascular complications, ranging from sinus arrhythmias to decompensated heart failure **(Delavar et al., 2022)**.

While cardiotoxicity is associated with nearly all chemotherapeutic agents, the cardiotoxic effect of anthracyclines is particularly concerning **(Becker et al., 2023)**. Historically, cardiotoxicity refers to a subclinical or clinical decline in the left ventricular ejection fraction; however, it now includes the onset of any clinical or subclinical manifestations of cardiovascular metabolism and function **(Lee et al., 2023)** .

Mechanisms of Dox-induced cardiac dysfunction:

Despite almost 60 years of research, the mechanisms to explain DIC are not completely understood. It seems to be a multistep process, with different potential pathways involved that leads to cardiomyocyte death. Until now, the main mechanisms that have been proposed by various research groups include oxidative stress, iron metabolism, Ca^{2+}homeostasis dysregulation, sarcomeric structure alterations, gene expression modulation, and apoptosis **(dos Santos and dos Santos Goldenberg, 2018)**.

Oxidative stress

One of the major mechanisms of DIC is strongly linked to mitochondrial dysfunction, leading to an increased generation of intracellular ROS and oxidative stress. Mitochondria are the most injured intracellular organelles upon cell exposure to DOX. One of the contributing factors for the accumulation of DOX in the inner mitochondrial membrane is its high-affinity binding to cardiolipin **(Wenningmann et al., 2019)**.

Cardiolipin is a phospholipid present in the inner leaflet of the mitochondrial membrane and is known for maintaining mitochondrial structure, function, cardiac energy metabolism, and cell survival **(Paradies et al., 2019)**. Mitochondrial toxicity arising from the cardiolipin-bound DOX is majorly mediated through oxidative stress **(Shi et al., 2023)**.

ROS formation initiated by DOX is intricate and occurs at several stages. The quinone fragment of anthracyclines is subjected to univalent reduction, forming semiquinone radicals via NADPH cytochrome P-450 reductase activity. Subsequently, the semiquinone form of DOX is oxidized by oxygen molecules, reverting to the initial quinone form and synthesizing superoxide anion radicals. This transformation also causes "leaks" in the electron transport chain, resulting in redox-homeostasis disturbances and activation of multiple proinflammatory cascades **(Rochette et al., 2015)**.

DOX accumulation in mitochondria leads to enhanced production of ROS and reactive nitrogen species as well. These reactive species in turn cause peroxidation of lipids and oxidative damage to DNA and proteins, resulting in mitochondrial DNA (mtDNA) damage, loss of ATP levels, peroxidation of cardiolipin, and mitochondrial permeability transition **(Wenningmann et al., 2019)**.

A close interaction between ROS, mtDNA damage, and the ETC can result in the formation of a vicious loop in two ways: enhanced ROS levels can directly inactivate the electron transport chain and result in further ROS formation. Alternatively, mtDNA damage caused by increased ROS levels can

inhibit ETC proteins aggravating mitochondrial dysfunction and ROS formation **(de Oliveira and Niederer, 2016)**.

Altogether, this cycle of events results in the release of cytochrome c as well as the release of additional apoptogenic factors from mitochondria, hence initiating the apoptotic pathway. Because mitochondria are abundantly present in the energy-demanding cardiac tissue—20%–40% of its cellular volume—the production of free radicals through oxidative metabolism in cardiomyocytes upon exposure to DOX is likely high, hence making the heart a highly susceptible tissue to DOX-mediated oxidative damage **(Wallace et al., 2020)**.

DOX and endothelial cells Endothelial dysfunction

DOX-related ROS and reactive nitrogen species (RNS) significantly destabilize endothelial activity. This impairment carries considerable cardiovascular risk, and increases nonhigh-density lipoprotein (non-HDL) cholesterol in the blood Cappetta **(Incalza et al., 2018)**.

At the beginning of doxorubicin cardiomyopathy due to the inflammation, ischemia, and hypoxia of the myocardium, doxorubicin is characterized by an increase in the level of endotlin-1, followed by activation of type A and B receptors, which leads not only to vasoconstriction but also to the release of nitric oxide, adrenomedullin, and prostacyclin **(Syukri et al., 2022)**.

Nitric oxide (NO) is a versatile molecule that is crucial in the pathogenesis of heart failure, ischemia/reperfusion injury, and cardiomyopathy. Humans have 3 types of NOS: eNOS, iNOS, and nNOS. DOX binds to endothelial nitric oxide synthase (eNOS), prompting the formation of semiquinone radical DOX. This radical reduces free oxygen to superoxide radicals **(Syukri et al., 2022)**.

This interaction with eNOS creates an imbalance between superoxide and NO levels, with a decrease in nitric oxide and an increase in reactive oxygen and nitrogen species formation, contributing to doxorubicin-induced myocardial damage **(Fachri et al., 2021)**.

DOX also amplifies iNOS transcription and protein expression, leading to nitrotyrosine formation and increased mitochondrial superoxide levels in cardiac tissue. This cascade subsequently increases cardiomyocyte apoptosis and myocardial dysfunction **(WIJAYA et al., 2020)**.

Disruption of NO metabolism leads to excessive formation of RNS, especially nitrosonium cations, peroxynitrite, S-nitrosothiols, nitroxide anions, higher nitrogen oxides, and dinitrosyl iron complexes, which stimulate cell death through the development of nitrosative stress **(Tharmalingam et al., 2017)**.

4.2. DOX and SMC

It is crucial to consider its impact on smooth muscle cells (SMCs) when discussing its implications in vascular wall remodeling. DOX enhanced SMC tone by disrupting acetylcholine-induced endothelium-dependent relaxation both in vivo and ex vivo. This ultimately leads to a series of

cardiovascular changes, namely medial hypertrophy, increased peripheral vascular resistance, added afterload on the heart, and the development of left ventricular 4 myocardial hypertrophy **(Bosman et al., 2021)**[53].

Endothelial cell apoptosis and a decline in eNOS expression contribute to increased vascular tonus, endothelial mucoid edema, endothelitis, deposition of modified lipoproteins in the intima, and other processes, all contributing to the development of DOX-induced cardiomyopathy and vascu- lopathy **(Luu et al., 2018)**[54].

Administration of DOX is also associated with a decrease in NO bioavailability, resulting in increased vascular tone, arterial wall stiffness, and formation of inter-endothelial gaps. When we examined the cardiotoxic effects of DOX on SMCs, it is noteworthy that there was a shift in SMC behavior. They switch from a contractile state to a synthetic state, and can even differentiate into macrophage-like cells and migrate to the in- tima **(Xu et al., 2020)**[55].

This phenomenon contributes to low-grade inflamma- tion within the vascular wall, triggering stromal-vascular changes such as mucoid and fibrinoid swelling, necrosis, sclerosis, and hyalinosis, which in turn increases the stiffness of the vascular wall. Another significant concern is the manner in which DOX af- fects the calcium balance. DOX disturbs calcium homeostasis stress by interfering with Ca2 + - ATPase pumps in the sarco/endoplasmic reticulum and cell membranes **(Aziz et al., 2019)**.

Doxorubicin and its metabolite doxorubicinol bind to car- diac ryanodine receptors (RyR2) and sarco/endoplasmic reticu- lum Ca2 + - ATPase (SERCA2A) and detrim entally alter their activ- ity, thereby impairing sarcoplasmic reticulum Ca2 + uptake **(Avagimyan et al., 2021)**[58].

Doxorubicin and myocardium metabolism

The myocardium is an energy-dependent and energy-intensive structure. Hence, its metabolism is an adaptive and self-regulating functional biochemical system that switches between metabolic phenotypes to maintain optimal performance under variable conditions **(Avagimyan and Kakturskiy, 2022)**[62].

5.1. DOX and sirtuins (SIRT) system

5.1. DOX and sirtuins (SIRT) system Sirtuins (SIRT) are nicotinamide adenine dinucleotide (NAD +)- dependent deacetylating enzymes that play a key role in main- taining normal myocardial function. They participate in many metabolic and homeostatic processes, including gluconeogenesis, fatty acid oxidation, oxidative phosphorylation, and endothelial function **(de Lima Junior et al., 2016)**[65].

DOX disrupts the functioning of SIRT by inhibit- ing SIRT3 (a mitochondrial sirtuin) and mitochondrial NAD + - dependent protein deacetylase. Therefore, SIRT3 plays a crucial role in

regulating mitochondrial bioenergetics by maintaining optimal redox homeostasis and controlling fatty acid oxidation and pyru- vate utilization **(Sun et al., 2023)**[67].

Furthermore, anthracyclines inhibit SIRT1 expression, exacer- bate DOX-induced cardiotoxicity, and disrupt mitochondrial bio- genesis and function. Sirtuin-1 is activated in response to an in- crease in the AMP/ATP ratio, and is closely related to the influence of AMPK and PCG-1a on energy metabolism. SIRT1 deficiency leads to NF- κB activation. SIRT1 deacetylates peroxisome proliferator- activated receptor-gamma co-activator-1 (PGC-1 α), thereby activat- ing a series of genes that contribute to mitochondrial dysfunction. This includes a reduction in the concentration and activity of Nrf1, which intensifies LPO (Wu et al., 2022)[68].

5.2. DOX and topoisomerase II

The cardiotoxicity of anthracycline drugs is also associated with inhibition of the α and β isoforms of topoisomerase II (Top-2) [69]. Interestingly, the molecular mechanism underlying the anticancer activity of the drug is inactivation of the α-isoform of topoisomerase II (Top II- α) in tumor cells. By binding to DNA and Top-2, DOX generates a Top2-DOX-DNA triple cleavage complex that triggers cell death **(Su et al., 2022)**[70].

However, similar changes also occur in the myocardium, and the pronounced sensitivity of the myocardium to DOX is attributed to the relatively high level of Top-2 β expression in cardiomyocytes **(Kuang et al., 2023)**[71]. Experimental studies have shown that species-specific deletion of Top-2 β in mouse cardiomyocytes protects against DOX-induced double-stranded DNA breaks, and development of progressive heart failure **(Deng et al., 2014)**[72].

5.3. DOX and iron

The non-enzymatic reaction of ferric iron with the ketone and hydroxy group of doxorubicin forms doxorubicin-Fe^{2+} free radical complexes, which interact with the negatively charged cell membranes and result in lipid peroxidation **(Kagan et al., 2021)**. The iron homeostasis changes, with the accompanied mitochondrial accumulation of iron, contribute to the doxorubicin-induced apoptosis in the cardiac tissue **(Sangweni et al., 2022).**

Also, hemochromatosis can lead to a higher susceptibility to doxorubicin-induced cardiotoxicity. Since, the increased reactive oxygen species ruptures the lysosomes rich in iron and degrades ferritin leading to cardiac toxicity **(Xie et al., 2024)**. Thus, iron-chelating agents have proven efficacious in decreasing DOX-induced cardiotoxicity **(Fojtu et al., 2017)**.

5.4. DOX and renin-angiotensin-aldosterone system (RAAS)

The effect of DOX on the renin-angiotensin-aldosterone system (RAAS) was also notable. DOX is associated with an increase in angiotensin II (AT-II) synthesis and intensified signaling through its receptors. Elevated levels of AT-II are observed in both the myocardium and paraventricular nucleus

of the hypothalamus. This suggests that AT-II plays a pivotal role in the pathogenesis of anthracycline cardiomyopathy by influencing remodeling of the myocardium and blood vessels to affect the central mechanisms regulating the cardiovascular system **(Saavedra, 2017)**[78].

DOX administration significantly increased the activity of the myocardial isoform of angiotensin-converting enzyme (ACE). This heightened ACE activity increased infiltration of macrophages in the my- ocardium, which can express ACE. Notably, myocardial infiltration by these macrophages intensifies with each successive course of DOX-containing chemotherapy **(Geisberg and Sawyer, 2010)**[80].

AT-II can initiate apoptosis in ventricular cardiomyocytes regardless of the pro-apoptotic potential of anthracyclines. Therefore, the myocardium undergoes extensive damage owing to both the direct toxicity of anthracyclines and apoptosis mediated by AT-II **(Huang et al., 2018)**[81].

Moreover, AT-II can cause fibrosis and inflammation in the myocardium. Cardiac fibroblasts, which are responsible for producing matrix proteins, when stimulated by AT-II, various signaling pathways are activated, including mitogen-activated protein kinases (MAPKs) and extracellular signal-regulated kinases (ERK1/2)**(Nattel and Harada, 2014).**

This activation results in the overexpression of collagen type 1 and 3 genes and increases the density and proliferation of fibroblasts. Furthermore, low grade inflammation associated with angiotensin II acts as a favorable microenvironment to trigger the mechanisms of myocardial fibrosis. This creates a foundation for various rhythm and conduction disturbances, and the progression of heart failure **(Avagimyan, 2022)**[82].

5.5. DOX and cardiac fibrosis

Treatment with Dox in cancer patients leads to blockade of mRNA transfer and inhibits protein synthesis of MMP-1 (Matrix metalloprotease -1) in tumor cells. It is helpful in cancer because of this mechanism; there is a reduction in the tumor cell's mobility. However, it activates other MMP's like MMP-2 and MMP-9, which show toxicity in the heart by increasing collagen formation in the cardiac tissues **(Goetzenich et al., 2009)**. An increase in collagen leads to myocardium fibrosis. These two MMP's also activate the TGF-β and phosphor-SMAD3 signaling and this enhanced collagen deposition in the cardiac muscle cells **(Goetzenich et al., 2009)**.

The induction of myocardial fibrosis can manifest even at doses considered noncardiotoxic. Beyond the previously outlined mechanisms, the stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) signaling pathway is strongly associated with the low- grade inflammatory mechanisms mentioned above **(Wang et al., 2021a)**.

7. DOX and Inflammation

When examining the role of the inflammatory cascade in the development of anthracycline cardiomyopathy, inflammasomes have been found to have distinct importance, specifically the NLR

Family Pyrin Domain Containing 3 (NLRP3) inflammasome. It is a multiprotein complex that regulates the production of the pro-inflammatory cytokines interleukin-1β (IL-1β), IL-18, and gasdermin D by activating caspase-1 [90]. This inflammasome is triggered by nuclear factor kappa B (NF-κB) signaling, which correlates with DOX-related pathways of myocardial injury **(Zeng et al., 2020)**. [91].

The pathway begins with an assembled (active) inflammasome complex that realizes its effect through stress signals (e.g., ROS) and leads to the activation of caspase-1. Caspase-1 catalyzes the cleavage of these cytokines into biologically active forms, resulting in their release from the cells. It has been proven that DOX (a component of anthracycline) is an inflammasome activator, thus through the pathway described, it enhances the production of myocardial cytokines and macrophage infiltration **(Silvis et al., 2021)**[92].

Inflammasome signaling in atrial cardiomyocytes is sufficient to induce ar- rhythmias, as evidenced by the elevation of inflammasome activa- tion markers in the atria **(Yao et al., 2018)**[94].

7. DOX and myocardial atrophy

The transcription factors that regulate the development of autophagy in the myocardium are forkhead box O (FoxO) factors, namely FoxO1, FoxO3, FoxO4, and FoxO6. Autophagy plays a key role in maintaining homeostasis and the development of myocardial pathology. FoxO depletion prevents muscle loss and weakness by suppressing the autophagy-lysosome (ALS) and ubiquitin-proteasome (UPS) systems by inhibiting AKT activity **(Donlon et al., 2022)**. FoxOs regulate the promoters of nearly half of the atrophy genes, such as muscle RING finger 1 (MuRF1), atrogin-1/muscle at- rophy gene-1 (MAFbx), and B-cell lymphoma 2 (Bcl-2) 19-kDa in- teracting protein 3 (Bnip3)**(Moresi et al., 2022)**.

Muscle RING finger 1 (MuRF1) and Muscle Atrophy F-box (MAFbx)/atrogin-1 were identified over 10 years ago as two muscle-specific E3 ubiquitin ligases whose transcription is increased under atrophy-inducing conditions, resulting in their designation as markers of muscle atrophy. Atrogin-1 and MuRF-1 are two E3 ubiquitin ligases that mediate ubiquitin-mediated protein degradation **(Willis et al., 2019)**.

DOX activates FoxO1 phosphorylation, thereby increasing the level of FoxO1 in the nucleus, accompanied by an increase in MuRF1 expression. It should be noted that DOX-mediated activation of FOXO1 and its target genes has time and dose-dependent features. For example, a low dose of DOX (5 mg/kg) does not induce MuRF1 expression. In contrast, a higher dose of 20 mg/kg significantly increased marker levels (mRNA FoxO1 and atrog gin-1), which returned to normal 7 days after DOX injection **(Baskin, 2012)**

8. Doxorubicin and pathways of cellular deaths

To investigate the endpoint of DOX-induced cardiotoxicity, it is important to recognize the complex nature of the cell death mechanisms involved. Cardiomyocyte death (apoptosis, autophagy, pyroptosis and ferroptosis) plays a pivotal role in the pathogenesis of myocardial fibrosis, diastolic dysfunction, and ultimately heart failure associated with DOX-induced cardiotoxicity **(Galeone et al., 2024)** [100].

8.1. DOX-related apoptosis

Doxorubicin triggers cardiomyocyte death through various regulated cell death pathways, with apoptosis being the predominant mechanism **(Toda et al., 2023)**. By promoting the opening of the mitochondrial permeability transition pore (mPTP), doxorubicin leads to calcium accumulation within the mitochondria, resulting in the disruption of mitochondrial membrane potential (MMP) and the release of cytochrome c, ultimately initiating apoptosis **(Qu et al., 2022)**.

Oxidative stress resulting from doxorubicin also enhances apoptosis through the peroxidation of cardiolipin, a sensitive marker of oxidative stress, leading to mPTP opening and subsequent cytochrome c release **(Wang et al., 2021b).**

Formation of DOX-Top2 β-DNA complexes induces genotoxic stress, which promotes p53 phosphorylation and initiates DOX-induced apoptosis **(Yu et al., 2020)**.

An additional pathway of damage to cardiomyocytes involves the peroxisome proliferator-activated receptor (PARP) enzymes formed by DOX oxidative stress, ultimately resulting in apoptotic cell death (Schirone et al., 2022).

8.2. DOX-related autophagy

Autophagy is a homeostatic process by which cytoplasmic components are degraded and recycled under normal and stress conditions through lysosomal pathways. Autophagy has emerged as a major regulator of cardiac homeostasis and function. The level of autophagy in cardiac muscle is low under normal conditions, whereas it is upregulated in response to pathological stress **(Nieto-Torres and Hansen, 2021)**.

Under physiological conditions, autophagy is essential for optimal cellular function and survival as it removes damaged or unwanted proteins and organelles. Under pathological conditions, autophagy may be stimulated to induce toxic effects **(Cui et al., 2021)**.

Excessive autophagy activation can cause damage to organelles such as the mitochondria and endoplasmic reticulum, releasing compounds into the cytoplasm (e.g., cytochrome c and calcium) that can induce cell death **(Foufelle and Fromenty, 2016)**.

The activation of autophagy begins with the formation of a phagophore through a system of autophagy proteins (Atg proteins). The phagophore, also known as a double-membrane structure,

sequesters bulk cytoplasmic components, such as abnormal intracellular proteins, excess or damaged organelles, and invading microorganisms. The phagophore expands to a sealed, double-membrane vesicle called the autophagosome **(Rothermel and Diwan, 2021)**.

Beclin-1 plays an important role in the initial steps of autophagosome formation by mediating the localization of other Atg proteins to the phagophore. Elongation of the autophagosome requires the interaction of several Atg proteins (Cao et al., 2016).

A proposed mechanism responsible for DOX-induced autophagy is that DOX administration results in damage to the mitochondria and induction of Beclin-1 expression, leading to accelerated autophagy and cardiomyopathy. Other groups also demonstrated that anti-apoptotic protein Bcl-2 can form a complex with Beclin-1 to inhibit autophagic apoptosis and autophagosome formation in cardiomyocyte **(Prerna and Dubey, 2022).**

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8.3. DOX-related pyroptosis

Pyroptosis is an autonomous, genetically programmed form of cell death that is tightly regulated through inflammasome activation and subsequent induction of proinflammatory caspase-1 (as well as caspases 3, 4, and 11). This intricate process leads to cell lysis and the release of proinflammatory cytokines, notably IL-1 β and IL-18, via inflammasomes **(Grakova et al., 2023)**.

A key trigger of pyroptosis involves activation of caspase-1, which subsequently activates gasdermin D (GSDM-D), a key executioner of pyroptosis. Following cleavage by caspase-1, GSDM-D liberates its N-terminal domain, leading to the formation of pores on the plasma membrane. This pore formation facilitates the release of IL-1 β and IL-18 **(Klimov et al., 2023)**.

8.4. DOX-induced ferroptosis

DOX-related elevation in myocardial iron content, is a crucial factor in the development of cardiotoxicity due to ferroptosis. Ferroptosis is a form of programmed oxidative necrotic cell death that involves iron-dependent lipid peroxidation **(Fratta Pasini et al., 2023)**.

DOX intercalation into mitochondrial DNA decreases heme synthesis, reduces iron utilization, and promotes iron accumulation. DOX causes heme degradation, which releases free iron and impairs heme synthesis necessary for iron use, resulting in iron overload and ferroptosis in the mitochondria. The administration of DOX is also linked to an increase in HO1 levels, which catalyzes heme degradation, leading to the release of Fe2 + into the mitochondria **(Tadokoro et al., 2020)**.

DOX-induced activation of ubiquitin-proteasome system

The Ubiquitin proteasome system (UPS) is an ATP-dependent proteolytic system composed of numerous ubiquitin ligase enzymes and a large proteolytic complex called the proteasome. The UPS plays a role in the protein breakdown that occurs during muscle damage. The UPS requires

polyubiquitination of proteins through ubiquitin ligase enzymes, including E1 (ubiquitin-activating enzyme), E2, and E3(Gaytan et al., 2023).

The polyubiquitinated proteins that are damaged or deemed unnecessary are degraded by the proteasome. Specifically, two muscle-specific E3 ligases, Muscle Atrophy F-box (MAFbx)/atrogin-1 and Muscle-Ring Finger-1 (MuRF-1), contribute to the UPS-mediated protein degradation in cardiac muscle. Numerous studies have indicated that DOX treatment stimulates UPS in cardiac muscle, leading to cardiac muscle damage **(Wang and Wang, 2015)**.

Specifically, DOX treatment activates UPS through mitochondrial ROS production in cardiac muscle (Montalvo et al., 2020). Indeed, DOX administration significantly increases both mitochondrial H_2O_2 production and MAFbx, whereas antioxidant protects mitochondria against DOX-induced oxidative stress and attenuates the expression of atrogin-1/MAFbx in cardiac muscle **(Gilliam et al., 2012)**.

DOX-mediated calpain activity

Calpain is an intracellular calcium-dependent cysteine protease (Khorchid and Ikura, 2002; Vickers, 2017). Calpain exists as an inactive proenzyme in the cytosol. When intracellular calcium levels increase, the proenzyme form of calpain is converted to its active form, which cleaves cytoplasmic and nuclear substrates, leading to apoptosis **(Elmogheer, 2024)**.

Calpain activation has been implicated in myocardial injuries, including ischemia/reperfusion myocardial injury, pressure overload-induced cardiomyopathy, and heart failure. It has been demonstrated that DOX treatment causes calcium overload, which increases calpain activity **(Zhang et al., 2024)**.

Calpain activation in cardiomyocytes treated with DOX resulted in myofilament protein degradation and necrosis, while calpain inhibitors preserved the myofilament protein degradation (Lim et al., 2004). These studies indicate that calpain activation is one of the contributors that cause DOX-induced cardiomyopathy **(Hamaamin and Aziz, 2022).**

DOX-mediated autophagic signaling

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DOX-induced cardiotoxicity: clinical aspects

Since the late 1970s, DOX-induced cardiotoxicity (DIC) has been recognized as a complication of chemotherapy **(Lefrak et al., 1973)**[5]. The first case report in the literature was that of a 23-year-old patient with osteosarcoma, who was treated for 9 months with DOX. One month after the end of treatment, the patient died due to development of congestive heart failure **(Lefrak et al., 1973)**[8].

A second report describes the case of an 11-year-old patient, also with osteosarcoma, who died 9.5 years after the end of chemotherapy with DOX as a result of progressive heart failure with late severity **(Goorin et al., 1990)**.

In 1991, long-term cardiotoxic effects were identified in patients with acute lymphoid leukemia in childhood **(Lipshultz et al., 1991)**. Patients with childhood cancer and those treated with DOX have a high risk of developing symptomatic cardiac events at an early stage, and this risk remains high within 30 years after treatment. In addition, it is estimated that one in eight DOX-treated patients will be afflicted with severe cardiac disease **(Raj et al., 2014)**.

DIC manifests in several forms, ranging from asymptomatic electrocardiography (ECG)- changes to decompensated cardiomyopathy characterized by decreased left ventricular ejection **fraction (Octavia et al., 2012)**. According to their clinical manifestation, these cardiotoxic events can be classified into three types: (1) acute, occurring during or immediately after treatment which is usually reversible; (2) early-onset chronic progressive cardiotoxicity, occurring within 1 year after exposure to chemotherapeutic treatment; and (3) late-onset chronic progressive cardiotoxicity, occurring 1 or more years after the end of treatment. The two chronic forms are considered irreversible, with a poor prognosis and a limited to heart failure therapy **(Raj et al., 2014)**.

Acute cardiotoxicity is characterized by depression of myocardial contractility that may be reversible within 1 week when discontinuing the DOX treatment **(Carvalho et al., 2014)**. In some patients, complications have already been described, such as hypotension; pericarditis; myocarditis; supraventricular, ventricular, or sinus (more common) tachycardia; ST-T wave changes; decrease in QRS complex; prolongation of QT interval; and increase in serum levels of brain natriuretic peptide and cardiac troponin [3, 12–14]. However, this type of cardiotoxicity is very rare and affects less than 1% of patients **(Mancilla et al., 2019)**.

Early-onset chronic progressive cardiotoxicity is characterized by systolic or diastolic ventricular dysfunction within 1 year after the completion of DOX treatment. It can be progressive and occurs in 5–35% of the cases. In the majority of adult patients, early cardiotoxicity is related to the development of a chronic dilated cardiomyopathy, with a decrease in the mass and wall of left ventricle **(Raj et al., 2014)**.

In the pediatric patient, in addition to chronic dilated cardiomyopathy, restrictive cardiomyopathy characterized by increase in the wall stiffness of the left ventricle cavity may also occur in isolated moments. The typical manifestation of these cardiomyopathies is the progressive reduction of the ejection fraction. Other events, including severe electrical conduction changes, damage to cardiac valves, and/or depression of contractility may also be observed **(Bloom et al., 2017)**.

Finally, late-onset chronic progressive cardiotoxicity is characterized by cardiac dysfunction after a latency period of 1 or more years following the completion of DOX treatment [12, 13]. In this type of cardiotoxicity, there is a period during which the patient is asymptomatic (normal cardiac function).

After that, chronic dilated and/or restrictive cardiomyopathy can be manifested with subsequent development of congestive heart failure **(Mancilla et al., 2019).**

Doxorubicin and cardiomyopathy:

Despite their high efficacy, ANT act non-selectively, causing damage not only to the cancer cells but also to the healthy cells, including cardiomyocytes. Those effects are associated with the occurrence of CTRCD, manifested by a wide range of left ventricle (LV) contraction functions **(Perez et al., 2019)**. Until 2021, there was no uniform definition of cardiotoxicity related to cancer therapy. The common denominator, however, was the development of left ventricular systolic dysfunction (LVSD) with a reduction in left ventricular ejection fraction (LVEF) **(Matusik et al., 2024).**

In 2021, International Cardio-Oncology Society (IC-OS) published a standardized definition of termed cancer therapy-related cardiac dysfunction (CTRCD). According to Herrmann et al., the following can be distinguished: symptomatic CTRCD associated with heart failure (HF) and structural abnormalities, impaired cardiac function, impaired myocardial perfusion and/or volume overload and asymptomatic CTRCD with assessment of LVEF unrelated to HF. There is a 3-point severity scale for asymptomatic CTRCD: (1) mild, when EF ≥ 50% with > 15% decrease in global longitudinal strain (GLS) from baseline or increase in previously tested troponin/natriuretic peptide levels; (2) moderate, when EF falls ≥ 40–49%; and (3) severe, when EF drops to < 40% **(Herrmann et al., 2022)**.

Dilated cardiomyopathy:

Dilated Cardiomyopathy is a disease of the heart muscle characterized by left ventricular or biventricular dilatation and systolic dysfunction in the absence of pressure overload or coronary artery disease sufficient to explain the observed myocardial dysfunction **(Bozkurt et al., 2016**).

This is in addition to changes in many systems such as loss of parasympathetic tone and increased resistance to natriuretic peptides that normally antagonize the sympathetic nervous system and the activation of the renin–angiotensin–aldosterone system. Collectively, these responses are referred to as neurohormonal activation **(Van Bilsen et al., 2017).**

The term 'neurohormone' reflects the original observation that many of the molecules that are produced by the neuroendocrine system affect the heart in an endocrine manner. However, many of classical neurohormones such as norepinephrine and angiotensin II are now known to be synthesized directly within the myocardium and act in an autocrine or paracrine manner. Secondary neurohormonal changes contribute to reverse remodeling and ongoing myocyte damage **(Hartupee and Mann, 2017).**

The circulatory changes arising from impaired myocardial pump function activate a series of compensatory mechanisms, includes activation of the sympathetic nervous system and renin–angiotensin–aldosterone system, leading to changes which maintain the cardiovascular homeostasis

and the cardiac output through increased salt and water retention, peripheral arterial vasoconstriction, increased contractility and inflammatory mediators, which are involved in cardiac repair and remodeling **(Chiorescu et al., 2022)**.

Cardiac remodeling in response to a myocardial insult or an underlying genetic abnormality has been classically considered the hallmark of dilated Cardiomyopathy. Cardiac remodeling can be defined as molecular, cellular and histological myocardial changes that determine macroscopic alterations in the size, shape, and function of the cardiac muscle **(Merlo et al., 2018).**

The most common presenting manifestations of dilated cardiomyopathy are congestive heart failure, circulatory collapse, arrhythmias and thromboembolic events. Symptoms of heart failure may include shortness of breath, fatigue, cough, orthopnea, paroxysmal nocturnal dyspnea and edema **(Weintraub et al., 2017).**

Other types of cardiomyopathies:

Hypertrophic cardiomyopathy:

Hypertrophic cardiomyopathy is typically defined by the presence of unexplained left ventricular hypertrophy which occurs in a non-dilated ventricle in the absence of other cardiac or systemic disease capable of producing the observed increased left ventricular wall thickness, such as pressure overload (e.g., long-standing hypertension, aortic stenosis) or infiltrative disorders (e.g. amyloidosis)**(Lazzeroni and Centorbi, 2021)**.

In half of the cases, it is familial but still being sporadic in the other half. However, its mode of inheritance is autosomal dominant. The most common pattern of hypertrophy is asymmetrical septal hypertrophy although the degree and location widely vary. It can present catastrophically with sudden cardiac death, ventricular arrhythmias or insidiously with symptoms of heart failure **(Houston and Stevens, 2014)**.

Restrictive cardiomyopathy:

Restrictive cardiomyopathy is characterized by nondilated left or right ventricle with diastolic dysfunction. The restrictive cardiomyopathies are a heterogenous group of myocardial diseases. The three major causes of restrictive cardiomyopathy are: cardiac amyloidosis, cardiac sarcoidosis and cardiac hemochromatosis. Each one of them is challenging to diagnose, and the recognition of each disease entity is frequently delayed. It typically leads to diastolic heart failure from poor filling during diastole and classic heart failure symptoms. Sudden death is rare, however, syncope may occur **(Muchtar et al., 2017)**.

Arrhythmogenic right ventricular cardiomyopathy:

Arrhythmogenic right ventricular cardiomyopathy is a heritable heart-muscle disorder that causes progressive replacement of right ventricular myocardium by fibrofatty tissue. Mutations in

genes encoding desmosomal proteins play a key role in the pathogenesis of the disease **(Corrado et al., 2017)**.

Its diagnosis can be achieved by demonstrating the functional and structural changes of the right ventricle, electrocardiogram depolarization and repolarization abnormalities, ventricular arrhythmias, and fibrofatty replacement through endomyocardial biopsy. Symptoms of heart failure are uncommon. The primary symptoms are syncope, atypical chest pain, an initial episode of ventricular tachycardia and recurrent ventricular tachycardia **(Sayed et al., 2020)**.

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