Complications of chemotherapy, a basic science update

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Summary

Anthracyclines, discovered 50 years ago, are antibiotics widely used as antineoplastic agents and are among the most successful anticancer therapies ever developed to treat a wide range of cancers, including hematological malignancies, soft tissue sarcomas and solid tumors. However, some anthracyclines, including doxorubicin, exhibit major signs of cardiotoxicity that may ultimately lead to heart failure (HF). Despite intensive research on doxorubicine-induced cardiotoxicity, the underlying mechanisms responsible for doxorubicin-induced cardiotoxicity have not been fully elucidated yet. Published literature so far has focused mostly on mitochondria dysfunction with consequent oxidative stress, Ca²⁺ overload, and cardiomyocyte death as doxorubicin side effects, leading to heart dysfunction. This review focuses on the current understanding of the molecular mechanisms underlying doxorubicin-induced cardiomyocyte death (i.e.: cardiomyocyte death, mitochondria metabolism and bioenergetic alteration), but we will also point to new directions of possible mechanisms, suggesting potent prior or concomitant alterations of specific signaling pathways with molecular actors directly targeted by the anticancer drugs itself (i.e. calcium homeostasis or cAMP signaling cascade). The mechanisms of anticancer cardiac toxicity may be more complex than just mitochondria dysfunction. Partnership of both basic and clinical research is needed to promote new strategies in diagnosis, therapies with concomitant cardioprotection in order to achieve cancer treatment with acceptable cardiotoxicity along life span.
In the late years, there is an increase in the number of new cases of cancer. Treatment by chemotherapy, radiation, and/or immunotherapy has strongly increased life expectancy of cancer patients, many of them are cured. Unfortunately, some of them exhibit major signs of cardiotoxicity of anticancer treatment that may ultimately lead to heart failure (HF) [1]. The cardiac toxic effects may be irreversible (type I) or reversible (type II). For instance, anthracyclines use is linked to type I cardiotoxicity. Type II cardiac effects are reversible and damage is not cumulative, typically trastuzumab. Anthracyclines, discovered in 1963, are antibiotics closely related to the natural product daunomycin, and widely used as antineoplastic agents. One of the anthracyclines frequently used is doxorubicin (trade name Adriamycin™; also known as hydroxydaunorubicin). It is used in the treatment of a wide range of cancers, including hematological malignancies, many types of carcinoma, soft tissue sarcomas and has demonstrated significant activity against solid tumors [2,3]. Anthracyclines are among the most successful anticancer therapies ever developed and are effective against more types of cancer than any other class of chemotherapeutic agents [2,3]. However, their clinical use is markedly hampered by the risk of severe irreversible cardiotoxicity. Doxorubicin has antioncologic actions but also cardiotoxic side effects whose mechanisms have not yet been fully elucidated. Doxorubicin is lipophilic, influencing cellular uptake, retention, duration, and protein or lipid targets and thus, pharmacokinetic/pharmacodynamic, which may be involved in side effects appearing after therapy termination. There is large clinical evidence showing cancer therapy-induced cardiac toxicity [4,5]. Moreover, it seems that there are clearly distinct clinical manifestations between early and late phase of doxorubicin cardiotoxicity. However, there is more evidence that these two phases may not be as distinct, pointing a continuum starting with the first drug exposure and continuing for weeks and decades after treatment stop [6–8]. To date, based on the ROS and iron hypothesis, it seems that the best cardioprotective agent is the iron chelator dexrazoxane [10], but it’s clinical use is limited because of the secondary malignancies observed in some clinical trials [13,14]. Moreover, from plentiful antioxidants and iron chelators tested, results are often ambiguous. Even if they had cardioprotective effects in cell culture and mice models, they were rarely efficient in human [10]. A number of other theories have emerged, among them: implication of p53 [15,16], topoisomerase IIβ (TopIIβ) involvement [17,18] and impaired autophagy signalling [19–21]. Two supplementary pathways have gained interest and will be reviewed in more details below: disruption of mitochondria bioenergetics [22] and interference with Ca²⁺ signalling [23].

**Molecular mechanisms and signaling pathways in anthracycline-induced cardiotoxicity**

Despite more than 40 years of research and use in cancer therapy, cardiotoxicity issue is still unsolved and not fully explained. This is probably due to the numerous targets of anthracyclines and to the variety of technical approaches ranging from acute exposure to doxorubicin or its metabolites to analysis of chronic effects after single or multiple doses treatment in animals. The most commonly evocated hypothesis to explain anthracycline cardiotoxicity emphasizes a role for both reactive oxygen species (ROS) and iron. Several reviews have already covered it [10–12]. To date, based on the ROS and iron hypothesis, it seems that the best cardioprotective agent is the iron chelator dexrazoxane [10], but it’s clinical use is limited because of the secondary malignancies observed in some clinical trials [13,14]. Moreover, from plentiful antioxidants and iron chelators tested, results are often ambiguous. Even if they had cardioprotective effects in cell culture and mice models, they were rarely efficient in human [10]. A number of other theories have emerged, among them: implication of p53 [15,16], topoisomerase IIβ (TopIIβ) involvement [17,18] and impaired autophagy signalling [19–21]. Two supplementary pathways have gained interest and will be reviewed in more details below: disruption of mitochondria bioenergetics [22] and interference with Ca²⁺ signalling [23].

**Disruption of mitochondrial bioenergetic**

Alterations in energy metabolism and mitochondrial function have recently appeared as important contributors to the pathophysiology of heart failure [24–26]. Defects in different steps of mitochondrial bioenergetics, including reduction of oxidative capacity of mitochondria, changes in the profile of energy...
substrate utilization, disturbance of intracellular energy transfer, defects in energy signaling pathways [22,27] and recently, mitochondrial biogenesis [28] have been described. In fact, in a chronic anthracycline treatment in rabbit, decreased mRNA levels of the key mitochondrial biogenesis regulator, Peroxisome-proliferator-activated-receptor Gamma Co-activator1 alpha (PGC1α) and of its downstream targets Nuclear Respiratory Factor 1 (NRF1) and Transcription Factor A mitochondrial (TFAM) [28] were observed. Moreover, doxorubicin affects ADP-stimulated respiration in isolated intact heart mitochondria [29], oxygen consumption in human cancer cell lines [30] and cytochrome c oxidase (COX) activity [31]. Finally, in heart diseases, the mitochondrial permeability transition pore has been identified as an early vulnerability event [32] and anthracyclines have been shown to induce permeability transition pore opening in human hearts [33].

The two main metabolic signaling pathways are adenosine monophosphate-activate protein kinase (AMPK, sensor of the AMP/ATP ratio) and Sirtuin 1 (SIRT1, deacetylation sensor of the NAD+/NADH ratio) [34]. A complex interaction between these pathways seems to exist in cardiac cells. They both appear to regulate mitochondrial biogenesis and metabolism as well as oxidative stress via the transcriptional co-activator PGC-1alpha [35]. Regarding anthracycline cardiotoxicity, several studies have shown that doxorubicin reduces the protein level of AMPK in spontaneously immortalized mouse embryonic fibroblasts and H9C2 cardiomyocytes [36], in ex vivo perfused rat heart [37] and in hearts from doxorubicin-treated rats [38]. Inhibition of AMPK by doxorubicin has been linked to SIRT1 dysfunction and p53 accumulation [36]. In this regard, the cardiotoxic effect of doxorubicin is reduced by resveratrol, which induces an upregulation of SIRT1, leading to p53 deacetylation [16] or reduced oxidative stress [39]. Similarly, adiponectin, which increases the expression of AMPK, is also protective against the cardiotoxic effect of doxorubicin, and the cardioprotection can be reversed by the addition of dorsomorphin, an AMPK inhibitor [40]. Altogether these studies suggest that mitochondrial bioenergetics and metabolic signaling pathways could be valuable therapeutic targets to prevent anthracycline cardiotoxicity. Limiting cardiotoxicity of anthracyclines is possible when the cumulative dose is low, however, the anti-cancer response may not be efficient. Needs for safe doxorubicin cardioprotection urge, and pharmacological activation of mitochondria biogenesis might be a way to explore.

Cardiomyocytes death signaling pathways in anthracycline-induced cardiotoxicity

Recent data suggest that anthracycline cardiotoxicity could be linked to direct anthracycline-induced alteration of several signaling pathways. However, an attractive and canonical model to explain the primary mechanisms for doxorubicin-induced cardiomyopathy remains the cardiomyocyte loss through death pathways. Doxorubicin-induced apoptosis signaling pathways is largely documented. Apoptosis hallmarks and mitochondria injuries have been revealed since the 90s in endomyocardial biopsies of anthracyclines treated-patients [41]. Apoptosis could be triggered by DNA damage as anthracycline mechanisms of cytotoxicity induce DNA alkylation and cross-linking. Recently, Zhang et al. showed a new protective pathway through cardiomyocyte specific deletion of topoisomerase II β (Top II β) in a mouse model. Top II β/þ mice treated with 25 mg/kg of doxorubicin for 16 h had a reduced ejection fraction compared to Top II β/– mice. In Top II β/þ cardiomyocytes, doxorubicin-induced mitochondrial dysfunction and oxidative phosphorylation pathways as well as DNA-double strand breaks (DSB) which was strongly reduced in Top II β/þ cardiomyocytes [42]. Moreover, the cardioprotective effects of dextroroxane involve iron chelation as well as interference with Top II β, which suggest that Top II β could be a new therapeutic target for dox-induced cardiotoxicity [17].

Frequently, publications favour the involvement of free radical-induced oxidative stress due to the generation of reactive oxygen species (ROS) as the main contributor to cardiotoxic side effects [43]. Doxorubicin-induced disruption of iron metabolism through iron regulatory protein-1 (IRP-1) inhibition lead to intracellular Fe accumulation, which reinforces the oxidative stress [44]. ROS generation involved contributors, such as endothelial nitric oxide synthase reductase [45], direct respiratory chain failure [46], dysregulation of calcium handling or adrenergic dysfunction [47]. Apoptosis (regulated, energy-dependent and active form of death), necrosis (controlled/uncontrolled and energy-independent cell death) and/or autophagy are the most suggested cellular ways of death. Apoptosis signaling pathways are barely summarized herein as extrinsic and intrinsic pathways converging on the downstream effectors caspases-3, 6 and 7:

• extrinsic pathway started with the binding of death ligands with Fas, TNF alpha, and TRAIL with subsequent respective receptors, and lead to caspase-8 and 3 activation. Doxorubicin mediates part of its cardiotoxicity side effects through the Fas/Fasl death pathway with several associated partners. Indeed, doxorubicin-induced cardiomyocyte apoptosis, ROS and peroxynitrite formation could be reduced by counteracting FasL effect [48]. The upregulation of Fas/Fasl is also obtained by Ca++/calcineurin signaling pathway and NFAT4 activation [49]. This is a selective pathway as another NFAT family member (NFAT5) is degraded in neonatal rat cardiomyocyte treated by doxorubicin [50]. NF-xB activated by doxorubicin-induced ROS generation also has a pro-apoptotic effect with Fasl, Fas, c-Myc and p53 activation [51,52]. Recent data have also highlighted possible crosstalk between NF-xB pro-apoptotic signaling and cyclic AMP but in non-cardiac cells [53]. Other factors, such as FLIP...
Doxorubicin-induced ROS generation leads to cytosolic calcium handling alterations with calcium release from the sarcoplasmic reticulum (SR) (see calcium section for details). Calcium is then pumped in mitochondrial structure located near the SR until calcium overload resulting in loss of mitochondrial membrane potential by opening of mitochondrial permeability transition pore and cytochrome c release [56]. Several actors and pathways have been implicated in this cardiomyocyte death intrinsic signal: direct doxorubicin interaction or indirect ROS generation lead to ERK1/2 and p53 tumour suppressor protein activation [57], a pathway upstream of Bax. Indeed, p53 inhibitor, p53−/− knock out mice or siRNA-p53 decrease Bax activation, and doxorubicin-induced apoptosis in H9C2 neonatal rat cardiomyocytes and mouse heart [58–60]. In addition, p53 may downregulate the prosurvival factor mammalian target of rapamycin (mTOR) in other cell types [60]. However, even if p53 involvement in the doxorubicin pathophysiological mechanism of apoptosis is a consensus, recent data have shown that cardiomyocyte p53 specific ablation is not sufficient to block doxorubicin-induced cardiac fibrosis and cytoskeleton changes which occur in response to cardiomyocyte loss [61]. This observation could be explained by the increased incidence of perivascular lesions induced by doxorubicin, leading to impaired oxygen supply and subsequent ischemic cell death. In addition, generated ROS may directly release cytochrome c from mitochondria or increasing Bax translocation independently of p53 [62,63].

GATA4 is another transcriptional factor regulating apoptotic pathway with its Bcl-Xβ interaction, according to its role as a survival factor and regulator of cardiac development. GATA4 is downregulated by doxorubicin by a mechanism involving inhibition of Akt phosphorylation and activation of GSK3β, a negative regulator of GATA4 [64,65]. More recent findings have shown a novel mechanism of GATA4 downregulation at the transcription level, which involves the nuclear factor CBF/NF-Y in a p53-dependent manner [66].

Other factors, such as p300 transcriptional co-activator, ARC (apoptosis repressor with caspase recruitment domain) as well as phosphatase Ser/Thr phosphatase PP1 may be involved in doxorubicin-induced intrinsic apoptosis. Indeed, p300 is depleted in doxorubicin probably through p38 MAPK activation and a p300 hyperphosphorylation or a p300 overexpression prevents doxorubicin-induced apoptosis [67,68]. The ARC component prevents Bax translocation in the intrinsic pathway and counters the extrinsic death pathway of Fas, FADD and caspase-8. Its protein level is strongly depressed in neonatal rat cardiomyocytes and mouse heart treated by doxorubicin by the ubiquitin system and overexpression prevents in part doxorubicin-induced cardiomyocyte apoptosis [69,70]. PP1 is activated by doxorubicin, which then in turn dephosphorylates Akt and Bad, leading to caspase-3 activation [71]. Additional doxorubicin mechanisms present a possible cardiac mitochondrial biogenesis disruption and intrinsic apoptosis by shutting down the prosurvival and biogenesis inductor pathway HO-1/Akt/Nrf2 [72]. ROS oxidative stress following doxorubicin treatment also leads to MAPKs and SAPKs activation (especially JNK and p38), modulating apoptotic cell death pathway in part through mPTP opening modulation [73,74]. Additional data from the group of Wei have implicated the Rho-associated coiled coil containing protein kinase-1 protein (ROCK-1) in the regulation of apoptosis and cell survival [75].

mPTP opening event and thus mitochondria permeabilization is generally identified as an apoptosis inductor. However, more recent data obtained from cyclophilin-D deficient mice (cyclophilin-D is a critical regulator of mPTP opening via its ANT interaction) show an increased resistance against necrotic inductor i.e. calcium overload while classical apoptotic inducers still lead animals to death. This data suggest that mPTP opening triggers necrosis rather than apoptosis [76,77]. Thus, necrosis has been shown to be increased in doxorubicin-treated mice heart in concomitance with an inflammatory pattern i.e. pro-inflammatory cytokine and immune cell infiltration [78]. In fact, all the doxorubicin alteration events already described ie oxidative stress, lipid peroxidation, SR or mitochondrial calcium homeostasis alteration, mitochondrial dysfunction or DNA damage contribute to necrosis [46,79]. Other specific pattern of anthracycline cardiotoxicity leading to necrosis involves sarcomere disruption named “sarcopenia” with titin degradation and thus, enhanced myofilament degradation due to doxorubicin-induced activation of calpains (calcium-dependent proteases) [80].

Thus, cardiac myocyte loss following activation of both apoptotic, necrotic pathways provides an attractive explanation for anthracycline-induced cardiotoxicity [73] and mitochondria represent the final crosstalk [33]. The specific form of doxorubicin-induced cell death is variable depending on time course therapy and drug amount. In this sense, a stress scale is hypothesized ranging from mild stress with autophagy induction removing aggregates and damaged organelles, average stress with apoptosis and mitochondria involvement to an intense stress with necrosis because of ATP depletion [9]. Alternative death forms have been also observed following anthracycline treatment, such as oncosis and autophagy [81,82] as well as more recently, other protein degradation system, such as the ubiquitin proteasome system [83].
Autophagy, identified as a renewal mechanism in heart, is traditionally enhanced under pathological conditions (hypertrophy and heart failure) and seems to play a direct role in doxorubicin-induced myocardial dysfunction [84,85]. ROS, calcium homeostasis alteration, p53, Bcl2 and polyADP-ribose polymerase (PARP), which are known to play a role in the doxorubicin cardiotoxicity, are also involved in the process of autophagy [86–88]. A recent publication has shown that systemic doxorubicin administration results in altered cardiac gene and protein expression of mediators of the autophagy/lysosomal system and demonstrates that exercise training is cardioprotective by preventing doxorubicin-induced cardiac increases in autophagy signalling [89]. However, the precise mechanism linking doxorubicin, cardiomyopathy and autophagy is still lacking.

Proteolysis in cardiomyocytes is also mediated by the ubiquitin proteasome system (UPS), leading to the degradation of a large number of key cardiac transcription factors and of prosurvival factors. Therapeutic exposure to anthracyclines enhanced UPS and may represent an alternative mechanism involved in doxorubicin cardiotoxicity in neonatal cardiac myocytes [19,83]. Emerging data in basic science on targeted therapy and combined therapy are scarce. However, signaling pathways targeted by anticancer therapy in tumours (on target) and those implicated in cardiomyocytes survival are readily the same (off-target) [90]. Indeed, doxorubicin-induced cardiotoxicity alternative mechanism, independent of ROS generation, has been highlighted. Anthracyclines, as well as novel targeted therapies such as trastuzumab, have a negative effect on the prosurvival neuregulin/hergulin-Erb/HER2 pathway with potential novel miRNA involvement [91,92].

Role of intracellular calcium alterations in anticancer cardiotoxicity

Ca2+ is a key second messenger whose cyclic variations activate contraction and relaxation in cardiac myocytes. Thus, it is reasonable to think that the defects in contraction and relaxation due to chemotherapy may, at least in part, be due to alterations in Ca2+ cycling. In each heartbeat, Ca2+ activates the intracellular Ca2+ release channels located in the sarcoplasmic reticulum (SR), named ryanodine receptors (RyR), amplifying the initial Ca2+ signal. The subsequent increase in cytosolic Ca2+ concentration ([Ca2+]c) activates the contractile myofibers. Relaxation occurs when [Ca2+], decreases to diastolic levels by mainly the SR Ca2+–ATPase (SERCA), which pumps back Ca2+ to the SR and by the sarcolemmal Na+/Ca2+ exchanger (NCX) [93]. To our knowledge, there is no much published evidence that radiotherapy affects directly these Ca2+ handling elements in cardiomyocytes.

However, ionizing radiation is known to induce ROS and oxidative stress is known to have an impact on EC coupling, in particular with the redox sensitive RyR [94–96]. Thus, one can expect a possible direct effect of ionizing radiation on Ca2+ homeostasis in the remaining cardiomyocytes, which remains speculative at that time.

Here, we will focus on the effects of doxorubicin on Ca2+ signaling involved in EC coupling, although there is large evidence that doxorubicin also affects mitochondrial Ca2+ and function [23]. Several data point to alteration in [Ca2+]i, handling in cardiac myocytes as underlying the defects in contraction and relaxation. Doxorubicin binds to the RyR [97] and to calsequestrin (CSQ), ancillary protein located in the SR lumen [98]. Daunorubicin and its metabolite daunorubicinol are also able to bind to CSQ [99]. Daunorubicin exerts a byphasic action on single RyR. First, it binds to RyR and increases its open probability and then, upon oxidation of free SH groups, it decreases its activity to very low levels [100]. Treatment of isolated cardiac myocytes with doxorubicin increases the diastolic [Ca2+]i by releasing it from stores. This release of Ca2+ is involved in ROS production, which further increases RyR activity [101]. These data suggest that there is an oxidant independent effect of doxorubicin on RyR. Although because EC coupling elements, including the RyR are redox regulated [102], doxorubicin-induced ROS mediate or amplify doxorubicin effects on RyR. Acute or short term exposure to anthracyclines have shown a decrease in the amplitude of the [Ca2+]i transient, by releasing it from stores. This release of Ca2+ is involved in ROS production, which further increases RyR activity [101]. These data suggest that there is an oxidant independent effect of doxorubicin on RyR. Although because EC coupling elements, including the RyR are redox regulated [102], doxorubicin-induced ROS mediate or amplify doxorubicin effects on RyR. Acute or short term exposure to anthracyclines have shown a decrease in the amplitude of the [Ca2+]i transient, by releasing it from stores.

In a comparative study in which doxorubicin, or its metabolite doxorubicinol was introduced into the cell through the patch-clamp pipette, both metabolites decreased the amplitude of the [Ca2+]i transient and slowed contraction and relaxation [103], although they had opposite effects on action potential duration. In another study in intact cells, doxorubicin acutely slowed time to peak and relaxation [Ca2+]i transients without affecting its amplitude. These alterations in kinetics were ascribed to oxidative stress [104]. Ca2+/calmodulin kinase II (CaMKII) is also involved in doxorubicin effects on EC coupling. Isolated cardiac myocytes exposed to doxorubicin for 30 min showed an increase in diastolic [Ca2+]i and of ROS production. This was accompanied by an increase in Ca2+ sparks occurrence, decrease of the SR Ca2+ load and, as a consequence weaker [Ca2+]i transients [105]. Further analyses showed that ROS scavenging only partly rescued the effects. CaMKII was phosphorylated after doxorubicin application, but not oxidized. Inhibition of CaMKII or experiments in CaMKII KD cardiomyocytes attenuated doxorubicin effects on [Ca2+]i, although they were not completely abolished [105], suggesting that both CaMKII and ROS are involved in doxorubicin effects on cardiac Ca2+ handling.

In an early study, papillary muscles incubated with doxorubicin or its main metabolite, doxorubicinol, showed impairment in SERCA function. These effects were more potent for the
metabolite than for doxorubicin, while doxorubicin is a more effective anticancer, thus, suggesting that the anticancer efficacy and cardiac toxicity could be dissociated [106]. Doxorubicin effects on SERCA may involve free SH oxidation [107]. However, SERCA overexpression worsens the outcome of mice after chronic treatment with doxorubicin [108].

Doxorubicin effects on [Ca²⁺], after single or cumulative doses of doxorubicin in vivo have been investigated. A decrease in the expression of RyR has been suggested or demonstrated in this context [109,110] late (13 to 18 weeks) but not early (1 week) after treatment [109]. By using an analog of doxorubicin, which cannot be metabolized into doxorubicinol, Gambbiel et al. suggested that it is doxorubicinol and not doxorubicin that is involved in RyR downregulation [110].

Alteration of β-adrenergic signaling by chemo and radiation therapy

Besides its key roles in regulating cardiac function and remodeling, β-adrenergic (β-AR) signaling plays an important role in apoptosis as well as tumorigenesis [111] and are thus of particular interest in doxorubicin-induced cardiomyopathy. Doxorubicin induces an alteration of β-AR signaling through a decrease in the expression of β1-AR receptor [112], a downregulation of protein Gs [113] and a decreased activity of adenylyl cyclase (AC 5 and 6) [114]. Conjointly, the inhibition of phosphodiesterase-5 (PDE-5) attenuated dox-induced apoptosis [115]. Bernstein et al. also showed a differential cardiotoxic role of β1-AR/CARDIOPROTECTIVE role of β2-AR partially mediated through inhibitory G protein in the development of cardiotoxicity induced by doxorubicin using β1-/-, β2-/- and β1/β2-/-mice [116]. Furthermore, Zhang et al. demonstrated that β-AR signaling could induce both cell death through PKA, CAMKII, and SR Ca²⁺ overload and cardioprotection through exchange protein activated by cAMP (EPAC), which is ERK-dependent [102].

Although data cross-linking doxorubicin-induced cardiac toxicity and EPAC are scarce, many of EPAC downstream effectors, such as mTOR, Rac I and CAMKII have been implicated in doxorubicin cardiotoxicity. Several studies showed that the inhibition of Rac I, a protein activated by Epac1 implicated in DNA damage induction by Top II, attenuated the side effects of doxorubicin both in vitro and in vivo [117–119]. Moreover, inhibition of mTOR has been shown to be cardioprotective and reverse doxorubicin resistance in many types of cancerous cells as well as inhibition of small protein G Rho A [18,120–122]. Therefore, β-adrenergic signaling could be a potential strategy as doxorubicin triggers many of its effectors PKA, CAMKII and EPAC. Indeed, carvedilol, a beta-adrenergic blocking with potent alpha adrenergic and antioxidant properties, has been found to be protective against doxorubicin-induced ROS generation and apoptosis [123]. There is also an urgent need to investigate myocytes damage induced by radiation as well as interactions between radiation therapy and chemotherapy (for a complete review, see Chargari et al. 2013 from the E Deutsch team in the same issue).

Rac pathways in radiation-induced cardiovascular damage [125]. However, except in the scope of fibrosis, basic science studies concerning altered signaling pathways induced by radiotherapy or combined radio- and chemotherapy are still completely lacking, thus, conclusions are completely speculative.

Conclusion

The underlying mechanisms of anthracycline-induced cardiotoxicity have been the focus of intensive investigations since its discovery during the 60 s. However, even if some lines of evidence have been proposed, precise mechanisms are not clearly understood yet. Indeed, the incidence of heart failure increases in a dose-dependent manner (2–5% for a cumulative dose of 240–360 mg/m² and 400–450 mg/m² respectively) and can reach 10% for elderly patients [126] still nowadays. The use of dexrazoxane is limited to patients receiving more than 360 mg/m² as it may reduce the efficiency of doxorubicin anti-tumoral effects [126]. Therefore, new therapeutic strategies with decreased cardiotoxicity but with good antineoplastic efficiency still need further investigation.

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