Anthracyclines and Heart Failure

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Since their discovery more than 50 years ago, anthracyclines have become the mainstay for the treatment of many cancers. However, anthracyclines are associated with a risk of heart failure, with the risk proportionate to the cumulative exposure; cardiac injury appears to occur with every dose, and cardiac-biopsy specimens obtained within hours after a single dose of an anthracycline (e.g. doxorubicin or daunorubicin) show pathologic changes.[1] Much effort has gone into finding ways to prevent anthracycline cardiotoxicity, yet advanced heart failure remains a consequence of anthracycline exposure. Moreover, symptomatic heart failure often occurs years after cancer treatment, making it difficult to evaluate preventive strategies.

The dominant theory of how anthracyclines cause heart damage involves the generation of reactive oxygen species, which results in damage to DNA, proteins, and lipids and leads to cellular dysfunction and myocyte death. However, results from a recent study by Zhang et al.[2] suggest that the first step in cardiac myocyte damage from anthracyclines is independent of reactive oxygen species and depends instead on drug interactions with a particular type of topoisomerase, an enzyme that affects the tension and topologic features of DNA.

Anthracyclines disrupt tumor growth by binding to and blocking the function of topoisomerase II (TOP2). Topoisomerases break, twist, and reseal the phosphate backbone of DNA and, in so doing, permit a readjustment in the tension of the double helix during replication and transcription. Anthracyclines intercalate into DNA and form complexes with TOP2 that disrupt the activity of the enzyme and activate a DNA-damage response, leading to cell death. There are several forms of topoisomerase. Rapidly dividing tumor cells express high levels of topoisomerase II alpha (TOP2A). TOP2 beta (TOP2B) is ubiquitously expressed; cardiomyocytes express TOP2B but not TOP2A. Anthracyclines target both TOP2A and TOP2B.

Anthracyclines are thought to cause cardiomyocyte damage by driving reactions that result in the formation of free radicals, which in turn can react with and disrupt the function of many cellular constituents, causing dysfunction and cell death. Numerous studies in isolated cells and in animals have shown cardioprotective effects of antioxidants, lending support to the hypothesis that, as a consequence of anthracycline exposure, reactive oxygen species wreck cardiomyocytes (Fig. 1). However, clinical trials of antioxidants for the prevention of anthracycline-induced cardiac injury have been disappointing. Nevertheless, dexrazoxane, a compound that chelates iron and prevents hydroxyl radical formation in the presence of anthracyclines, prevents cardiac injury, lending support to the hypothesis regarding reactive oxygen species. (Dexrazoxane has been approved by the Food and Drug Administration for the prevention of anthracycline cardiotoxicity.)

On the other hand, some research has challenged the hypothesis regarding reactive oxygen species. Using mouse cells in culture, Lyu et al.[3] have shown that anthracycline-induced DNA breaks and cell death in a cardiomyocyte cell line depend on the presence of Top2b. Building on this finding, Zhang et al. genetically engineered mice to lack Top2b specifically in their cardiomyocytes. In contrast with control mice, the mutant mice did not have acute or chronic cardiac injury after exposure to doxorubicin, a commonly used anthracycline. Nor did these mice have reductions in left ventricular ejection fraction, a key characteristic of doxorubicin cardiotoxicity.

Zhang et al. observed the formation of reactive oxygen species, consequent to interactions among doxorubicin, Top2b, and DNA in the wild-type mice. The formation of reactive oxygen species appeared to be caused by the disruption of mitochondrial function, rather than a consequence of reduction–oxidation cycling of doxorubicin quinones. Analysis of cardiac tissue from the doxorubicin-treated wild-type mice revealed
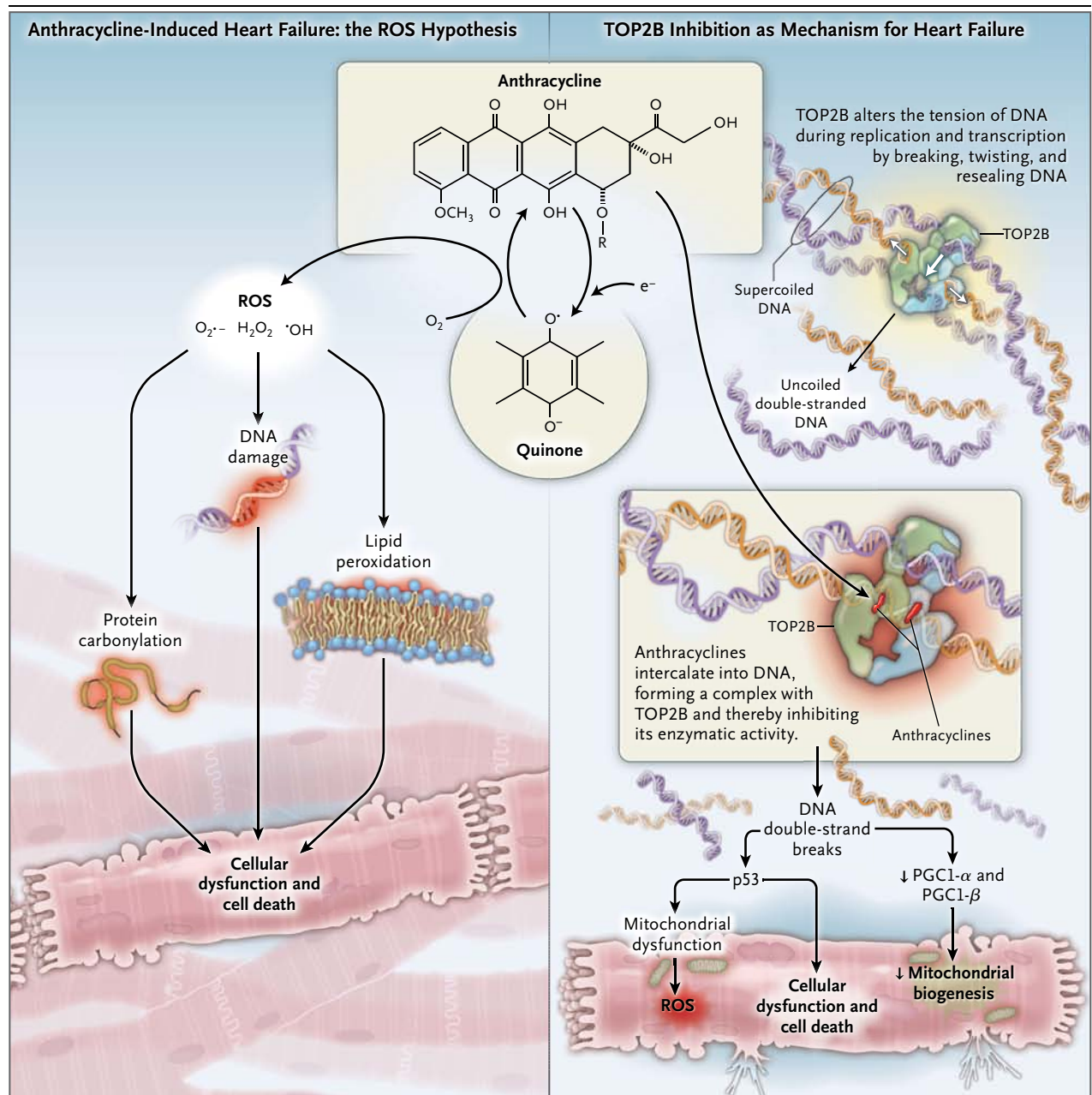
Figure 1. Mechanisms of Anthracycline-Induced Injury to Cardiac Cells.

The classic model of anthracycline cardiotoxicity involves the generation of reactive oxygen species (ROS) by the quinone moiety common to all anthracyclines. An alternative model, supported by a recent study by Zhang et al.,[2] posits that toxicity is caused by the disabling of the function of topoisomerase II beta (TOP2B) by the anthracyclines. Without functional TOP2B, double-stranded DNA breaks accrue, leading to events such as the activation of p53 tumor-suppressor protein, mitochondrial dysfunction, and the generation of ROS that result in cardiac cell death. PGC1-α and PGC1-β denote peroxisome-proliferator–activated receptor α coactivator 1α and 1β.

the activation of DNA-damage–response pathways by means of the suppression of transcription factors known to be critical for regulation of mitochondrial biogenesis (Fig. 1). These changes were not present in cardiac tissue from the mu-

tant mice, a finding consistent with the observed protection against cardiotoxicity.

Dexrazoxane was originally developed as a TOP2 inhibitor. In cells, dexrazoxane appears to prevent doxorubicin binding to TOP2B and thus

prevents DNA breaks and cell death. An alternative mechanism for the cardioprotective effect of dexrazoxane may therefore involve prevention of the binding of anthracyclines to TOP2B, rather than iron chelation and prevention of damage to cells from reactive oxygen species. However, the effect of dexrazoxane on TOP2A may reduce the antitumor efficacy of anthracyclines and, ironically, limit its usefulness.

Research is needed to determine whether these findings have clinical relevance. In the event that they do, the implications of this work are exciting. The development of inhibitors specific to TOP2A may lead to efficacious antitumor therapies that have no effect on the heart. It is also possible that a small molecule that selectively binds to TOP2B could prevent its interaction with anthracyclines and thus prevent cardiac cell death.

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2. Zhang S, Liu X, Bawa-Khalfe T, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med 2012;18:1639-42.
3. Lyu YL, Lin C-P, Azarova AM, Cai L, Wang JC, Liu LF. Role of topoisomerase IIβ in the expression of developmentally regulated genes. Mol Cell Biol 2006;26:7929-41.