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EDITORIAL COMMENT

(Less) Time and Energy

Toward a Better Understanding of the Chronology of Anthracycline-Induced Cardiotoxicity*

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In this issue of *JACC: CardioOncology*, Díaz-Guerra et al[1] make important contributions to our understanding of the timeline for the onset and progression of anthracycline-induced cardiotoxicity (AIC). The investigators systematically and longitudinally characterized cardiac structural and functional responses in a commonly used mouse model of chronic AIC wherein 5 mg/kg of doxorubicin (DOX) is administered intraperitoneally (i.p.) once weekly for 5 weeks. They established that this protocol led to a steady reduction in body weight after completion of the 25 mg/kg cumulative dose, consistent with many published reports. Notably, this significant weight loss did not coincide with reductions in food intake and activity across the same time period. These revealing dietary data typically are not presented in studies of AIC and indicate that malnourishment does not cause DOX-induced weight loss, suggesting that other processes such as muscular atrophy likely drive this common phenotype. Indeed, the investigators demonstrate that the cardiac atrophy characteristic of AIC was identified as early as 1 week into the treatment protocol and persisted throughout the study period.

The investigators then turned their attention to the metabolic alterations induced by repeated DOX exposures. Serum glucose was reduced at all time points, but no other durable or significant abnormalities were detected in systemic metabolism. Myocardial fluorodeoxyglucose uptake on positron emission tomography was profoundly diminished by DOX exposure as low as 5 mg/kg (week 1), and quantitative reverse transcriptase polymerase chain reaction identified down-regulation of key transcripts related to glucose uptake (*Glut1* and *Glut4*). The investigators then present quantitative reverse transcriptase polymerase chain reaction data for selected transcripts related to regulation of fatty acid oxidation (*Cpt2*, *Acot1*, *Acox1*, *Crat*, *Pdk4*), glycolysis (*Hk2*), and the tricarboxylic acid cycle (*Pdk4*). Although these findings do not enable the reader to draw any substantiated conclusions about the effects of DOX on myocardial metabolic substrate use, earlier focused studies demonstrated that acute and chronic anthracycline exposure blunt fatty acid oxidation in cardiomyocytes, and broader metabolic reprogramming has been detailed in multiple more recent metabolomic studies (reviewed by Wallace et al).[2]

In their elegant Figure 6A, the investigators depict the use of high-resolution respirometry (using the Oroboros O2k respirometer) to demonstrate DOX-induced decreases in oxidative metabolism at all time points. Importantly, the reduction in oxygen consumption was evident at week 1, the earliest time point, and remained similar in magnitude across other time points through week 15. Other measured parameters, such as oxidative phosphorylation (OXPHOS) coupling efficiency and proton leak were unchanged in both the DOX and control groups. Finally, transmission electron microscopy was performed to characterize DOX-induced changes in mitochondrial abundance and morphology at each time point. No significant changes were observed at week 1, but by week 15, mitochondrial size was slightly decreased and mitochondrial number was increased, indicating that functional abnormalities

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precede structural alterations in DOX-exposed cardiac mitochondria. The investigators then assayed selected markers of mitochondrial biogenesis (PGC1α), fusion (OPA1), fission (DRP1) and mitophagy (PINK1 and PRKN) and found no differences that could contribute to the changes in mitochondrial abundance or function observed at week 15.

The primary contribution of this study to the extensive literature on AIC is the systematic approach to characterizing the time course through which structural and functional abnormalities arise in a commonly used mouse model. In particular, the finding that both cardiac atrophy and impaired oxidative metabolism are induced by a single low dose of DOX (5 mg/kg i.p.) is striking. Most published mouse studies present such readouts either after a single high dose of DOX (most typically 20 mg/kg i.p.) or after the cumulative administration of multiple smaller doses (often 5 mg/kg weekly for 5 weeks, as in the present study). Such approaches implicitly assume that a high dose is required to provoke acute or subacute effects or that repeated cumulative exposure to smaller doses is required to induce AIC pathobiology. Here the investigators show persuasively that neither widely held assumption is entirely accurate and that both cardiac atrophy and mitochondrial injury predate the development of overt contractile dysfunction.

Although the fidelity of any mouse model to the human condition rightly should be questioned, the finding that the pathobiology of AIC is "front-loaded" finds interesting parallels in the developing clinical literature on the topic. Historically, AIC has been conceptualized as a phenotype that can arise unpredictably from an ostensibly latent state years after exposure to anthracyclines.[3] More recent studies, particularly those using more sensitive imaging modalities for detection such as cardiac magnetic resonance imaging, have shown that cardiac injury actually occurs during or soon after anthracycline exposure, and its incidence is closer to a rule than an exception. With particular reference to the findings presented by Díaz-Guerra et al,[1] recent studies have shown that anthracyclines compromise myocardial energetics[4] and induce cardiac atrophy[5] within 6 weeks after the completion of chemotherapy. Whether these and similar findings should prompt screening for AIC while on treatment or shortly after the conclusion of chemotherapy is more properly the topic of a different editorial. Here the investigators take advantage of the relative tractability of a mouse model to demonstrate that 2 well-documented aspects of AIC pathophysiology, atrophy and mitochondrial dysfunction, arise entirely within the first week of exposure and do not progress thereafter.

The heart has the highest adenosine triphosphate requirement of any organ, largely because of the necessity for constant contraction and relaxation. In the uninjured heart, up to 95% of the requisite adenosine triphosphate is generated by OXPHOS, primarily using fatty acids as substrates. Many types of cancer, somewhat like the failing heart, are characterized by decreased OXPHOS and increased reliance on glucose (the Warburg effect) and other alternative substrates, including glutamine and ketone bodies (reviewed by Finley).[6] Although mitochondrial injury likely contributes in an incidental manner to the anticancer efficacy of anthracyclines and extant kinase inhibitors, drug development efforts in the oncology space recently have focused intensely and intentionally on cellular metabolism and energetics.[7] As the heart's constitutively high energy requirement likely represents a specific susceptibility to cancer therapy-induced cardiotoxicity, we would do well to scrutinize the effects of such novel agents on cardiomyocyte mitochondrial function carefully in the preclinical arena.

In their Discussion section, the investigators present the persuasive argument that targeting therapies to address metabolic compromise at early time points could mitigate the risk for developing clinically evident AIC. Interestingly, multiple extant therapies with some efficacy against AIC may exert benefit in part by favorably altering mitochondrial function to reduce oxidative stress. Enalapril mitigates mitochondrial injury in a rat model of AIC,[8] carvedilol (but not the beta-1 adrenergic receptor-selective antagonist atenolol), blunts DOX-induced oxidative stress and mitochondrially mediated cell death,[9] and spironolactone protects both contractile function and redox status in human AIC.[10] There is considerable enthusiasm for developing "mitotrope" drugs that are designed intentionally to enhance mitochondrial function to treat patients with heart failure of any etiology, and here Díaz-Garcia et al[1] remind us that AIC may be a particularly fruitful target for such novel therapies.

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