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EDITORIAL COMMENT

Functional Genomics Illuminates Mechanisms of Anthracycline Cardiotoxicity

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Anthracyclines such as doxorubicin remain foundational cancer therapies across pediatric and adult oncology, contributing substantially to improved survival in multiple malignancies.[1] Their clinical utility, however, is constrained by cardiotoxicity that can emerge during treatment or years later, limiting cumulative dosing and shaping long-term cardiovascular outcomes among cancer survivors.[2] Despite decades of investigation, risk stratification remains imprecise, and prevailing mechanistic models fail to fully explain the marked interindividual variability in susceptibility.[2,3] These gaps highlight the need for agnostic discovery approaches capable of identifying cardiotoxicity mediators beyond established candidate pathways.

In this issue of *JACC: CardioOncology*, McDermott-Roe et al[4] present a functional genomics framework to interrogate the molecular determinants of doxorubicin cardiotoxicity. Using genome-wide CRISPR/Cas9 loss-of-function screens, the authors systematically identify modifiers of doxorubicin-induced injury across immortalized cardiomyocytes and human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). This approach builds on seminal work showing that human cardiomyocyte models recapitulate patient-specific susceptibility to anthracycline cardiotoxicity and can uncover clinically relevant genetic and pharmacologic modifiers.[5,6]

In contrast to these earlier studies that focused on patient-derived susceptibility, the current work by McDermott-Roe et al[4] leverages unbiased, genome-scale perturbation to define cardiomyocyte-intrinsic pathways governing both toxicity and intracellular drug handling. A key conceptual advance lies in the parallel interrogation of 2 complementary phenotypes: cardiomyocyte cell death and intracellular doxorubicin accumulation. Whereas cell death represents a tractable and scalable screening endpoint, it preferentially captures late-stage injury and may miss earlier manifestations of cardiotoxic stress, including mitochondrial dysfunction and metabolic perturbations. Similarly, each in vitro model system carries distinct strengths and limitations: immortalized cardiomyocytes enable high-throughput discovery but lack mature cardiac structure and physiology, whereas hiPSC-CMs retain human genetic context yet exhibit fetal-like transcriptional programs and incomplete maturation. Orthogonal validation across these complementary systems reinforces biological relevance. At the same time, there remains a need for approaches that better capture tissue-level complexity, cell-cell interactions, and systemic influences on cardiotoxicity, whether through advanced human organoid platforms or in vivo models.

Among the most compelling findings is the identification of retinoic acid receptor alpha (RARA) signaling as a cardioprotective axis. Loss of RARA sensitized cardiomyocytes to doxorubicin-induced toxicity, whereas pharmacologic activation with the selective RARA agonist tamibarotene conferred protection. Transcriptomic profiling further revealed that RARA activation mitigated doxorubicin-mediated

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repression of mitochondrial and metabolic gene programs, implicating preservation of transcriptional and energetic resilience as a protective mechanism. These results resonate with prior human genetic studies identifying anthracycline susceptibility variants in the retinoic acid signaling pathway, particularly involving retinoic acid receptor gamma.[7,8] RARA and retinoic acid receptor gamma are closely related nuclear retinoic acid receptors that bind shared response elements and regulate overlapping transcriptional programs governing cellular metabolism, differentiation, and stress responses,[9] providing a coherent biological link between human genetic susceptibility and cardiomyocyte-intrinsic pathways. More broadly, systematic comparison of cardiomyocyte-based functional genomics with loci emerging from large-scale human genome-wide association studies of anthracycline cardiomyopathy could help prioritize biologically convergent pathways and refine translational relevance.

The study also reframes anthracycline cardiotoxicity by implicating lysosomal homeostasis and intracellular drug handling as key determinants of cardiomyocyte injury. Through CRISPR-based screens for doxorubicin accumulation, the authors identify SPNS1, a regulator of autophagic lysosome reformation, as a critical modifier. SPNS1 deficiency resulted in lysosomal expansion, impaired autophagic flux, and marked intracellular doxorubicin hyperaccumulation, accompanied by increased DNA damage and cell death. These observations align with emerging evidence that autophagy and lysosomal dynamics influence cardiomyocyte vulnerability to chemotherapeutic stress.[10-12] Nutrient deprivation reduced doxorubicin accumulation and toxicity independent of canonical mammalian target of rapamycin signaling, suggesting that metabolic state and lysosomal turnover directly influence intracellular drug fate. Together, these findings shift emphasis away from passive diffusion and nuclear damage alone, highlighting intracellular sequestration and organelle homeostasis as central contributors to cardiotoxicity.

Several strengths of this work warrant emphasis. The agnostic functional genomics approach enables unbiased discovery of cardiotoxicity mediators, whereas validation in both immortalized cardiomyocytes and hiPSC-CMs enhances confidence in biological relevance. At the same time, important limitations remain. The absence of in vivo validation leaves open questions regarding physiological relevance, and the contribution of human genetic variation within RARA, SPNS1, and related pathways to clinical cardiotoxicity remains unknown. Additionally, the impact of therapeutically modulating these pathways on antitumor efficacy requires careful consideration before translational application.

Taken together, this work is best viewed not as a definitive mechanistic account, but as a scalable discovery platform for identifying candidate pathways that merit deeper investigation. Looking ahead, this study shows how functional genomics can serve as a powerful discovery engine for cardio-oncology, particularly when integrated with human genetic and pharmacogenomic data. Critical next steps include validating candidate pathways identified through in vitro screening using in vivo models and human-relevant systems that better capture tissue context, multicellular interactions, and systemic influences on cardiotoxicity. More broadly, these findings align with the current movement toward incorporating human cardiomyocyte-based studies earlier in the preclinical evaluation of cancer therapeutics. Although animal models remain essential, they may fail to capture human-specific liabilities, leading to cardiotoxicity that becomes apparent only after clinical exposure. For instance, an investigational chimeric antigen receptor T-cell therapy has shown unanticipated cross-reactivity to human cardiac proteins that was not detected in preclinical animal testing, leading to severe cardiac adverse events in initial clinical trials.[13] In this context, scalable, human-centered platforms offer a complementary strategy to interrogate cardiomyocyte-intrinsic vulnerability, identify pathways governing intracellular drug handling and stress tolerance, and prioritize candidate targets for deeper validation. Systematic integration of such approaches alongside traditional toxicology pipelines could help mitigate the risk of unforeseen cardiotoxicity, refine candidate selection, and inform rational mitigation strategies before widespread clinical deployment.

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