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Mitochondrial topoisomerase I (Top1mt) is a novel risk factor for anthracycline-associated cardiotoxicity.

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Anthracycline, and especially doxorubicin (DOX), are among the most widely used anticancer drugs. However, a significant number of patients treated with DOX develop cardiotoxicity and identification of predicting factors for DOX toxicity remains a clinical challenge. Mitochondria are the only cellular organelles containing metabolically active DNA outside the nucleus and Top1mt is the only specific mitochondrial topoisomerase in vertebrates. MtDNA lesions and free radical-associated mitochondrial dysfunction have been found in the hearts of patients treated with DOX.
Using Top1mt knockout mice, we show that the function of Top1mt is critical to limit DOX-induced heart failure. Top1mt KO mice show hypersensitivity to DOX with significant mitochondrial dysfunction, heart muscle damage and increased death rate. Our findings demonstrate the importance of mtDNA homeostasis for cardiac tolerance to DOX and suggest that Top1mt single nucleotide polymorphisms (SNP) could predict susceptibility to DOX-induced cardiotoxicity. Two SNPs (rs11544484 and rs151194834) are under investigation in genomic DNA from 300 women treated for breast cancer with anthracyclines. About 20% have measurable cardiac dysfunction.

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