Anthracycline cardiotoxicity: looking for new therapeutic approaches targeting cell senescence?

Shariq Abid1,2, Larissa Lipskaia1,2, and Serge Adnot1,2*

1INSERM U955 and Département de Physiologie, Hôpital Henri Mondor, AP-HP, DHU A-TVB, 94010 Créteil, France; and 2Université Paris-Est Créteil (UPEC), Créteil, France

This editorial refers to ‘Co-administration of resveratrol with doxorubicin in young mice attenuates detrimental late-occurring cardiovascular changes’ by N. Matsumura et al., pp. 1350–1359.

Anthracycline cardiotoxicity remains a serious problem in paediatric and adult cancer survivors.1 Acute anthracycline-induced cardiotoxicity typically occurs within the first treatment week and early-onset cardiotoxicity within a year after treatment completion. The late-onset form of anthracycline cardiotoxicity occurs in young mice and is followed by normal cardiac function. The young doxorubicin-treated mice had normal cardiac function but lower cardiac mass compared to control mice. An older age, all doxorubicin-treated mice developed systemic hypertension without left ventricular hypertrophy. Angiotensin II infusion increased systemic arterial blood pressure and increased myocardial hypertrophy in the doxorubicin group. In keeping with these results, previous studies showed that juvenile doxorubicin exposure impaired cardiac function, which is consistent with the hypothesis.2

The article by Matsumura et al. published in this issue addresses this important problem and provides new insight into late-onset anthracycline cardiotoxicity.3 The authors developed an elegant model, in which juvenile mice were exposed to clinically relevant doses of doxorubicin that did not induce acute cardiotoxicity at young ages but were followed in adulthood by cardiotoxicity upon administration of an angiotensin II infusion. The young doxorubicin-treated mice had normal cardiac function but lower cardiac mass compared to control mice. At an older age, all doxorubicin-treated mice developed systemic hypertension without left ventricular hypertrophy. Angiotensin II infusion increased systemic arterial blood pressure in both groups but failed to induce left ventricular hypertrophy in the doxorubicin group. In keeping with these results, previous studies showed that juvenile doxorubicin exposure impaired blood vessel development, as shown by a decrease in capillary density.4,5 The same mice subjected to myocardial infarction as adults were at higher risk for heart failure and showed less neovascularization. That doxorubicin-induced cardiotoxicity can be revealed later in life in response to systemic hypertension or other stressors argues for an initial cellular or molecular insult whose effects remain clinically silent but make the heart more vulnerable to stressors occurring later in life.

Since the initial discovery of anthracyclines, their cardiotoxic effects have been chiefly attributed to excessive reactive oxygen species production.3 The proposed mechanism is that the potent oxidative stress induced by therapeutic anthracycline doses leads to acute DNA damage and subsequent myocardial-cell apoptosis, causing acute myocardial dysfunction.5 Recent studies suggest that another consequence of DNA damage response activation by anthracyclines is the induction of cell senescence.4,6,7 In contrast to replicative cell senescence caused by telomeric attrition, premature cell senescence results from damage to either genomic or telomeric DNA, with p53-dependent upregulation of the cyclin-dependent kinase inhibitors p21, and expression of p16INK4a.8 A difference with apoptotic cells is that senescent cells accumulate in injured tissues, where they remain metabolically active, and express a robust senescent-associated secretory phenotype (SASP), which is proinflammatory.9 Numerous studies have demonstrated that doxorubicin exposure induces senescence in vivo, as detected by increased p16INK4-positive cell counts, upregulation of p53 effector genes and SASP factors such as IL-1β and IL-6, and the appearance of senescence markers such as SA-β-GAL activity in cardiac tissues.4,6,7 Thus, two distinct cellular responses to anthracyclines have been identified, cell apoptosis and cell senescence, which both result from DNA damage response activation and may potentially produce different forms of anthracycline cardiotoxicity according to the dose or administration regimen. With low doxorubicin doses such as those used by Matsumura et al.3 and Huang C et al.,4 cell senescence may be the predominant cardiac effect, with no overt cardiac dysfunction at the time of administration but with a subsequent increase in susceptibility to cardiac stressors. The upregulation of several genes involved in the cell senescence programme reported by Matsumura et al., including the cyclin-dependent kinase inhibitor 1A (p21), is consistent with this hypothesis.3 Moreover, Matsumura et al. report a maladaptive cardiac response to a pressure load induced by angiotensin II, which is now considered a potent inducer of cell senescence in the cardiovascular system.9

One possibility emerging from these results is that senescence of myocardial cells or other cardiac-cell types may be the predominant effect of low-dose anthracycline, mimicking some of the alterations produced by ageing and leading to cardiotoxicity later in life. Indeed, subtle signs of cardiac dysfunction such as decreased peak systolic strain-rate values are detected after the induction of myocardial-cell senescence10 and have also been reported during the latent phase preceding doxorubicin-induced cardiotoxicity.11

Identifying cell senescence as a prominent pathogenic mechanism of doxorubicin-induced cardiotoxicity opens doors towards new therapeutic approaches. Potential strategies for counteracting the deleterious effects of senescent cells include interfering with pathways that induce the senescence programme, targeting the SASP to combat the adverse effects of senescent cells, and eliminating senescent cells.10 Matsumura

* Corresponding author. Tel: +33 149 812 681; fax: +33 149 812 667, E-mail: serge.adnot@inserm.fr

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author(s) 2018. For permissions, please email: journals.permissions@oup.com.
et al. demonstrated that concomitant resveratrol treatment normalized the adaptive left-ventricular response to systemic arterial pressure elevation and prevented the subsequent development of heart disease. This finding is of special importance, since resveratrol is now considered a life-extending drug. Resveratrol increases the longevity of yeasts, nematodes, and flies and also exerts anti-ageing effects on mice kept on a high-fat diet. Moreover, resveratrol protects against cell senescence, in particular angiotensin II-induced senescence possibly by inducing autophagy. Although this later aspect was not specifically investigated by Matsumura et al., these authors showed clearly that resveratrol corrected the doxorubicin-induced upregulation of p53 effector genes in myocardial tissue. Combined with recent evidence that senescent-cell elimination can be induced pharmacologically in a chemotherapy-induced cardiotoxicity model, these findings further support premature cardiomyocyte senescence as a target for preventing doxorubicin-induced cardiotoxicity. Interventions aimed at preventing cell senescence or eliminating senescent cells might therefore be effective against doxorubicin-induced cardiotoxicity. Further studies are needed to explore these novel therapeutic approaches.

Acknowledgement
The authors thank for the discussion and suggestions from members of Adnot lab.

Conflict of interest: none declared.

References