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EDITORIAL COMMENT

Premature Cardiac Senescence

An Unsung Hero in Chemotherapy-Induced Cardiotoxicity?*

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The mechanisms of anthracycline-induced left ventricular (LV) dysfunction have been traditionally attributed to cellular DNA damage, mitochondrial dysfunction, the formation of reactive oxygen species, and associated cardiomyocyte death. Additionally, inflammation and maladaptive remodeling of the extracellular matrix (myocardial fibrosis) also contribute to LV dysfunction and heart failure symptoms following anthracycline therapy.[1] In recent years, premature cellular senescence has emerged as a fascinating and novel biological mechanism mediating the detrimental effects of anthracyclines on cardiac tissue.

Cellular senescence is a state of cell-cycle arrest in which cells become resistant to apoptosis or any other cell death mechanism.[2] Senescent cells develop a senescence-associated secretory phenotype (SASP) producing proinflammatory cytokines, chemokines, matrix metalloproteinases, and extracellular matrix components that may affect the local microenvironment and adjacent cells.[3-6] Mitochondrial dysfunction and increased reactive oxygen species production are also often associated with cellular senescence and have recently been recognized as an underlying cause of the senescence phenotype.[4,7]

From a cancer perspective, it is generally accepted that cellular senescence induced by anthracyclines is a critical mechanism that prevents the propagation of tumor cells.[8] Problematically, cardiomyocytes, endothelial cells, and cardiac fibroblasts are also susceptible to cellular senescence induced by anticancer therapies[3]; interestingly, the characteristics and markers of anthracycline-induced senescent cells are similar to those markers present in senescence induced by other stimuli—natural aging or the persistent presence of a stressor—including upregulation of antiapoptotic genes, DNA damage, and the development of a proinflammatory SASP.[6] The persistent accumulation of senescence in the heart and the inflammation induced by SASP factors have been associated with maladaptive cardiac remodeling and the development of late onset LV dysfunction.[9] These observations have led investigators to explore the use of senotherapeutic agents to either 1) selectively promote the elimination of senescent cells (senolytic drugs); or 2) modulate the SASP factors or the senescent phenotype (senomorphic drugs) as a therapeutic strategy to prevent or treat anthracycline-induced LV dysfunction.[3]

In this issue of *JACC: CardioOncology*, Linders et al[10] present an interesting study challenging the notion that the prevention of cardiac cell senescence is an effective strategy to ameliorate LV dysfunction induced by anthracyclines. These researchers used novel 3-dimensional dynamic engineered heart tissues (EHTs) generated by mixing human induced pluripotent stem cell–derived cardiomyocytes and human neonatal ventricular cardiac fibroblasts and growing them on a flexible scaffold. In an effort to recapitulate clinical chemotherapy regimens for breast cancer and lymphoma, the EHTs were exposed to 4 microdoses of 0.1 μM/L doxorubicin every 7 days, reflecting the peak concentration found in the plasma of patients after the administration of 50 to 70 mg/m^2 doxorubicin. To test the efficacy of senescence

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inhibition, the EHTs were cotreated with 2 different senomorphic agents: resveratrol, a sirtuin 1 activator, and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), an AMPK activator, both of which prevent cellular senescence.[7,11] At the end of the experiment, the systolic and diastolic function of the flexible structure, the gene and protein levels of senescence markers, SASP components, and mitochondrial function were measured.

Using these methods, the investigators report up-regulation of senescence genes and proteins (p16, p53, and p38MAPK) in the EHTs after just 2 doses of doxorubicin, similar to the up-regulation of those markers in the LV tissues of patients with severe cardiotoxicity induced by anthracyclines. At a functional level, the EHTs exhibited contractile and mitochondrial dysfunction, denoted by the decrease in oxygen consumption, adenosine triphosphate-linked respiration, and respiratory reserve in cardiomyocytes. These findings are consistent with the observations that mitochondrial dysfunction is causally associated with senescence and doxorubicin toxicity.[4] Cotreatment with AICAR and resveratrol prevented EHT cells from becoming senescent, but unexpectedly, EHTs exhibited increased cell apoptosis and fibrosis. This resulted in either not having a beneficial impact at a functional level in the case of resveratrol or worsening of contractility and dilation in the case of AICAR.

These results, although unexpected, underscore the complexity of senescence and raise several questions and hypotheses. First, it is plausible that cellular senescence may serve as a protective mechanism that prevents cardiomyocyte death, specifically during treatment, as it might be more beneficial to preserve a cell that is capable of retaining some degree of contractility. Second, it is known that the long-term accumulation of senescent cells in cardiac tissue and the proinflammatory effects of their SASP on healthy cells may trigger more senescence and injury to the remaining healthy cells and promote excess collagen deposition and fibrosis in the cardiac tissue; therefore, perhaps assessing the optimal timing of post-doxorubicin senolysis might be a better approach. Finally, from a clinical perspective, the interpretation and translation of the results are limited by the nature of the in vitro experiments. Further preclinical animal studies are warranted to determine the efficacy of prevention and treatment of LV dysfunction induced by anthracyclines, especially in tumor-bearing animals, to ensure that the senotherapeutic agent will not jeopardize the effectiveness of the anticancer treatment.

In summary, robust evidence recognizes cellular senescence as an emerging key pathophysiological mechanism of LV dysfunction induced by anthracyclines. This study by Linders et al[10] underscores the complexity of the mechanism and the need for more research on the modulation of premature senescence as a therapeutic strategy.

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