Circulation Research

EDITORIAL

Doxorubicin-Induced Ascension of Resident Cardiac Macrophages

Paul W. Burridge, Edward B. Thorp

Doxorubicin-induced cardiomyopathy (DiCM) remains a significant cause of heart failure in cancer patients. For example, a recent clinical trial confirmed that 14.5% of doxorubicin-treated breast cancer patients experience a decrease in left ventricular ejection fraction of greater or equal to 10%.[1] DiCM can occur either as an early (during the first year after treatment) or late consequence, with the latter manifestation thought to be a long-term consequence of the acute doxorubicin insult.[2] It is known that DiCM is a result of cardiomyocyte cell death,[3] assessed by an increase in troponins in the peripheral blood. The mechanism for how doxorubicin causes cardiomyocyte cell death is thought to be a combination of DNA damage and the generation of reactive oxygen species that triggers mitochondrial dysfunction. Despite the known link between reactive oxygen species and DiCM, antioxidant therapies such as N-acetylcyteine have failed in patients.[4] Thus, uncovering mechanisms associated with DiCM is of high clinical significance.

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Cardiomyopathy in general is increasingly associated with inflammation and evidence of activated immune cells within the myocardium, including innate macrophages. During ischemic cardiomyopathy, distinct populations of recruited versus resident cardiac macrophages contribute to myocardial inflammation and reparative processes that regulate ventricular remodeling. The origin of these immune subpopulations is key, as we now appreciate that macrophage ontogeny imprints macrophage function. For example and during ischemic insult, monocyte-derived macrophage subsets populate the heart from the circulation and are proinflammatory.[5] In contrast, resident cardiac macrophages originate from yolk sac-derived erythromyeloid progenitors, self-renew locally, and exhibit nonoverlapping cardioprotective functions after cardiac ischemia.[6] During nonischemic cardiomyopathy, resident cardiac macrophages have been implicated in the heart's adaptive response to pressure overload.[7] In an animal model of DiCM, a role for macrophages had been shown where NLRP3 (NLR family pyrin domain containing) deficiency reduced macrophage anti-inflammatory cytokine IL (interleukin)-10, in association with enhanced susceptibility to DiCM.[8] However, beyond this, very little has been understood of the extent, contribution, and potential source of cardiac macrophage subsets during DiCM. Taken together, therefore, it is possible that a patient's predisposition to DiCM may be tied to how the heart handles the initial doxorubicin insult, combined with crosstalk with the innate immune response.

In this issue of *Circulation Research*, Zhang et al[9] newly explore the effects of doxorubicin on resident cardiac macrophage subpopulations. To do this, the research team used complementary cutting edge approaches, including macrophage lineage tracing and parabiosis in experimental mice to track and discover a protective role for cardiac resident macrophages after administration of doxorubicin. Although the findings suggest that peripheral proinflammatory monocyte-derived myocardial macrophages predominate during DiCM, resident cardiac macrophages ultimately mobilize and self-renew (Figure) in response to doxorubicin, and function to reduce adverse cardiac remodeling.

Key Words: Editorials ■ cardiomyopathies ■ doxorubicin ■ heart failure ■ macrophages ■ troponin

Correspondence to: Paul W. Burridge, PhD, Feinberg School of Medicine, Northwestern University, 300 E Superior St, Tarry 3-705, Chicago, IL 60611, Email paul.burridge@northwestern.edu; or Edward B. Thorp, PhD, Feinberg School of Medicine, Northwestern University, 300 E Superior St, Tarry 3-705, Chicago, IL 60611, Email ebthorp@northwestern.edu

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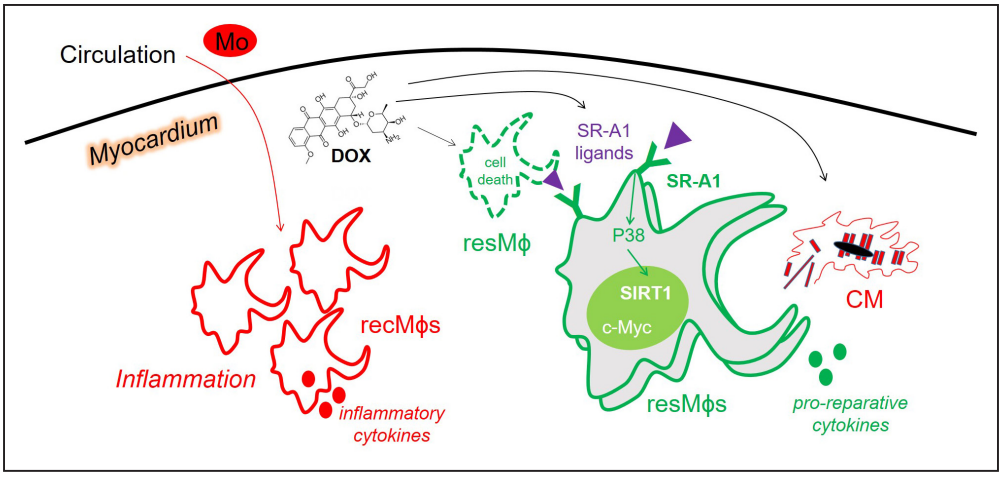

Figure. Working model.
Depicted is a schematic of recruited (rec) vs resident (res) macrophages (Mϕs) within the myocardium during doxorubicin (DOX)-induced cardiomyopathy (DiCM). Recruited Mϕs predominate in number and are derived from circulating monocytes (Mo), whereas resident Mϕs initially die, then proliferate and are cardioprotective, including though the potential clearance of dying cardiomyocytes (CMs). This proliferative response requires the Mϕ surface receptor SR-A1 (scavenger receptor A1), which is activated by SR-A1 ligands, the latter of which may be triggered by DOX. SR-A1 initiates a P38, SIRT1 (sirtuin-1), cellular-Myc (c-Myc) signaling axis that promotes Mϕ proliferation.

The molecular mechanism by which cardiac resident macrophages resist cardiotoxicity by doxorubicin is through the phagocyte cell surface SR-A1 (scavenger receptor A1; also known as MSR-1 and CD204), which was both necessary and sufficient for cardioprotection. This is because SR-A1 was required to activate the transcription factor cellular-Myc (c-Myc) to promote resident cardiac macrophage proliferation. SR-A1 had been linked to macrophage proliferation in atherosclerosis,[10] however, underlying intracellular molecular mechanisms were unclear. Furthermore, prior studies have shown that SR-A1 is critical for cardiac repair after myocardial infarction and that deficiency of SR-A1 predisposes experimental mice to cardiac rupture after myocardial infarction.[11] In the case of permanent coronary occlusion myocardial infarction, many resident cardiac macrophages die[12] and, therefore, the rescue of surviving macrophages may also depend on SR-A1 in this scenario. As to what may be triggering SR-A1 signaling during DiCM, SR-A1 ligands can be generated by products of doxorubicin-induced lipid peroxidation in the heart. For example, lipid peroxidation adduct malondialdehyde is capable of modifying proteins for recognition by SR-A1 on phagocytic cells.[13] Furthermore, elevated cell death in the myocardium may stimulate phagocytic signaling by SR-A1.

Macrophage proliferation is known to be triggered by multiple cytokine receptor pairings that include M-CSF (macrophage colony-stimulating factor) signaling, IL-4 receptor activation, and GM-CSF (granulocyte-macrophage colony-stimulating factor) pathway activation.[14] M-CSF-induced proliferation is linked to activation of c-Myc. In the case of Zhang et al,[9] forced lentiviral expression of c-Myc was able to stimulate macrophage proliferation and improve cardiac function in doxorubicin-impaired experimental mice. The investigators propose that c-Myc works cooperatively with NAD-dependent deacetylase SIRT1 (sirtuin-1) and is activated by a TAK1-MKK4-P38 mitogen-activated protein kinase signaling cascade. Thus, newly elucidated is SR-A1 as a regulator of macrophage proliferation via activation of c-Myc intracellular signaling.

Despite our current appreciation of the importance of immune cells to cardiac disease, as well as the clinical importance of DiCM, our mechanistic understanding of how doxorubicin affects cardiac immunology remains vague. The studies of Zhang et al[9] are a good start, nevertheless, a number of important and outstanding questions remain. This includes why select patients experience cardiotoxicity while others may tolerate higher chemotherapy doses. It is interesting to speculate that genetic predisposition or preexisting metabolic state may influence the mobilization of cardiac immune cells to doxorubicin. Also, to what extent do innate immune cell subpopulations activate the adaptive arm of the immunity to calibrate cardiac inflammation during DiCM? Taken together, the findings of Zhang et al[9] point to a new cardioprotective role of cardiac resident macrophages during DiCM. Future endeavors may consider immunomodulatory strategies that promote cell survival of those resident cardiac macrophages, which initially succumb to cell death by doxorubicin or aging. In addition, higher resolution approaches such as single-cell sequencing and in patients, may reveal yet additional cell subpopulations that uniquely tune the severity of DiCM.

ARTICLE INFORMATION

Affiliation

From the Feinberg School of Medicine, Northwestern University, Chicago, IL.

Disclosures

None.

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