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"WNT5A MEDIATES DOXORUBICIN-INDUCED CARDIOMYOPATHY THROUGH INDUCTION OF SENESCENCE"

By

Eun-Ah Sung
Cell Biology, Neuroscience and Physiology Program
B.S. Hanyang University, 2014
M.S. Seoul National University, 2016

Thesis Advisor: Junichi Sadoshima, MD, PhD
Professor and Chair
Department of Cell Biology and Molecular Medicine

Friday, October 10th, 2025
Medical Science Building, G609
10:00 A.M.

Join Zoom presentation

https://rutgers.zoom.us/j/91308064273?pwd=2uj0GinCtXfWd5KPUpaGC7TUnadalb.1

Meeting ID: 913 0806 4273
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ABSTRACT

Heart failure and cancer are leading causes of death in the United States. The chemotherapeutic agent doxorubicin (DOX) is a widely used, but its clinical use is limited by cardiotoxicity that leads to cardiomyopathy and heart failure. Senescence is defined by irreversible cell cycle arrest, resistance to apoptosis, and a senescence-associated secretory phenotype (SASP). Elimination of senescent cardiomyocytes (CMs) improves cardiac function, implicating senescence as a key driver of DOX-induced cardiomyopathy. Autophagy, a lysosome-dependent degradation mechanism essential for cellular quality control, is inhibited in DOX-cardiotoxicity. Our prior work demonstrated that suppression of autophagy during aging increases CM senescence, suggesting that impaired autophagic flux and enhanced senescence are shared mechanisms underlying aging- and DOX-associated cardiac dysfunction. Here, we identify Wnt5a, a non-canonical Wnt ligands, as a central mediator of DOX-induced cardiomyopathy. Wnt5a expression was elevated in neonatal rat CMs, human CMs and mouse hearts in a CM-specific manner. Recombinant Wnt5a induced senescence in CMs and non-myocytes. CM-specific Wnt5a knockout alleviated DOX cardiomyopathy. Selective downregulation of Wnt5a in senescent cells attenuated DOX-induced cardiac dysfunction and senescence, highlighting a pathogenic role of Wnt5a from senescent cells. Wnt5a inhibited autophagic flux by upregulating Rubicon, a negative regulator of autophagy. Rubicon deletion in CMs restored autophagic flux, reduced senescence and improved cardiac function upon DOX treatment. Importantly, administration of Wnt5a inhibitor suppressed DOX-induced senescence and cardiomyopathy without compromising the antitumor efficacy of DOX. Taken together, these findings establish Wnt5a as a key mediator of DOX-induced cardiotoxicity through regulation of autophagy and senescence. Targeting Wnt5a signaling or enhancing autophagic flux may provide promising therapeutic strategies to mitigate DOX cardiomyopathy while preserving its anticancer benefits.