TRANSCRIPTIONAL AND POST-TRANSCRIPTIONAL CONTROL OF Nrf2 IN THE HEART BY THE DEUBIQUITINASE CYLD

by

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ABSTRACT

The cylindromatosis (CYLD) is a K63-linked deubiquitinase (DUB) that has been linked to the regulation of multiple physiological or pathological processes, such as neural development, inflammation and fibrosis. However, a novel paradigm for CYLD has been recently postulated; namely that of CYLD as a mediator of cardiac disease. Nuclear factor, erythroid-2 related factor 2 (Nrf2), a master antioxidant transcription factor, has been shown to suppress cardiac pathological remodeling and dysfunction via downregulation of reactive oxygen species formation (ROS). It is normally regulated by Kelch-like ECH associated protein 1 (Keap1). However, the regulatory link between CYLD and Nrf2 in the diseased heart has heretofore been unclear. In this study, a potential role of CYLD in the control of Nrf2 signaling in the heart is proposed. I found that, in a mouse model of pressure overload-induced cardiac remodeling and dysfunction via transverse aortic constriction (TAC), knockout of CYLD attenuates cardiac oxidative stress, pathological remodeling and dysfunction associated with upregulation of Nrf2-mediated antioxidant signaling. At the molecular level, CYLD inactivates MAPK/AP-1 and c-Myc pathways which are required to activate Nrf2-operated antioxidant defense in cardiomyocytes. Moreover, CYLD is capable of suppressing autophagy-dependent posttranscriptional upregulation of Nrf2 expression via activation of mammalian target of rapamycin complex 1 (mTORC1), contributing to cardiomyocyte necrosis.
Taken together, these results reveal that CYLD functions as a mediator of cardiac pathological remodeling and dysfunction via facilitating cardiomyocyte death by suppressing Nrf2-driven antioxidant defense. CYLD may serve as an important target for future therapies.