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"The role of Fat4 in pressure overload-induced cardiac dysfunction"

by
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Thursday, January 27th, 2022
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ABSTRACT

Fat atypical cadherin 4 (Fat4) is a ubiquitously expressed giant protocadherin that has been shown to regulate polarity, proliferation, and survival in various cell types. Recent work has indicated that Fat4 negatively regulates cardiomyocyte proliferation and organ size during embryonic heart development through inhibition of the Hippo pathway effector yes-associated protein (Yap). However, its role in adult heart homeostasis or stress response remains unknown. We generated cardiomyocyte restricted Fat4 homozygous knockout mice (Fat4cKO) and found Fat4 is dispensable for maintaining baseline cardiac function. Wild type mice subjected to transverse aortic constriction (TAC), which generates pressure overload (PO) stress, cardiac remodeling and eventually heart failure, had rapid upregulation of myocardial Fat4 mRNA and protein. Conversely, Fat4 expression was downregulated in myocardial biopsies of heart transplant recipients compared to donors. Normalization of PO-induced Fat4 upregulation using cardiomyocyte restricted Fat4 heterozygous deletion (Fat4hcKO) suppressed compensatory hypertrophy and worsened cardiac pathology after 1-week PO in mice. This was associated with reduced activation of pro-growth and pro-survival pathways including focal adhesion kinase (Fak)/rous sarcoma oncogene (Src) and Yap. Fat4 deficient mice also had accelerated development of HF with increased cell death and myocardial fibrosis, while hypertrophy was comparable to littermate controls following chronic PO stress. In vitro experiments using rat neonatal ventricular myocytes demonstrated Fat4 was activated by neurohormonal stimulation and knockdown of Fat4 enhanced H2O2-induced apoptosis, suggesting Fat4 may be upregulated in cardiomyocytes during PO to limit cell death in a cell autonomous manner. To elucidate the mechanism underlying differences observed in Fat4 regulation of Yap in adult hearts, we mapped the Fat4 interactome, which revealed enrichment of focal adhesion (FA) components. In addition, activation of myocardial RhoA, a molecule indispensable for PO induced activation of Yap and Fak/Src mediated FA signaling, was impaired in Fat4hcko compared to littermate controls in response to acute PO. Our results reveal distinct Fat4 functions in fetal cardiac growth and adult cardiac stress response and demonstrate that Fat4 protects against PO-induced cardiac injury through engaging FA signaling and Yap activation.