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HFWM: - Title: Intact DNA repair in differentiated cardiomyocytes is essential for maintaining cardiac function in response to physiological as well as pathological stimuli

Authors:
M De Boer1, M Te Lintel Hekkert1, I Krabbendam-Peters1, JHJ Hoeijmakers2, DJ Duncker1, 1Erasmus Medical Center, Division of Experimental Cardiology, Department of Cardiology, Thoraxcenter - Rotterdam - Netherlands (The), 2Erasmus Medical Center, Department of Molecular Genetics - Rotterdam - Netherlands (The),

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Introduction: DNA in every cell is continuously being damaged and DNA repair systems are essential for protection against DNA damage-induced aging-related diseases. Evidence indicates that DNA damage is associated with heart failure. We have shown that unrepaired endogenously generated DNA damage drives the early onset of progressive heart failure. Here we studied the effects of physiological as well as pathological stimuli on cardiac function in a mouse model with deficient DNA repair. Methods: To increase the burden of DNA damage, we generated mice with cardiomyocyte-restricted inactivation of DNA repair endonuclease XPG (aMHC-Xpgc/−). To induce physiological left ventricular (LV) hypertrophy, mice were exposed to 11 wks of voluntary wheel running. Another subset of mice was subjected to 8 wks of pressure overload by transverse aortic constriction (TAC) to produce pathological LV hypertrophy. LV function was assessed at age 16 wks. Results: Cardiomyocyte-restricted inactivation of Xpg resulted in systolic as well as diastolic LV dysfunction, demonstrated by decreases in fractional shortening (49%), LVdP/dtP40 (36%) and LVdP/dtmin (42%) compared to WT (all p<0.05), while LV end-diastolic lumen diameter (LVEDD) was markedly increased (36%; p<0.05). Physical activity has been shown to be beneficial for maintaining and improving cardiac function in mice after myocardial infarction. In contrast, exercise failed to ameliorate LV remodeling and dysfunction in aMHC-Xpgc/−, as it produced further increases in LVEDD (9%) and relaxation time constant tau (41%) compared to sedentary aMHC-Xpgc/− (both p<0.05). Moreover, myocardial collagen content was increased (159%) and the number of ?H2A.X-positive nuclei, an indicator of DNA damage, was elevated (45%; both p<0.05). TAC-induced LV hypertrophy was similar in both groups (WT 38%, aMHC-Xpgc/− 34%; both p<0.05) compared to corresponding control. In WT, LV hypertrophy was accompanied by minimal LV dilation (14%; p<0.05) and modest changes in LV function. Conversely, TAC in aMHC-Xpgc/− produced severe LV dysfunction and resulted in overt congestive heart failure, demonstrated by aggravation of LV dilation (24%) and marked increases in LV end-diastolic pressure (286%), lung fluid weight (102%) and myocardial fibrosis (338%; all p<0.05). Interestingly, TAC resulted in a reduction of ?H2A.X-positive nuclei (28%; p<0.05). However, TUNEL staining revealed elevated levels of cell loss (96%; p<0.05). Conclusion: Cardiomyocyte-restricted loss of DNA repair protein Xpg increases cardiac vulnerability to develop heart failure in response to exercise training and particular to pressure overload. These findings underscore the importance of genomic stability for maintenance of cardiac function, not only during basal conditions, but also in response to physiological and pathological stimuli.