218

A TRANSGENIC MODEL OF PRELAMIN A ACCUMULATION LEADS TO CARDIAC DYSFUNCTION IN MICE

D Brayson, A M Shah, C Shanahan *King's College London*

doi:10.1136/heartjnl-2013-304019.218

Ageing is a potent risk factor for cardiovascular (CV) disease. Mutations in the LMNA gene, which encodes the nuclear intermediate filament proteins lamins A & C, lead to a number of premature ageing syndromes, e.g. Emery Dreifuss muscular dystrophy (EDMD), which can lead to dilated cardiomyopathy (DCM) and heart failure. Some of these mutations affect lamin A processing, resulting in the accumulation of the lamin A precursor, prelamin A. Importantly, recent studies have shown that the mechanisms of premature ageing observed in patients with lamin A mutations may also occur during normal ageing processes. This led us to postulate that accumulation of prelamin A in the heart may mimic 'age-related' cardiac dysfunction. To test this, we generated a novel line of targeted transgenic mice that accumulate prelamin A specifically in cardiomyocytes, by expressing a modified prelamin A gene driven by the myosin light chain 2 ventricular (MLC2v) promoter. These mice were born without any obvious phenotype but manifested retarded growth by 3 weeks of age and had a significantly attenuated lifespan (~5 weeks) with the cause of death appearing to be heart failure. Their failure to thrive was also underscored by a muscular dystrophy like appearance. At 4 weeks age, echocardiography showed a marked dilatation of the cardiac chambers and a decline in cardiac function in vivo, e.g. ejection fraction (EF) was substantially depressed in transgenic mice (20.9±3.6%) compared with wildtype (56.7±11.2%, P=0.01), indicating DCM and heart failure. Cardiac histology showed marked cardiomyocyte disarray, profound fibrosis (Picro-sirius Red staining), and expression of senescence markers (senescence-associated beta-galactosidase). Analyses of molecular events indicated severe disruption of the LINC complex and perinuclear intermediate filament network as a number of components (SUN 2, Nesprin 2, Desmin) underwent significant expression changes and/or were mislocalised. Additionally, immunohistochemistry and western blot for CD45 and CD68 confirmed increased numbers of inflammatory cells in hearts overexpressing prelamin A. In conclusion, prelamin A accumulation in cardiomyocytes causes a pathogenic response leading to decline in cardiac function and, ultimately, death. Further investigation aims to establish the precise mechanisms underpinning the response of the heart to accumulation of prelamin A.