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Sarcomere permanent morphometric changes underlie cardiac programming in intrauterine growth restriction

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Purpose: Intrauterine growth restriction (IUGR) is associated with cardiovascular remodelling and dysfunction persisting into adulthood, resulting in dilated and less efficient hearts. However, evidence of direct fetal programming of cardiac cytoarchitecture is scarce, and the underlying molecular mechanisms remain to be elucidated. Here we show that IUGR is associated with direct changes of Sarcomere morphometry that persist in adulthood and altered fetal gene expression of sarcomere components that are in line with the reported dilation of the heart. These results identify an important mechanism within the process of fetal programming of cardiac disease at the subcellular scale.

Methods: IUGR was induced in 8 New Zealand pregnant rabbits. Puppies were assigned to: i) fetal (30 days of gestation) or ii) young adult (70 days postnatally) groups. Fetal cardiac function was assessed by echocardiography. IUGR-gene expression profile was analyzed by a bioinformatic gene set analytic tool. Sarcomere quantitative morphometric changes were assessed by multiphoton microscopy based on the SHG signal, called second harmonic generation microscopy (SHGM).

Results: Fetal echocardiography showed that ductus venosus and aortic isthmus pulsatility index were increased in IUGR rabbits, revealing a reduced cardiac performance. Additionally, both systolic and diastolic cardiac function was compromised by IUGR, illustrated by a lower systolic ring displacement and annular velocity, and an increased isovolumetric relaxation time. Gene set analysis suggested that the sarcomeric M-band (GO: 0031430) functional term was over-represented in IUGR hearts ($p < 0.001$). Results provided by SHGM showed that resting sarcomere length, defined by the distances between the two Z-discs, was shorter in IUGR fetuses ($p < 0.01$). Distances between intrasarcomeric A-bands was also shorter under IUGR ($p < 0.03$). Additionally, thick-thin filaments overlap was also shorter in IUGR fetuses ($p < 0.05$). We assessed the postnatal persistence of all sarcomere morphometric changes in adult myocardium ($p < 0.05$).

Conclusion: Results reported here suggest that IUGR induces permanent changes of cardiac sarcomeres in fetal life to cope with the adverse intrauterine environment. Importantly, these changes persist postnatally and might explain the stiffer and less contractile hearts of adult IUGRs, resembling hallmarks of high-pressure cardiac disease models. Since sarcomere changes persist in adulthood, this could be one of the molecular mechanisms leading to abnormal cardiac function in IUGR that may explain a proportion of cardiomyopathies with fetal origin.