Female gender-specific dysregulation of miR-29b and its target AKT-3 in experimental and clinical cardiac hypertrophy under pressure overload

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Introduction
Sustained pressure overload (PO) stress can elicit in the left ventricle (LV) from aortic stenosis (AS) patients a harmful remodelling, characterized by cardiomyocyte hypertrophy and interstitial fibrosis. Regression of LV hypertrophy after aortic valve replacement (AVR) surgery exhibits sex-related differences. Repression of miR-29 and the consequent aberrant activity of the AKT pathway are key elements in the maladaptive LV remodelling. Both miR-29 and AKT exhibit gender-related dysregulation under different pathological conditions.

Purpose
To study sex-specific expression patterns of miR-29b and its target AKT-3 in the LV myocardium of AS patients, and of mice subjected to transverse aortic constriction (TAC) and after TAC release (de-TAC).

Methods
The subjects of the study were AS patients of both sexes and male and female mice subjected to TAC (4 weeks) and de-TAC (1 week). LV expressions of miR-29 and AKT-3 were determined by qPCR. Primary fibroblasts were isolated from mouse LV. LV morph-functional changes were followed by echocardiography.

Results
LV miR-29b was downregulated in male mice (fold-change = 0.6±0.1*) while up-regulated in females (fold-change: 2.7±0.8*) after TAC. MiR-29b and its target AKT3 correlated negatively (r = -0.52**) only in females. AKT3 mRNA levels correlated positively with the interventricular septum thickness (r=0.57*), posterior wall thicknesses (r=0.5***) and LV mass (r=0.54***) in female, but not in males. Regression of LV hypertrophy after de-TAC was higher in females than in males (13.4 % vs 6.8%) and the LV expression of AKT3 was lower in females than in males (7.3±1.3 vs 10.5±1.1*). Females subjected to oophorectomy presented after TAC higher LV levels of AKT3 compared to intact females (6.1±1.0 vs 3.2±0.2*). In cultured primary fibroblasts, the profibrotic effect of rTGF-beta mediated by miR-29b down-regulation was observed in cells obtained from males only. In female primary fibroblasts, oestrogens induced dose-dependent up-regulation of miR-29 and down-regulation of AKT-3. Linear regression analysis revealed myocardial AKT-3 expression as a predictor of LV mass regression after AVR in AS women but not in men.

Conclusion
miR-29b and its target AKT-3 exhibit a sex-specific regulation in the LV under PO. AKT-3 overexpression is related with maladaptive hypertrophy in TAC-female mice and in AS women. These results provide insights on the molecular mechanisms involved in gender-related differences in cardiac remodelling.
Conclusion

Mir-29b and its target AKT-3 exhibit a sex-specific regulation in the LV under PO. AKT-3 overexpression is related with maladaptive hypertrophy in TAC-female mice and in AS women. These results provide insights on the molecular mechanisms involved in gender-related differences in cardiac remodelling.