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Heterozygous cardiomyocyte-specific deletion of ErbB4 sensitizes to development of pregnancy-related cardiomyopathy

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Background: Peripartum cardiomyopathy (PPCM) is a potentially life-threatening disease in women without known cardiovascular disease; PPCM is characterized by left ventricular (LV) systolic dysfunction towards the end of pregnancy and/or in the first months postpartum. The underlying mechanisms of PPCM are incompletely understood, but there is recent evidence that impaired cardiomyocyte expression of the tyrosine kinase ErbB4 receptor plays a role. ErbB4 is the main receptor of neuregulin-1, a protective and regenerative paracrine factor in the heart. Homozygous deletion of ErbB4 is lethal.

Purpose: To test the hypothesis that mice with heterozygous (HZ) cardiomyocyte-specific deletion of ErbB4 (ErbB4+/–) are more susceptible to PPCM.

Methods: Cardiac morphology and function was evaluated by echocardiography with a Vevo 2100 Imaging System during 2 pregnancies and 6 weeks postpartum (n=7–9) or during non-pregnant control conditions in HZ (ErbB4+/–) and wild type controls (n=9–10). Then, hearts were excised for analyses of myocardial fibrosis, macrophage infiltration, capillary density and cardiomyocyte cross sectional area.

Results: When compared to pregnant wild type controls, pregnant ErbB4+/– mice developed significant LV dilatation (2 weeks after the 2nd delivery: LVIDd +16% ± 2%, $p<0.05$) and dysfunction (6 weeks after the 2nd delivery: EF –23% ± 3%, $p<0.001$), increased heart to body weight ratio (+7% ± 4%, $p<0.05$) and increased cardiomyocyte cross sectional area (+28% ± 7%, $p<0.01$). Non-pregnant ErbB4+/– mice also developed LV dilatation and dysfunction, albeit slower than pregnant ErbB4+/– mice. On histology, however, myocardial tissue of pregnant ErbB4+/– mice did not show macrophage infiltration, neither fibrosis, nor reduced capillary density.

Conclusions: Heterozygous cardiomyocyte-specific deletion of ErbB4 sensitizes to peripartum LV dilatation and cardiomyocyte hypertrophy and systolic dysfunction without profound cardiac injury, features that are frequently present in PPCM patients and may explain their high chance for recovery. These data reinforce a compensatory role for neuregulin-ErbB4 signaling during hemodynamic overload, and confirm that this signaling pathway is important to protect the maternal heart during peripartum stress.