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Background. Stimulation of endothelial cells (EC) with NRG-1 increases survival and proliferation of EC, activates angiogenesis, and controls paracrine signaling of EC.
We generate a new tamoxifen-inducible mice model of EC-specific ErbB3 overexpression to investigate the role of ErbB3 in myocardial ischemia and heart failure. In the present study, we compared cardiac function and fibrosis development in EC cell-specific ErbB3 overexpressing mice versus control after the Isoproterenol (ISO)-induced model of cardiac injury, which culminates in cardiac fibrosis development.

Methods. VE-Cadherin-driven Cre recombinase (VECad-Cre-ERT2) expressing mice with overexpression of human ERBB3 (generated in MHIR Mouse Transgenic Core) were used to create tamoxifen-dependent EC-specific ErbB3 overexpressing mice (ErbB3EC/OE). The cardiac injury was induced by an IP injection of ISO (160 mg/kg). Echocardiography was performed in conscious mice with a VisualSonics Vevo 2100 imaging system at the baseline and every week for one month after the injection of ISO. Left ventricle function was recorded at parasternal short axis view in M-mode and calculated as a fractional shortening. Immunohistochemistry analysis was done using the Masson trichrome and Picrosirius Red staining. Quantification of fibrosis was performed using ImageJ software.
Shapiro-Wilk test was used as a test for normality. Normally distributed variables are expressed as mean ± SEM. Comparisons between multiple groups were performed using ordinary one-way ANOVA with Tukey's multiple-comparisons post-test.

Results. No significant changes between groups of mice in the heart dimensions and fractional shortening were found before and after ISO-induced cardiac injury (data not shown).
Masson trichrome staining revealed that the percent of fibrosis in the ErbB3 overexpressing mice group was significantly lower than in the wild-type animals after ISO injection. Picrosirius Red staining in polarized light revealed the same result as Masson trichrome staining. No sex differences were observed.

Conclusion. Our data demonstrated the critical role of EC-specific ErbB3 signaling in the protection of a heart against ISO-induced fibrosis development. Further studies are warranted to delineate the mechanisms contributing to EC-specific ErbB3-dependent protection against cardiac fibrosis.

ErbB3 receptors on endothelial cells prevent fibrosis after cardiac injury

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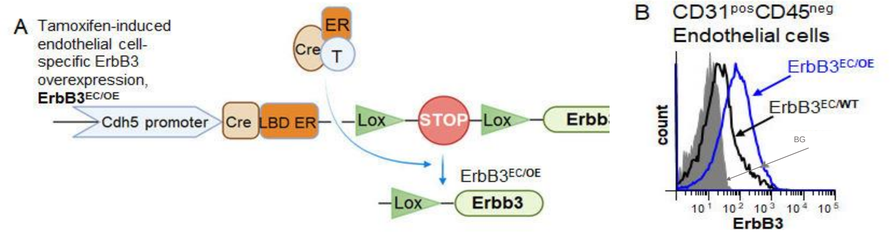

Fig. 1. A. Mouse generation strategy. **B**. Flow cytometric histogram showing the level of cell surface ErbB3 in cardiac endothelial cells from mice with overexpression of ErbB3 ($ErbB3^{EC/OE}$, blue) and control littermates ($ErbB3^{EC/WT}$, black), BG – background (closed grey).

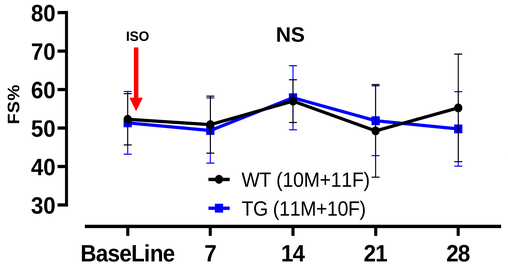

Fig. 2. Fractional shortening at different time points.
FS- fractional shortening
ISO – isoproterenol, NS – no significant,
WT – wild type,
TG – transgenic mice

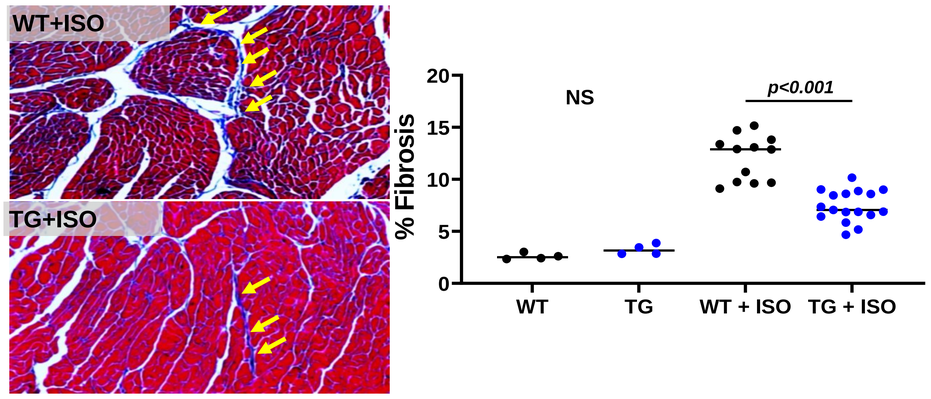

Fig. 3. Masson trichrome staining and data from ImageJ analysis. Ordinary one-way ANOVA with Tukey's multiple-comparisons post-test., n=12 (WT, 50/50 male/female) and n=16 (OE, 50/50, male/female). ISO – isoproterenol, NS – no significant, WT – wild type, TG – transgenic mice

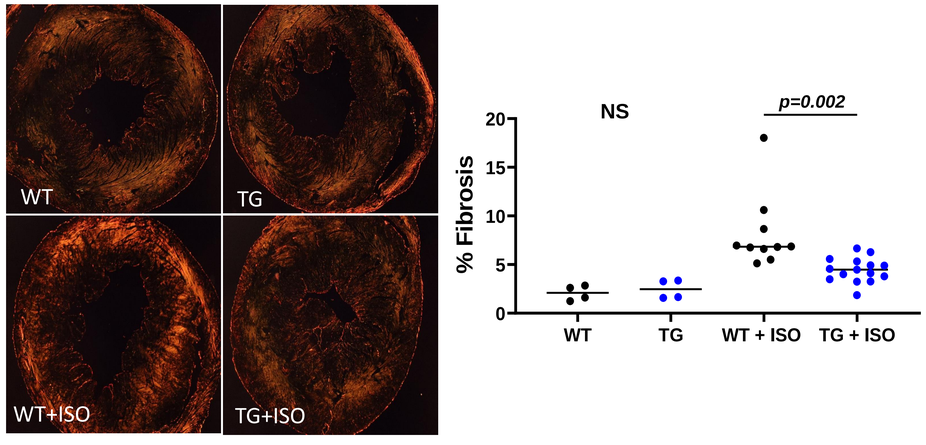

Fig. 4. Micrographs of Picrosirius red stained tissue sections observed under polarized light and data from ImageJ analysis. Ordinary one-way ANOVA with Tukey's multiple-comparisons post-test. n=12 (WT, 50/50 male/female) and n=16 (OE, 50/50, male/female). ISO – isoproterenol, NS – no significant, WT – wild type, TG – transgenic mice