Bidirectional cross-regulation between ErbB2 and β-adrenergic signaling pathways

Aims: Little is known about mechanisms of ErbB2 induction in the heart and its molecular sequela. Therefore, we investigated cardiac ErbB2 and uncovered a reciprocal relationship between ErbB2 and β1 and β2-adrenergic receptors (AR), supporting the role for β blockers in anthracycline and anti-ErbB2 cardiotoxicity prevention.

Methods and Results: We treated mice with β1 and β2-agonist isoproterenol and found that myocardial ErbB2 increased at 30 minutes and 24 hours. Inhibiting with specific β1- or β2-blockers did not completely reduce ErbB2 to baseline after isoproterenol indicating that either receptor stimulation can increase ErbB2. ErbB2 transfection of HEK293 cells up-regulated β2-AR and β2-AR transfection of HEK293 up-regulated ErbB2. Supporting these findings, isolated cardiomyocytes from cardiac-specific ErbB2-overexpressing (ErbB2tg) mice have amplified response to selective β2-agonist zinterol, whereas in ErbB2tg right ventricular trabeculae baseline force generation is markedly reduced with β2-antagonist ICI-118,551. Correspondingly, receptor binding assays and western blotting demonstrate that β2-ARs are markedly increased in ErbB2tg myocardium, and this effect is reversed by EGFR/ErbB2 inhibitor, lapatinib. Chronic treatment of mice with isoproterenol, with or without ErbB2 kinase inhibition, show that ErbB2 is protective and important in its transactivation role in the heart. These findings collectively suggest that ErbB2 levels are regulated by β-adrenergic signaling, and ErbB2 activity is important to cardioprotection in setting of β-adrenergic stress.

Conclusions: Here we show for the first time that ErbB2 and β-AR signaling are linked in a feedback loop in the heart, with β-AR activation leading to increased ErbB2 expression and activity, and increased ErbB2 activity regulating β2-AR expression. Since ErbB2 activity is important in situations of β-adrenergic stress, the use of β-blockers may reduce β-adrenergic stress induction of ErbB2 in the myocardium, so that the heart is not predisposed to adverse effects of anti-ErbB2 treatments during cancer therapy.

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