Abstract: Phosphoinositide 3-kinase gamma inhibition protects against anthracycline-induced cardiomyopathy by boosting cardiac autophagy

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Purpose: There are currently no efficient strategies to prevent chemotherapy-induced heart disease because of limited understanding of the underlying molecular mechanisms. We demonstrated previously that phosphoinositide 3-kinase γ (PI3Kγ) promotes maladaptive cardiac remodeling and that its inhibition prevents pressure overload-induced heart failure. Therefore, in this study, the cardioprotective effects of PI3Kγ inhibition were tested in a murine model of cardiomyopathy induced by the chemotherapeutic agent doxorubicin (DOX).

Methods: Mice expressing a kinase inactive PI3Kγ (PI3Kγ kinase-dead; KD) and their wild-type counterparts (WT) were exposed to DOX administration (a cumulative dose of 12 mg/kg, 4 mg/kg i.p. at 0, 7 and 14 days). Another group of WT mice was pre-treated with a PI3Kγ selective inhibitor (AS-605240; 10 mg/kg) before each DOX injection. Echocardiography was used to evaluate heart function 6 weeks after the first DOX injection. Cardiomyocyte apoptosis, collagen deposition, cardiac morphological alterations and signaling transduction were studied by TUNEL assay, Picrosirius Red staining, Electron microscopy and Western blot assay.

Results: Survival in the KD mice was significantly improved compared to the WT counterparts (% mortality WT DOX: 50%; KD DOX: 20%, *P<0.05), within 6 weeks from the first DOX administration. This was paralleled by preserved left ventricular systolic function in KD animals while WT mice suffered severe systolic impairment (% FS WT DOX: 20.5±1.3; KD DOX: 36.6±2.2, ***P<0.001). In line with these findings, cardiac atrophy, cardiomyocyte apoptosis and collagen deposition were significantly lower in KD than in WT hearts. Importantly, pharmacological inhibition of PI3Kγ with AS-605240 improved systolic function and survival in DOX-treated WT mice (% FS WT DOX: 23.4±3.7; WT+AS DOX: 38.9±1.9, ***P<0.001). Mechanistically, PI3Kγ was found to serve as a negative regulator of cardiomyocyte autophagy, through the phosphoAkt/mTOR signaling axis. Autophagy was more pronounced in DOX-treated KD hearts than in WT counterparts, as evidenced by increased expression of the autophagy marker LC3II. The enhanced autophagy was correlated with ultrastructural preservation of KD cardiomyocytes, while WT hearts displayed marked mitochondrial damage and vacuolization. Intriguingly, PI3Kγ inactivation fully prevented DOX-associated systolic failure and synergistically enhanced the anti-tumor activity of the drug, in both 4T1 and Her2/NeuT transgenic breast cancer models. This is beneficial from the role of PI3Kγ in regulating inflammation, as tumor-associated macrophage polarization from M1 (tumor suppression) to M2 (tumor promotion) was dampened by PI3Kγ inhibition.

Conclusion: Thus, targeting PI3Kγ may serve as a potential strategy to reduce the cardiotoxicity and enhance the anti-cancer effect of anthracycline.