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JDP2 AND ATF3 DEFICIENCIES DAMPEN MALADAPTIVE CARDIAC REMODELLING AND PRESERVE CARDIAC FUNCTION

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Rationale: c-Jun dimerization protein (JDP2) and activating transcription factor 3 (ATF3) are closely related basic leucine zipper proteins. Transgenic mice with cardiac expression of either JDP2 or ATF3 showed maladaptive remodeling and cardiac dysfunction. Surprisingly, JDP2 knockout (KO) did not protect the heart following transverse aortic constriction (TAC). Instead, the JDP2 KO mice performed worse than their wild type (WT) counterparts.

Objective: To test whether the maladaptive cardiac remodeling observed in the JDP2 KO mice is due to ATF3, ATF3 was removed in the context of JDP2 deficiency, referred as double KO mice (dKO).

Methods: Mice were challenged by TAC and followed by detailed physiological, pathological and molecular analyses.

Results: dKO mice displayed no apparent differences from WT mice under unstressed condition, except a moderate better performance in dKO male mice. Importantly, following TAC the dKO hearts showed low fibrosis levels, reduced inflammatory and hypertrophic gene expression and a significantly preserved cardiac function as compared with their WT counterparts in both genders. Consistent with these data, removing ATF3 resumed p38 activation in the JDP2 KO mice which correlates with the beneficial cardiac function.

Conclusions: Mice with JDP2 and ATF3 double deficiency had reduced maladaptive cardiac remodeling and lower hypertrophy following TAC. As such, the worsening of the cardiac outcome found in the JDP2 KO mice is due to the elevated ATF3 expression. Simultaneous suppression of both ATF3 and JDP2 activity is highly beneficial for cardiac function in health and disease.

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