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Letters to the editor

Response letter: "ATF3: A promoter or inhibitor of cardiac maladaptive remodeling"

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We thank Yang et al. for their important comments regarding our recent manuscript "ATF3-dependent cross-talk between cardiomyocytes and macrophages promotes cardiac maladaptive remodeling" by Koren et al. [1]. We completely agree with the authors that the discrepancy can be explained by the different models used in the studies. Our analysis is based on the phenylephrine (PE) infusion pressure overload model and ATF3 transgenic mice. The results from these studies are consistent with ATF3's role in promoting cardiac hypertrophy [1,2]. In contrast, studies using the transverse aortic constriction (TAC) model suggest a cardio-protective role for ATF3 [3–6].

The opposing functions of ATF3 observed in the two models may be explained by the timing and duration of ATF3 expression. In the PE model, ATF3 expression is induced transiently and involves the recruitment of macrophages to the heart in an ATF3 dependent manner [1]. In the TAC model, whereas the involvement of immune cells is yet to be determined, persistent ATF3 expression appears as cardioprotective [3]. However, prolonged adult cardiac ATF3 expression displays maladaptive cardiac remodeling [2]. So how can constitutive ATF3 expression lead to opposite outcome? Previously, we showed that ATF3 may switch between either an inhibition or an activation mode, depending on the cellular context and protein partner, i.e. ATF3 inhibits transcription as a homodimer from TPA response elements, but activates transcription as a heterodimer with CHOP10 [7]. Revealing whether ATF3 exhibits differential transcriptional activity in the TAC, ATF3-transgenic mice and PE models may provide an explanation for the resulting diverse outcomes.

Collectively, in mice models, ATF3 can play either a promoting or an inhibiting role in cardiac maladaptive remodeling processes. Significantly however, patients with dilated cardiomyopathy display high ATF3 expression levels [3]. Therefore, understanding the role of ATF3 in cardiac remodeling processes in different models is important for the development of novel therapeutic strategies to ameliorate cardiac function.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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