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Response to Letter Regarding Article, "Cardioprotective role of tumor necrosis factor receptor-associated factor 2 by suppressing apoptosis and necroptosis"

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To the Editor

We want to thank Drs. Jin-shan and Xue-bin for bringing up important questions regarding the clinical perspective of TRAF2 signaling in the heart. First, our study identified TRAF2 as a critical pro-survival factor by suppressing apoptosis and necroptosis in cardiomyocytes;[1] both forms of programmed cell death are critically involved in the pathogenesis of myocardial infarction and chronic heart failure.[2] We showed that ablation of TRAF2 predisposed the heart to pathological remodeling and heart failure by promoting death receptor (e.g., TNFR1) mediated apoptosis and necroptosis signaling.[1] TNFα production in the heart is significantly elevated in response to pathological stress, which induces cell death mainly through TNFR1. How TRAF2 is regulated in the heart in response the various pathological insults needs to be further investigated. Intriguingly, stimulation of TNFR2 triggers the degradation of TRAF2 through cIAP1-mediated K48-linked ubiquitination.[3] TRAF2 degradation triggered by TNFR2 would further increase TNFR1-mediated cell death by engaging the apoptotic and necroptotic signaling cascade more efficiently, as described in our study.[1] Other cellular stress, such as ultraviolet irradiation or translational inhibition, has been shown to promote TRAF2 degradation through Siah2-dependent ubiquitination. Moreover, recent studies suggest that TRAF2 activity is also tightly regulated by post-translational modifications such as phosphorylation, although the functional relevance of this regulatory mechanism in the heart is unknown. According to our model, reduced TRAF2 protein level or activity during pathological stress appears to be an important contributing factor to pathological remodeling and heart failure development.

Next, to assess the potential of TRAF2 as a therapeutic target, it will be important to examine whether activation of TRAF2 is sufficient to prevent ischemic cardiac cell death and the resultant pathological remodeling. Consistent with the results of our loss-of-function study, Mann and colleagues reported that transgenic mice with mild overexpression of TRAF2 in the heart had improved functional recovery and significantly less tissue injury after ischemia-reperfusion, when compared to littermate control mice.[4] In contrast,

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Disclosures

None.

transgenic mice expressing the dominant negative TRAF2 (E3 ligase inactive) showed the opposite effects.[4] These data indicate that activation of TRAF2 is sufficient to protect the heart from ischemic cardiac injury and dysfunction. Our *in vitro* data further showed that overexpression of the wild-type TRAF2 markedly inhibited TNFα-induced apoptosis and necroptosis in cardiomyocytes.[1] Therefore, the cardioprotective action of TRAF2 is primarily mediated through the inhibition of apoptosis and necroptosis. Further studies are needed to rigorously test TRAF2 as a therapeutic target in various experimental settings. It should be noted that overexpression of high levels of TRAF2 provoked cardiac hypotrophy and pathological remodeling.[5] Thus, overactivation of this pathway is detrimental to the heart, which might be the potential adverse effect associated with TRAF2.

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