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TNF Receptor-Associated Factor 6 (TRAF6) Mediating the Angiotensin-Induced Non-Canonical TGFβ Pathway Activation and Differentiation of c-kit+ Cardiac Stem Cells

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Abstract : Aims: TNF Receptor-Associated Factor 6 (TRAF6) acts as a multifunctional regulator of the Transforming Growth Factor (TGF)-β signaling pathway, and mediates Smad-independent JNK and p38 activation via TGF-β. This study was performed to test the hypothesis that TGF-β/TRAF6 is essential for angiotensin-II (Ang II)-induced differentiation of rat c-kit+ Cardiac Stem Cells (CSCs). Methods and Results: c-kit+ CSCs were isolated from neonatal Sprague Dawley (SD) rats, and their c-kit status was confirmed with immunofluorescence staining. A TGF-β type I receptor inhibitor (SB431542) or the small interfering RNA (siRNA)-mediated knockdown of TRAF6 were used to investigate the role of TRAF6 in TGF-β signaling. Rescue of TRAF6 siRNA transfected cells with a 3'UTR deleted siRNA insensitive construct was conducted to rule out the off target effects of the siRNA. TRAF6 dominant negative (TRAF6DN) vector was constructed and used to infect c-kit+ CSCs, and western blotting was used to assess the expression of TRAF6, JNK, p38, cardiac-specific proteins, and Wnt signaling proteins. Physical interactions between TRAF6 and TGFβ receptors were studied by coimmunoprecipitation. Cardiac differentiation was suppressed in the absence of TRAF6. Forced expression of TRAF6 enhanced the expression of TGF-β-activated kinase1 (TAK1), and inhibited Wnt signaling. Furthermore, TRAF6 increased the expression of cardiac-specific proteins (cTnT and Cx-43) but inhibited the expression of Wnt3a. Conclusions: Our data suggest that TRAF6 plays an important role in Ang II induced differentiation of c-kit+ CSCs via the non-canonical signaling pathway.

Keywords : cardiac stem cells, differentiation, TGF-β, TRAF6, ubiquitination, Wnt
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