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Abstract

Characterization of the Functions of TRAF4 in Xenopus Embryonic Development

By

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Tumor necrosis factor Receptor- Associated Factor (TRAF) protein family contains six members (TRAF1-6) which are identified by the presence of a conserved TRAF domain which is found in all TRAFs, as well as, a series of Zn Finger motifs and a RING domain. TRAFs mediate signaling downstream of TNF and Toll-like/Interleukin receptors by organizing signaling complexes which often affect major kinases, and lead to activation of transcription factors such as NFκB and AP1. The importance of TRAF-mediated signaling in immune, inflammatory and apoptotic responses has been well-established, except for TRAF4. When overexpressed, TRAF4 can associate with and modulate the signals of a number of receptors from the TNF-Receptor family, although the existence of such functions of TRAF4 at its normal physiological levels has not been confirmed by loss-function studies. On the other hand, loss of TRAF4 blocks migration of epithelial cells grown in culture. Targeted disruption of *traf4* gene in mice causes partial embryonic lethality and the surviving *traf4*-deficient mice exhibit impaired neural tube closure, axial, skeletal and tracheal malformations, indicating an essential role of TRAF4 in embryonic development. However, how TRAF4 functions in embryonic development is not known.

In this study, we characterized several functions of TRAF4 during embryonic development by using the frog, *Xenopus laevis* as our model system. We found that TRAF4 is necessary for neural crest formation and neural plate folding and that TRAF4 is a positive regulator of the BMP (Bone Morphogenetic Protein) signaling pathway. We also showed that TRAF4 is a new substrate for the ubiquitin ligase Smurf1, a BMP signaling pathway antagonist. Combining these findings, we established a model for how TRAF4 functions in the neural crest formation in Xenopus.

Moreover, we gathered data which suggest that TRAF4 affects Nodal signaling and mesoderm formation in Xenopus. We also investigated the roles of two other TRAFs, TRAF2 and TRAF6 in Xenopus embryonic development.

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