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Topic Category: 4106-ASIP Epithelial cell surface receptors and signaling

First Author: Shaik Rahaman
University of Maryland 3108 Skinner Building College Park, MD 20742
United States
Phone:
srahaman@umd.edu

First Author is a: Investigator
First Author is a member of: American Society for Biochemistry and Molecular Biology
First Author Degree:

Presentation Preference: Oral

Sponsor: Shaik Rahaman
Sponsor Phone: 2165349170
srahaman@umd.edu
Sponsor's Society: Biochemistry - American Society for Biochemistry and Molecular Biology (ASBMB) - Host Society
Keywords: 1. calcium signaling 2. Fibrosis 3. EMT

TRPV4 channels regulates matrix stiffness and TGFβ1-induced epithelial-mesenchymal transition

Shaik O Rahaman[1], Shweta Sharma[2], Rishov Goswami[1]. [1]University of Maryland, College Park, MD, [2]University of Maryland, college Park, MD

Epithelial-mesenchymal transition (EMT) has important functions in cellular processes including development, wound healing, oncogenesis, and fibrosis. Emerging data support a role for both a mechanical signal, and a biochemical signal, e.g., transforming growth factor β1 (TGFβ1), in EMT. Here, we report evidence showing that transient receptor potential vanilloid 4 (TRPV4), calcium-permeable channel and member of TRP superfamily, is the likely mediator of EMT in response to both TGFβ1 and matrix stiffness. Specifically, we found that: i) genetic ablation of TRPV4 blocked TGFβ1-induced EMT in normal mouse primary epidermal keratinocytes (NMEKs) as determined by changes in morphology and alterations of expression of EMT markers including E-cadherin (ECAD), N-cadherin (NCAD), and α-smooth muscle actin (α-SMA), and ii) TRPV4 deficiency prevented matrix stiffness-induced EMT in NMEKs over a pathophysiological range. Intriguingly, TRPV4 deletion in mice suppressed expression of mesenchymal markers, NCAD and α-SMA, in a bleomycin-induced murine skin fibrosis model. We found an increased co-localization of TRPV4 with NCAD, and decreased co-localization of TRPV4 with epithelial marker ECAD in skin tissues of bleomycin-treated wild-type mice compared to saline controls. Mechanistically, we found that: i) TRPV4 was essential for the nuclear translocation of YAP/TAZ (Yes-associated protein/transcriptional coactivator with PDZ-binding motif) in response to matrix stiffness and TGFβ1, ii) TRPV4 deletion inhibited both matrix stiffness- and TGFβ1-induced expression of YAP/TAZ proteins, and iii) TRPV4 deletion abrogated both matrix stiffness- and TGFβ1-induced activation of AKT, but not Smad2/3, suggesting a mechanism by which TRPV4 activity regulates EMT in NMEKs. Altogether, these data identify a novel role for TRPV4 in regulating EMT, and thus suggest that therapeutic targeting of TRPV4 may provide a selective approach to ameliorate the development of skin fibrosis and oncogenesis.

Support or Funding Information
AHA (13SDG17310007), Startup grant from University of Maryland, NIH (1R01EB024556-01), and NSF (CMMI-1662776) grants to SOR.