6 Matrix rigidity regulates a switch between TGF-β1-induced apoptosis and epithelial-mesenchymal transition.

Leight JL, Wozniak MA, Chen S, Lynch ML, Chen CS.
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Recommendations:

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RECOMMENDED

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Mounting evidence suggests that increased substrate/extracellular matrix (ECM) rigidity promotes tumorigenesis. Here, Leight and colleagues link this phenomenon mechanistically to transforming growth factor (TGF)-beta. On compliant substrates TGF-beta induces apoptosis, while on rigid substrates the cells undergo an epithelial-mesenchymal transition (EMT). The previously established Jekyll- and Hyde-like behavior of TGF-beta during tumor progression, therefore, appears to be controlled, at least in part, by matrix rigidity.

The cytokine TGF-beta can act as either a tumor suppressor or a tumor promoter, but the precise mechanism(s) that control the cellular response to TGF-beta are not well understood. Using classic epithelial model systems (Madin-Darby canine kidney [MDCK] and normal murine mammary gland [NMuMG] cells), Leight and colleagues demonstrate that changes in the cellular microenvironment play a prominent role in this process. By plating normal epithelial cells on fibronectin-coated polyacrylamide gels of varying elastic moduli, the authors show that TGF-beta induces an apoptotic response (i.e. nuclear fragmentation, caspase-3 activity) in cells plated on compliant substrates, whereas on rigid substrates, cells undergo EMT (i.e. elongated morphology, increased N-cadherin and Snail, mislocalized E-cadherin). The authors further demonstrate that matrix rigidity regulates phosphatidylinositol 3-kinase (PI3K)/Akt signaling, such that activation of PI3K reduces apoptosis on compliant gels, and inhibition of PI3K increases apoptosis on rigid gels.

This work highlights how mechanical cues from the tissue microenvironment interface with key signaling pathways in cancer (i.e. TGF-beta, PI3K/Akt), and reveals that epithelial cell responses to TGF-beta are highly sensitive to substrate rigidity.

Disclosures
None declared

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Comments:

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Abstract:

The transforming growth factor-β (TGF-β) signaling pathway is often misregulated during cancer progression. In early stages of tumorigenesis, TGF-β acts as a tumor suppressor by inhibiting proliferation and inducing apoptosis. However, as the disease progresses, TGF-β switches to promote tumorigenic cell functions, such as epithelial-mesenchymal transition (EMT) and increased cell motility. Dramatic changes in the cellular microenvironment are also correlated with tumor progression, including an increase in tissue stiffness. However, it is unknown whether these changes in tissue stiffness can regulate the effects of TGF-β. To this end, we examined normal murine mammary gland cells and Madin-Darby canine kidney epithelial cells cultured on polyacrylamide gels with varying rigidity and treated with TGF-β1. Varying matrix rigidity switched the functional response to TGF-β1. Decreasing rigidity increased TGF-β1-induced apoptosis, whereas increasing rigidity resulted in EMT. Matrix rigidity did not change Smad signaling, but instead regulated the PI3K/Akt signaling pathway. Direct genetic and pharmacologic manipulations further demonstrated a role for PI3K/Akt signaling in the apoptotic and EMT responses. These findings demonstrate that matrix rigidity regulates a previously undescribed switch in TGF-β-induced cell functions and provide insight into how changes in tissue mechanics during disease might contribute to the cellular response to TGF-β.

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