May 8th, 12:30 PM - 1:30 PM

Activation of the Epidermal Growth Factor Receptor (EGRF) is Required for CXCL12 Mediated ERK and Akt Signaling during Prostate Myofibroblast Phenoconversion

Jose A. Rodriguez-Nieves
University of Massachusetts Boston

Jill A. Macoska
University of Massachusetts Boston, Jill.Macoska@umb.edu

Activation of the Epidermal Growth Factor Receptor (EGRF) is required for CXCL12 Mediated ERK and Akt Signaling during Prostate Myofibroblast Phenoconversion

Jose A. Rodriguez-Nieves and Jill A. Macoska
The Center for Personalized Cancer Therapy and the Department of Biology, The University of Massachusetts, Boston.

Benign prostate hyperplasia (BPH), a condition of the prostate common in aging in men, is associated with urinary voiding dysfunction, or Lower Urinary Tract Symptoms (LUTS). Although inflammation and abnormal muscle contraction are known to be key players in the development of LUTS, tissue fibrosis may also be an important and previously unrecognized contributing factor. Tissue fibrosis arises from the differentiation of fibroblasts into myofibroblasts, which produce and secrete collagens and fibronectins that remodel the extracellular matrix (ECM). This differentiation process is usually accomplished by activation of the TGF-β/TGFβRII axis. However, in this study we report that the CXC-type chemokine, CXCL12, and its receptor, CXCR4, which are up-regulated with aging in the prostate, can drive this differentiation process as well. We have observed that CXCL12 can promote myofibroblast phenoconversion in the absence of exogenous TGF-β and can up-regulate the expression of myofibroblast genes (α-SMA, COL1, TGF-β) in primary and immortalized prostate fibroblasts. Recently we discovered that the activated CXCL12/CXCR4 axis signals through the EGFR and through downstream MEK/ERK and Akt pathways during myofibroblast differentiation, but not through Smad proteins. Smad proteins are the primary signaling proteins utilized by the TGFβRII. This suggests that CXCL12/CXCR4-mediated signaling events in prostate myofibroblast phenoconversion may proceed through non-canonical pathways that do not depend on TGF-β/TGFβRII axis activation or Smad signaling. Furthermore, we observed significant reduction in the activation of EGFR and ERK pathways when treating fibroblasts with an EGFR inhibitor as well as a pan-Metalloprotease inhibitor previous to chemokine treatment. Conversely, chemical inhibition of TGF-βRII or Smad3 activation did not prevent CXCL12-mediated EGFR, MEK/ERK activation or myofibroblast phenoconversion. Based on these findings, we hypothesize that EGFR activation by CXCL12/CXCR4 might be required for ERK and Akt activation during myofibroblasts conversion, and may be coupled to the shedding of extracellular ligands of EGFR by extracellular proteases.