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The endogenous cell-fate factor dachshund restrains prostate epithelial cell migration via repression of cytokine secretion via a CXCL signaling module

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Abstract

© 2015 American Association for Cancer Research. Prostate cancer is the second leading form of cancer-related death in men. In a subset of prostate cancer patients, increased chemokine signaling IL8 and IL6 correlates with castrate-resistant prostate cancer (CRPC). IL8 and IL6 are produced by prostate epithelial cells and promote prostate cancer cell invasion; however, the mechanisms restraining prostate epithelial cell cytokine secretion are poorly understood. Herein, the cell-fate determinant factor DACH1 inhibited CRPC tumor growth in mice. Using Dach1fl/fl/Probasin-Cre bitransgenic mice, we show IL8 and IL6 secretion was altered by approximately 1,000-fold by endogenous Dach1. Endogenous Dach1 is shown to serve as a key endogenous restraint to prostate epithelial cell growth and restrains migration via CXCL signaling. DACH1 inhibited expression, transcription, and secretion of the CXCL genes (IL8 and IL6) by binding to their promoter regulatory regions in chromatin. DACH1 is thus a newly defined determinant of benign and malignant prostate epithelium cellular growth, migration, and cytokine abundance in vivo.

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