A novel ACKR2-dependent role of fibroblast-derived CXCL14 in EMT and metastasis of breast cancer

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Background and Purpose
Cancer-associated fibroblasts (CAFs) constitute a major component of solid tumors and promote tumor growth, progression and metastasis. Our work has identified several novel CAF-derived factors that display distinct modes of action, including CXCL14. CXCL14 is an orphan chemokine that was shown to promote breast and prostate cancer growth through autocrine and paracrine mechanisms that involve induction of NOS1 in fibroblasts expressing CXCL14 (Augsten, PNAS, 2009, Augsten, Can Res, 2014). The aim of this study was to explore the clinical relevance of CXCL14 in breast cancer patients, the involvement of CXCL14 in tumor cell EMT, invasion and formation of lung metastasis and to identify a receptor for the orphan chemokine.

Expression in the tumor stroma is an independent marker of survival in breast cancer

CXCL14 expression in the breast tumor stroma, using RNA seq (left panel). Survival correlations of stromal CXCL14 was performed using Kaplan-Meier analysis (right panel). Multivariable analysis identifies stromal CXCL14 as an independent marker for prognosis (HR 1.877 (95% CI 1.123-3.138, p-value 0.016).

CXCL14 fibroblasts enhance breast cancer cell EMT and invasion in vitro and in vivo

CXCL14 fibroblasts enhance breast cancer cell migration

CXCL14-expressing fibroblasts enhance formation of lung metastasis in mice

ACKR2 is identified to mediate CXCL14 molecular signaling

Stable knockdown of ACKR2 abolish CXCL14 induced ERK signaling.

Breast cancer patients expressing high levels of CXCL14 and ACKR2 show enhanced EMT and adverse survival

Z-scores of EMT genes in TCGA dataset of breast cancer show enhanced EMT in patients with high expression of ACKR2 and CXCL14 (left panel). Patient with high expression of ACKR2 and CXCL14 has a decreased survival (right panel).

Paracrine effects of fibroblast-derived CXCL14 depend on ACKR2 and NOS1

Migration of MCF7 cells in response to NIH-ctr-cx or NIH-CXCL14 cells without (shCtr) or with stable knockdown of ACKR2 (left panel) or NOS1 (right panel).

Conclusion
Analyses of clinical samples demonstrate that CXCL14/ACKR2 signaling correlates with EMT in breast cancer and that stromal CXCL14 is an independent marker for poor prognosis. Tissue culture- and mouse experiments demonstrate EMT-inducing, pro-migratory and pro-metastatic effects of CXCL14 expressing fibroblasts. Furthermore, we show that expression of ACKR2 is required for CXCL14-induced molecular signaling and cellular responses. Collectively, data identify novel ACKR2-dependent clinically relevant roles of CXCL14 in breast cancer EMT, migration, invasion and metastasis.