CAFs strategies involved in cancer metastasis
Cancer associated fibroblasts as a potent cause for cancer metastasis

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Introduction
The beginning of a tumor consists in an in situ cell growing due to genetic alterations. The studies in recent years showed an increasing importance of tumor stroma in cancer development, by providing the favorable microenvironment to the tumor progression (“seed and soil” hypothesis). The most important cell type in tumor stroma are the cancer associated fibroblasts (CAFs), which is in charge of a wide range of functions promoting cancer development. CAFs are involved in metastasis through mechanisms by exerting motility signaling in cancer cells or themselves. Moreover, they are important crosstalk with many stromal components. The aim of this review is to analyze different metastasis-promoting mechanisms of CAFs to assess the possibility of it’s targeting to reduce patient death.

Motility stimulated by CAF-secreted paracrine factors

CAFs stimulate cancer cell’s motility, 1. CCL7 is recognized by adjacent cancer cell via CCR1 or CCR3, in order to induce cell motility ruffling, as shown in fluorescent CCL7-treated cell cocultures in comparison to non-treated ones. The crosstalk between cancer cell and CAF is via IL-1α secretion.

2. CAF-secreted FGFI induces Ras-MAPK-ERK1/2 signal downstream, resulting in the adhesion contacts disruption to facilitate cell migration.

3. Gal-1 affects to the integrin-β1 overexpression in order to improve cell adhesion with glycosylated ECM or cell surface components.

Exosome-mediated cell motility

CAFs also secrete MMPs, which degrade a variety of structural ECM components: collagen, fibronectin, laminin, etc. CAF-secreted MMP 2 and MMP 9 are associated with basement membrane collagen type IV degradation; while MMP 2 is also involved in collagen overexpression as same as MMP 3.

The ECM provides biomechanical and biochemical signals. The disruption of matrix-cellular homeostasis could enhance cancer progression and metastasis. CAF can exert ECM remodeling by ECM structure and stiffness modification through collagen (main ECM component) overproduction and crosslinking to extracellular matrix. The different states of fiber arrangement correspond to different tissue alteration. The higher ECM stiffness affects the mechano-sensing properties and favors cancer cell oriented migration (metastasis), by using the collagen fibers as tracts (Rho-ROCK signaling).

CAFs are also involved in ECM remodeling through cytokine signaling (specifically IL-6), which signals through GP130-JAK2. The focal Rho-ROCK pathway gives place to actomyosin contractility through MLCK phosphorylation, Rho and ROCK activation generates actomyosin contractility in both stromal and cancer cells, which enhances cytokine-ECM communication through membrane integrins. At all, Rho pathway generates contractile force in stromal fibroblasts to remodel the extracellular matrix and create tracks for collective migration of carcinoma cells.

Conclusions
• CAFs are involved in many metastasis-promoting functions via different mechanisms. It’s high diversity of effects shows the need of further investigation and more molecular mechanisms exploring, such as the new insights in their metastatic niche establishment.
• CAFs act by regulating motility of adjacent cancer cells, through secretion of paracrine and autocrine factors, inducing motility and more contacts formation.
• They exert biomechanical effects on the ECM by inducing their own cytoskeleton changes leading paths for cancer cell group migration
• Important CAF crosstalk with the microenvironment

Future perspectives
• Inhibition of CAFs also accelerates cancer progression precaution in anti-CAFs therapies
• Specific CAF pathways targeting can be effective, but complicated due to multiple interactions
• Future treatment can focus in reverting to normal phenotype restoring to normal stroma

References
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• Mekh, Leskin, & Cukiersman, 2015
• Paton & del Pozo, 2013
• Choi & Heffman, 2014
• Luza et al., 2012
• Jung et al., 2010
• CCL7: chemokine (C-C motif) ligand 7
• CCR: chemokine receptor
• IL-1α: interleukin 1α
• FGFI: fibroblast growth factor 1
• MAPK-ERK: mitogen activated protein kinase-extracellular signal-regulated kinase
• Gal-1: galactosamine 1
• FAK: focal adhesion
• ECM: extracellular matrix
• MMPs: matrix metalloproteinase
• IL-6: interleukin 6
• MLC: myosin light chain
• CaV1: Cav 1
• LOX: lysyl oxidase

ECM collagen fiber alignment and modulation

Rho-dependent actin cytoskeleton contractility of CAFs

Exosomes are multivesicular bodies secreted by CAFs, which have been proved to participate in many cancer-promoting effects, due to their content diversity. CAF-secreted Cd81 exosomes are able to induce cancer cell secreted Wnt1 protein association and maturation. The interaction of Wnt1 with Fzd6 affects the subsequent PCP complexes and disperses them in an asymmetrical way in the leading cell protrusions. As shown in cancer cell cocultures, the exosome treated cells presented protrusion formation and Fzd6 localization to the leading edge, favoring cell migration.

Fig. 1 Effects of different paracrine factors on cancer cell motility. Adapted from Jung et al., 2010

Fig. 2 Exosome-mediated cell motility. Adapted from Fakhraie, 2013

Fig. 3 ECM collagen fiber alignment and modulation. Adapted from Parton & del Pozo, 2013

Fig. 4 Rho-dependent actin cytoskeleton contractility of CAFs. Adapted from Helfman, 2013