REVIEW

CAF 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.

- CCL7: cemokine ligand 7
- CCR: chemokine receptor
- IL-1a: interleukin 1a
- FGF1: fibroblast growth factor 1
- MAPK-ERK: mitogen activated protein kinase-extracellular signal-regulated kinase
- Gal-1: galectin 1
- Fzd6: frizzled 6
- ECM: extracellular matrix
- MMPs: matrix metalloproteinase
- IL-6: interleukin 6
- MLC: myosin light chain
- Cav1: caveolin-1
- LOX: lysyl oxidase

Motility stimulated by CAF-secreted paracrine factors

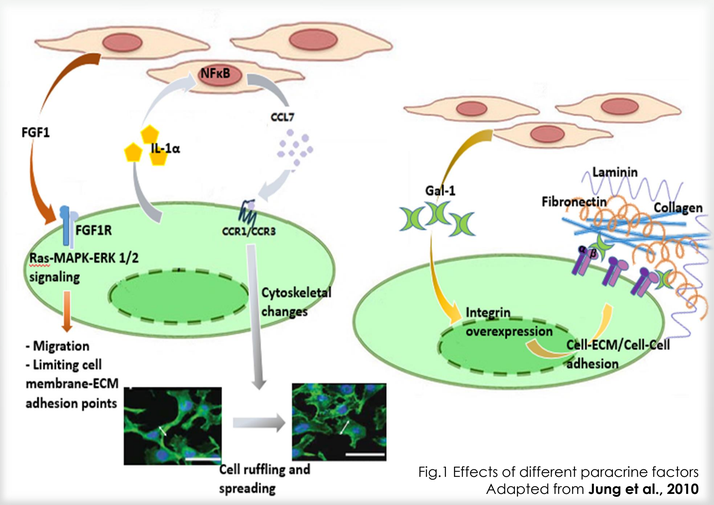

Fig.1 Effects of different paracrine factors
Adapted from **Jung et al., 2010**

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 no treated ones. The crosstalk between cancer cell and CAF is via IL-1α secretion.

2. CAF-secreted FGF1 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 glycolated ECM or cell surface components.

Exosome-mediated cell motility

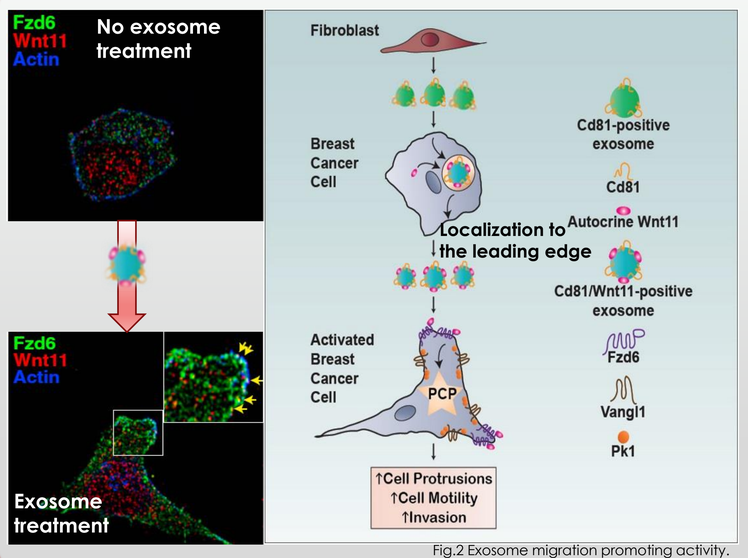

Fig.2 Exosome migration promoting activity.
Adapted from Luga et al., 2012

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 Cd-81 exosomes are able to induce cancer cell secreted Wnt11 association and its maturation. The interaction of Wnt11with Fzd6 affects the subsequent PCP complexes and disposes 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.

ECM collagen fiber alignment and modulation

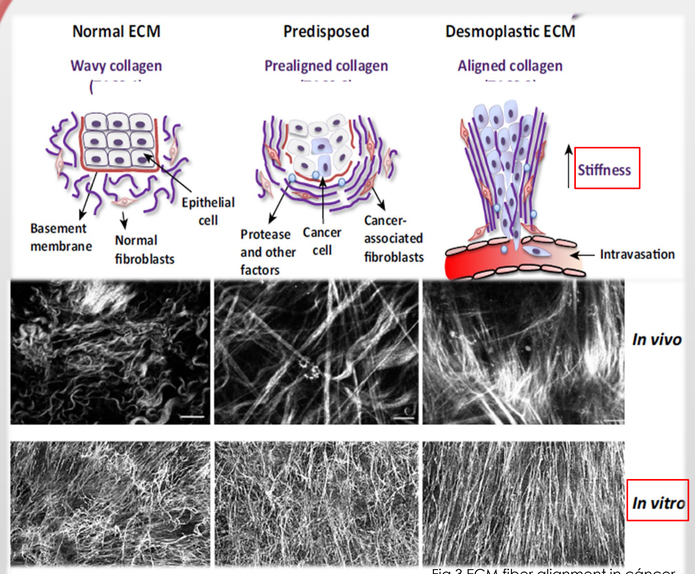

Fig.3 ECM fiber alignment in cáncer
Adapted from **Malik, Lelkes, & Cukierman, 2015**

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 elastin.

The different states of fiber arrangement correspond to different tissue alteration.

The higher ECM stiffness affects the mechanosensing properties and favors cancer cell orientated migration (metastasis), by using the collagen fibers as trails (Rho-ROCK signaling).

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

Rho-dependent actin cytoskeleton contractility of CAFs

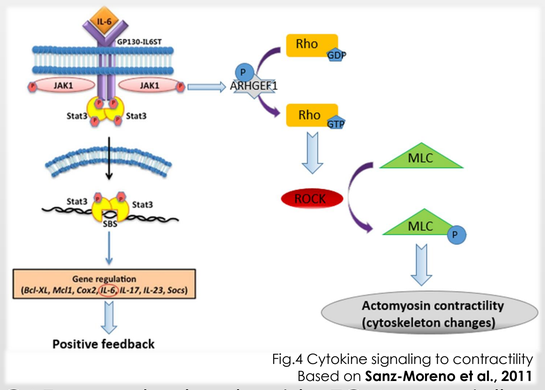

Fig.4 Cytokine signaling to contractility
Based on **Sanz-Moreno et al., 2011**

CAFs are also involved in ECM remodeling through cytokine signaling (specifically IL-6), which signals through GP130-IL6ST. The final Rho-ROCK pathway gives place to actomyosin contractility through MLC2 phosphorylation.

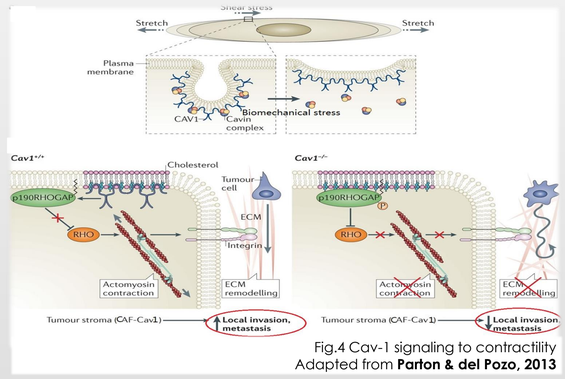

Fig.4 Cav-1 signaling to contractility
Adapted from **Parton & del Pozo, 2013**

Cav-1 is separated from the cavin complex by the stromal mechanical stress, which favors the recruitment of p190RHOGap disabling its inhibition on Rho.

Rho and ROCK activation generates actomyosin contractility in both stromal and cancer cells, which enhances cytoskeleton-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

- Han, Zhang, Jia, & Sun, 2015
- Malik, Lelkes, & Cukierman, 2015
- Parton & del Pozo, 2013
- Choi & Helfman, 2014
- Luga et al., 2012
- Jung et al., 2010