Cancer-associated fibroblasts, key drivers of tumorigenesis

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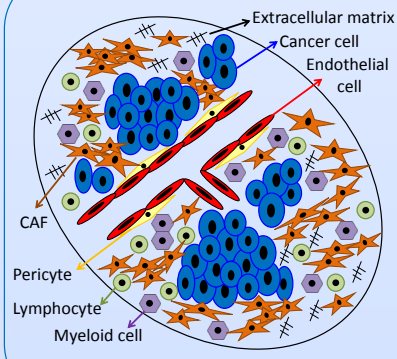
1. Aims

- To describe cancer-associated fibroblasts (CAFs) in the context of the tumor microenvironment.
- To state the essential role of CAFs on tumor progression, invasion and metastasis by acting as key suppliers of tumorigenic molecules, signaling cancer cells in a paracrine fashion.
- To review current preclinical and clinical trials on anti-cancer immunotherapy targeting CAFs or their crosstalk with cancer cells.

2. The tumor microenvironment

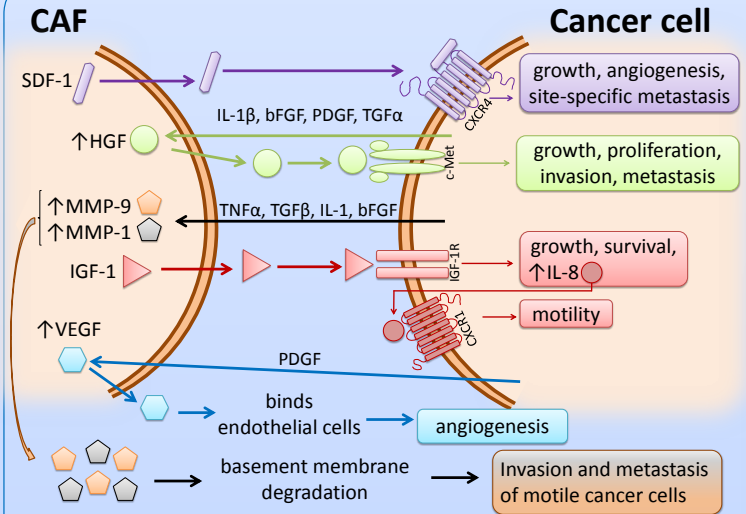


Main components of the tumor stroma (adapted from[2])

Cancer cells subsist in the **tumor microenvironment**, i.e., a local network of extracellular matrix components and stromal cells, the most abundant of which are **CAFs**[1].

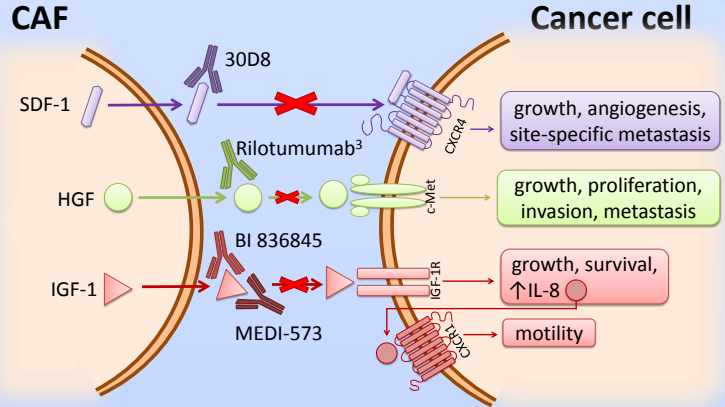
CAFs behave similarly to normal activated fibroblasts, but, unlike these, **their active state seems to be permanent**. They interact with tumor cells either through **direct contacts** or **paracrine signaling**[1,2].

3. CAFs – Cancer cells crosstalk



CAFs communicate with cancer cells in a **loop fashion** and provide them with **tumorigenic molecules**, including growth factors (HGF, IGF-1) and cytokines (SDF-1). They also **release factors acting on other cells** (e.g. VEGF binding endothelial cells) **and matrix metalloproteinases** (MMP-1, MMP-9), essential for cancer cell invasion and metastasis[1,2].

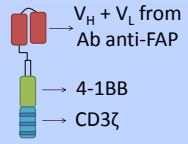
4. Therapy: Neutralization of CAFs-secreted factors



This strategy impairs the crosstalk between CAFs and cancer cells. By neutralizing a CAF-secreted factor using an antibody, the pathway it activates on cancer cells is blocked. It is a novel therapy, but already on clinical trials.

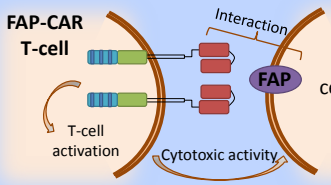
5. Therapy: Cytotoxic responses against CAFs (FAP⁺ cells)

T-cells with a chimeric antigen receptor (CAR)



Structure of a CAR

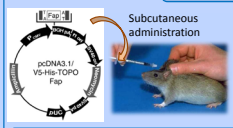
CARs are expressed on T cells. They combine the **specificity of antibodies** with the **effector function of T-cells**[4].



Unlike most cell types, CAFs are FAP⁺

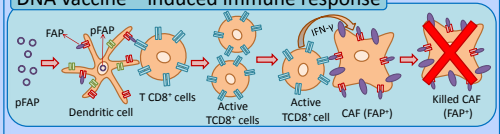
Mice are transfected with FAP-CAR T-cells. The domains V_H and V_L of the CAR recognize FAP⁺ cells specifically and directly. Next, T cells are activated and mediate cytotoxic responses towards FAP⁺ cells[4].

DNA vaccine



DNA vaccines against CAFs contain **pFAP** (a plasmid bearing the cDNA encoding the entire murine FAP)[5].

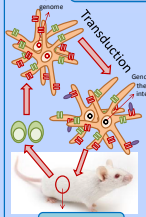
DNA vaccine – induced immune response



Upon vaccination, pFAP is released and enters murine dendritic cells. There, its protein product (FAP) is processed and presented by MHC-I, activating a TCD8⁺ cytotoxic response against FAP⁺ cells (mainly CAFs).

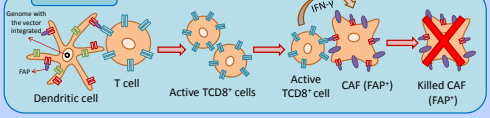
Promising results from preclinical data[5] → Lower primary tumor growth, Increased survival, Decreased metastasis

Dendritic cell vaccine (DC vaccine)

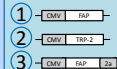


DCs derived from mice-extracted monocytes are transduced with a viral vector encoding FAP and/or TRP-2. Readministration of these DCs into mice triggers *in vivo* TCD8⁺-cell mediated killing of FAP⁺ cells (mainly CAFs) and/or TRP-2⁺ cells (some cancer cells)[6].

In vivo



Constructs transducted into DCs in preclinical trials[6]



Construct 3 had higher antitumor activity than construct 2 → New therapies should **focus on co-targeting tumors and their stroma**.

6. Conclusions

- Cancer progression is a dynamic process in which CAFs play an essential role.
- CAFs are the major source of tumorigenic factors not secreted (or at low rates) by cancer cells, including IGF-1, HGF, VEGF, SDF-1, MMP-1 and MMP-9. They signal tumor cells towards progression, invasion and metastasis.
- Using immunotherapy to target the tumor stroma has recently emerged as a novel anti-cancer therapeutic strategy. In this line, there are two approaches targeting the cross-talk between cancer cells and CAFs:
  - Neutralization of CAFs-secreted tumorigenic factors, aiming to block the pathways they trigger.
  - Enhancement of cytotoxic immune-responses towards CAFs in order to kill them.

7. References

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