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
- 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.
- 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.

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.

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)
- 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).

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