TUMOUR MICROENVIRONMENT AND PROTEOMICS

High grade serous ovarian cancer (HGSOC) and triple negative breast cancer (TNBC) have limited treatment options, as only few therapeutic strategies effectively kill cancerous cells and patients often develop resistance to standard therapies. The tumour microenvironment actively supports cancer pathology and is populated by a variety of cell types that also offer alternative routes for therapy. Our research focuses on cancer-associated fibroblast (CAFs), as we and others have shown that they play a major role in modulating cancer pathology. CAFs strongly influence the function of cancer and other stromal cells by secreting extracellular matrix (ECM) components, ECM modifiers, soluble factors and extracellular vesicles (EVs). We aim to understand the molecular mechanisms through which CAFs support cancer; and envisage targeting CAFs in combination with cancer cells as a promising strategy to hamper cancer growth and metastasis.

Our research primarily focuses on the role of CAFs in HGSOC and TNBC. These tumours contain vast regions of stroma, which are densely populated by CAFs, while CAFs were shown to play active roles in the progression of both diseases. Importantly, HGSOC cells and TNBC cells have few recurrent mutations, therefore limiting the availability of targeted therapies against cancer cells. As such, CAFs offer a valid alternative therapeutic opportunity in these tumour types (Santi et al., 2018). Proteomics, Domen et al., 2021, Cancer. We aim to decipher how CAFs create a tumour-promoting microenvironment and how we can block this process to make the tumour microenvironment unfavourable to cancer growth and tumours more vulnerable to therapeutic treatments; our overarching goal is to determine strategies that target CAFs for therapy.

CAFs can originate from normal fibroblasts resident at the site where the primary tumour develops. When a tumour starts developing, normal fibroblasts become activated. This activation induces extensive reprogramming of gene expression and protein levels, such that CAFs become able to secrete a plethora of soluble factors and ECM components that influence the function of surrounding cells and actively support cancer progression (Figure 1). CAFs were also shown to secrete EVs whose cargos could aid tumour progression by supporting cancer cell growth and invasion (Kuguratski et al., 2022, Science Signaling; Santi et al., 2018). Proteomics. While CAFs are the results of the reprogramming of normal cells, we aim to find ways to revert CAFs to a normal-like phenotype that does not support cancer and that improves response to therapies.

To understand how to target CAFs in tumours, it is essential that we understand how CAFs make the tumour microenvironment pro-tumorigenic and pro-metastatic, and how the molecular mechanisms that sustain CAF function. Our major interest is the role of cell metabolism (Kay et al., 2021, Front Oncol; Kay & Zanivan, 2021, Proteomics; Diaz et al., 2017, J Cell Sci; van der Reest, Lilla et al., 2018, Nature Metabolism). We are now further investigating the potential of targeting acetyl-CoA production in CAFs in cancer.

CAFs & metabolism

Metabolic alterations are a well-established hallmark of cancer. In the last few years, it is also important that in addition to the metabolism of cancer cells, also the metabolism of stromal cells is an important regulator of cancer pathology. We have also shown that the ECM proteins secreted by CAFs play an active role in the metastatic dissemination through facilitating the binding of the cancer cells to the blood vessels (Reid et al., 2017, JEMBO J). We have now found that CAFs also influence EC function by transferring functional proteins through EVs. In particular, CAFs could transfer plasma membrane and membrane-bound proteins to the surface of the endothelial cells. This process confers the ability of the endothelium to interact with other cell types, such as monocytes, which influence aspects of tumour progression, including antitumor immunity and metastasis. We therefore discovered another way through which CAFs make ECM pro-tumorigenic and we are investigating this aspect further (Santi et al., 2023; BiolRm).

The vasculature of solid tumours is often responsible for the progression and aggressiveness of disease. Initially, tumours recruit blood vessels to obtain nutrients and oxygen to sustain proliferation. Later on, the tumour vasculature becomes leaky and provides a route for cancer cells to escape and form distant metastases. Endothelial cells (ECs) line the inner layer of the vessel wall and regulate the functionality and growth of the vessel. Tumour blood vessels are typically embedded within a CAF-rich stroma, such that ECs directly interact with CAFs or are exposed to the factors that they secrete. Our group previously showed that CAFs secreted proteins that influenced blood vessel growth and functionality via altering endothelial cell behaviour (Hernandez-Fernaud, Rujengir et al., 2017, Nat Commun; Kuguratski et al., 2019, Sci Sign). We have also shown that the ECM proteins secreted by CAFs played an active role in the metastatic dissemination through facilitating the binding of the cancer cells to the blood vessels (Reid et al., 2017, JEMBO J). We have now found that CAFs also influence EC function by transferring functional proteins through EVs. In particular, CAFs could transfer plasma membrane and membrane-bound proteins to the surface of the endothelial cells. This process confers the ability of the endothelium to interact with other cell types, such as monocytes, which influence aspects of tumour progression, including antitumor immunity and metastasis. We therefore discovered another way through which CAFs make ECM pro-tumorigenic and we are investigating this aspect further (Santi et al., 2023; BiolRm).

News

This year, Britt Sterken has been awarded a DMM Conference Travel Grant Company of Biologists to present her work on the role of CAF metabolism in triple negative breast cancer at the EACR Cancer Metabolism meeting in Bilbao. She has also presented her work at the Cancer Metabolism Showcase and Workshop Virtual meeting. Emily Kay has also presented a poster on the immune-regulatory roles of CAFs in breast cancer at the EACR Cancer Metabolism meeting in Bilbao.

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CAFs – tumour blood vessel interaction

Figure 1 CAFs influence the behaviour of cancer, immune and endothelial cells

Cartoon showing that cancer associated fibroblasts (CAFs) with different phenotypes populate the tumour microenvironment and that CAFs secrete plethora of factors that influence the function of other cell types in the tumour.

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