High grade serous ovarian cancer (HGSOC) and triple negative breast cancer (TNBC) have limited treatment options for the patients, because only few targeted therapies effectively kill cancer cells. However, cancer cells are embedded within a stroma populated by different cell types, which offer novel opportunities for therapy. Among them are cancer associated fibroblasts (CAFs), which our lab and other groups have shown to play major roles to support cancer progression. 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). Our research focuses on understanding the molecular mechanisms through which CAFs promote cancer; we envisage that targeting CAFs in combination with cancer cells is 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 is densely populated by CAFs (Figure 2), while CAFs have been 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. Proteomics 2018). We aim to decipher how CAFs create a pro-tumorigenic and pro-metastatic microenvironment and how we can block this process; our overarching goal is to determine strategies to target CAFs for therapy.

We study how CAFs support cancer progression and the spread of metastases by directly influencing the behaviour of the cancer cells and of the tumour vasculature. In many solid tumours, the vasculature is responsible for the progression of the disease. Initially, tumours recruit blood vessels to obtain nutrients and oxygen to sustain the proliferation of the cancer cells. Later on, the tumour vasculature becomes leaky and provides a route for the cancer cells to escape and form distant metastases.

CAFs can originate from the normal fibroblasts resident at the site where the primary tumour develops. In the presence of cancer cells, 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 actively support cancer progression. CAFs have also been shown to secrete EVs, whereby their cargos can support tumour progression by supporting cancer cell growth and invasion (Santi et al. Proteomics 2018).

To understand how to target CAFs in tumours, it is crucial that we understand how CAFs make the tumour microenvironment pro-tumorigenic and pro-metastatic; that is how the molecular mechanisms that sustain these CAF functions. Our major interests are the roles of cell metabolism and extracellular vesicles secreted by CAFs. As CAF models for our research, we mostly use CAFs that we isolate from tumour tissues that patients kindly donate for research purposes (Hernandez-Fernaud, Ruengeler et al. Nat Commun 2017; Kugeratski et al. Sci Signal 2019). We have also shown that the ECM proteins secreted by CAFs play an active role in the metastatic dissemination by facilitating the binding of the cancer cells to the blood vessels (Reid et al. EMBO J 2017). Our ongoing work has found that CAFs influence EC behaviour also through the transfer of functional proteins mediated by EVs. We are currently investigating this process and its impacts on breast cancer progression.

CAFs & metabolism

Metabolic alterations are well-established hallmarks of cancer. It has been known for a long time that the metabolism of the cancer cells plays crucial roles in promoting and supporting cancer. In the last few years, it has emerged that also the metabolism of stromal cells is an important regulator of cancer. Several works have shown that cancer cells can hijack CAF metabolism by inducing CAFs to secrete metabolites that are necessary for their own growth. Instead, we have found that CAF metabolism also supports hallmarks of CAFs important for tumour progression and metastatic dissemination. Exploiting state-of-the-art mass spectrometry technologies to measure the proteome and metabolome of CAFs and corresponding normal fibroblasts isolated from breast cancer patients, we have found that increased levels of the amino acid proline are key to support the production of pro-tumourigenic ECM by CAFs. In particular, increased proline availability is necessary for the production of collagen, which is highly abundant ECM components with an extremely high content of proline residues. Moreover, we showed that targeting proline synthesis via inhibiting PPARγ, an enzyme essential for the production of proline from glutamine, reduced tumour growth and strongly inhibited metastatic spread in vivo (models of breast cancer (Figure 2)) (Kay et al. BioRxiv 2020). We are investigating further the potential of targeting proline metabolism in cancer.

News

This year, Britt Sterken has joined our team as post-doctoral fellow funded by Breast Cancer Now and she works on how cell metabolism supports pro-tumourigenic and pro-metastatic hallmarks of CAFs in TNBC. Teresa Glauser has joined the group to do her PhD and she works on the role of metabolism in the generation of pro-tumourigenic extracellular matrix in HGSOC.

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