In solid tumours, cancer cells are embedded within a stroma populated by different cell types. Cancer associated fibroblasts (CAFs) are a major non-neoplastic stromal cell population, which our lab and other groups have shown play crucial roles in cancer progression. In fact, CAFs have a unique ability to establish crosstalk signaling with cancer cells and other stromal cells by secreting soluble factors, extracellular matrix (ECM) components and modifiers, and physically interacting with surrounding cells. Thus, our research focuses on CAFs; we envisage that targeting CAFs rather than, or in combination with, cancer cells is a promising strategy to hamper cancer growth and metastasis.

Our research primarily focuses on the role of CAFs (Fig. 1) in breast and high-grade serous ovarian (HGSO) cancers because these tumours contain a sizeable proportion of stroma, which is heavily populated by CAFs. Furthermore, CAFs have been shown to play key roles in the progression of both diseases. Importantly, ovarian cancer cells have few recurrent mutations and this limits the availability of targeted therapies against the cancer cells. Therefore, CAFs offer a valid alternative therapeutic opportunity in this tumour type. We aim to decipher how CAFs contribute to tumour progression and metastasis; our overarching goal is to determine strategies to target these cells for therapy.

We study how CAFs promote invasive behaviour of the cancer cells and support their uncontrolled growth, and how CAFs facilitate tumour growth and the spread of metastases by altering the tumour vasculature. Endothelial cells (ECs) are a key cellular component of the blood vessels; they line the inner layer of the vessel wall and regulate the functionality and growth of the vessel. 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, the normal fibroblasts become activated. This activation induces extensive reprogramming of gene expression and protein levels, such that CAFs become highly contractile and secrete plethora of soluble factors and ECM components that promote the progression of cancer (Santi et al. Proteomics 2018; 18:e1700167). It is therefore crucial to better understand the mechanisms that lead to and sustain CAF activation, 2) how CAFs alter the tumour microenvironment, and 3) how the surrounding stromal and cancer cells react to these changes. Our group has a strong expertise in mass spectrometry (MS)-based proteomics (van den Biggelaar et al., Blood 2014; 123:e22-e36; Patel et al., Mol Cell Proteomics 2015; 14:621–34; Diaz et al. J Cell Sci 2017; 130:697–711; Hernandez-Fernaud, Ruengeler et al., Nat Commun 2017; 8:14206). We are currently investigating the role of stromal CLIC3 in HGSO cancers to assess its potential as an effective target for this type of cancer, particularly for blocking metastasis, which is the major cause of patient lethality.

CAFs & hypoxia

Intratumoral hypoxia, CAFs release factors that promote blood vessel growth. (Cartoon by Alice Santi)

Figure 1

Immunofluorescence staining of breast cancer CAFs. Cyan = cell nuclei; magenta = vimentin filaments; grey = actin cytoskeleton

Figure 2

When there is intratumoral hypoxia, CAFs release factors that promote blood vessel growth. (Cartoon by Alice Santi)