Cancer associated fibroblasts: heterogenous modifiers of treatment response

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The presence of stromal elements has long been known to correlate with the response of solid tumours to a range of therapies, and the molecular mechanisms involved are subject to intense study. Cancer associated fibroblasts (CAFs) are commonly the most numerous cellular components of the tumour stroma, particularly in breast cancers, and have consequently attracted detailed investigation. These studies have revealed extraordinary complexity in expression profile and function within CAF populations, which varies depending on the molecular characteristics of the cancer cells and between individuals (1-3). A new study by Hofer *et al.* (4) provides further insights into the diversity of CAFs and the mechanisms behind their impact on the response of breast cancers to cytotoxic chemotherapies.

The repertoire of CAF subtypes has been extensively defined in breast cancer in many recent studies but a standardised classification system for CAFs has yet to be adopted, rather multiple studies have identified distinct CAF subsets based on their own gene expression profiling data. Interestingly, these profiles vary between and within the different types of invasive cancers. For example, CAFs in invasive ductal carcinoma no special type cancers express higher levels of prolyl 4-hydroxylase (P4H), platelet-derived growth factor receptor alpha (PDGFRα), and chondroitin sulfate proteoglycan (NG2), while CAFs in invasive lobular carcinoma are enriched for fibroblast activation protein alpha (FAP), fibroblast-specific protein-1 (FSP1), and platelet-derived growth factor receptor beta (PDGFRβ) (5). However, these bulk characteristics mask CAF heterogeneity within the molecular subtypes or within individual cancer cases. For example, Sebastian *et al.* characterised CAF heterogeneity within triple negative breast cancers (TNBC) and identified three key CAF subsets (6). Myofibroblastic CAFs (myCAFs) express alpha-smooth muscle actin (αSMA) and secrete dense stromal matrix that potentially forms a barrier limiting infiltration of T cells and chemotherapeutic agents to the tumour thereby promoting immune evasion and therapy resistance. Inflammatory CAFs (iCAFs) express inflammatory cytokines that recruit pro-tumour and restrict anti-tumour immune components contributing to immunosuppression. Antigen-presenting CAFs (apCAFs) are characterised by high expression of MHCII that potentially activates anti-tumour immunity by promoting T cell activation and polarisation of macrophages. Bartoschek *et al.* identified alternative CAF classes that showed differential spatial distributions within tumours: matrix CAFs, expressing high levels of ECM components that were primarily located at the invasive front of tumours; vascular CAFs, expressing vascular regulatory genes and situated close to the vasculature; and developmental CAFs, expressing stem cell markers and developmental genes (2). In a comprehensive

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study, Costa *et al.* identified 4 distinct CAF subpopulations, which they termed CAF-S1 through to S4, based on expression of 6 fibroblast markers: integrin β1 (CD29), FAP, αSMA, PDGFRβ, FSP1 and caveolin 1 (CAV1) (1). Of these, only CAF-S1 and CAF-S4 were positive for the expression of αSMA, which is a characteristic feature of myofibroblasts. Luminal A subtype tumours were relatively enriched with the CAF-S2 sub-population ($CD29^{Low}$ FAP^{Neg} $FSP1^{Neg-Low}$ αSMA^{Neg} $PDGFR\beta^{Neg}$ $CAV1^{Neg}$), while TNBCs were enriched in CAF-S1 ($CD29^{Med}$ FAP^{Hi} $FSP1^{Low-Hi}$ αSMA^{Hi} $PDGFR\beta^{Med-Hi}$ $CAV1^{Low}$) and CAF-S4 ($CD29^{Hi}$ FAP^{Neg} $FSP1^{Low-Med}$ αSMA^{Hi} $PDGFR\beta^{Low-Med}$ $CAV1^{Neg-Low}$), and human epidermal growth factor receptor 2 (HER2) positive cancers were enriched in only CAF-S4. However, there is even heterogeneity within these CAF classes, since RNA sequencing of CAF-S1 cells further identified that these consist of several sub-clusters, including iCAF and extra-cellular matrix producing myCAF (ECM-myCAF) components (4,7), thereby combing elements of both CAF classifications described earlier.

The presence of certain CAF subsets also correlates with outcomes generally, or sometimes after specific therapies hinting at mechanistic roles in resistance pathways. For example, the ratio of FSP1-positive CAFs to podoplanin-positive CAFs was associated with improved progression-free and overall survival (8). Only a minority of studies have taken the next step of delineating the molecular mechanisms responsible for the influence of CAFs on cancer cell response to therapy; a study by Su *et al.* represents a notable example (9). A CAF subset positive for CD10/GPR77 was identified in cancers showing resistance to neoadjuvant chemotherapy. Co-culture of breast cancer cells with CAFs isolated from chemo-resistant biopsies demonstrated therapy resistance to docetaxel. Mechanistically, CD10/GPR77 positive CAFs were found to protect and expand the chemotherapy-resistant cancer stem cell population through secretion of interleukin-6 (IL6) and interleukin-8 (IL8). Chemotherapy resistance has also been shown to be driven by secretion of interferon β1 from CAFs, specifically in claudin-low TNBCs (10). Zhang *et al.* reported that CAFs secrete lactate, which leads to histone lactylation repressing ferroptosis, a type of iron dependent cell death resulting in doxorubicin resistance in TNBC (11).

In the current study (4), Hofer *et al.* assessed the cellular composition of the stroma in samples from 52 chemo-sensitive and 36 chemo-resistant TNBCs both pre- and post-chemotherapy by RNA sequencing. Interestingly, they found that chemotherapy drives changes in the composition of the TME in chemo-sensitive patients, with a substantial decrease in the proportion of ECM-myCAFs in favour of iCAFs—an effect that was not observed in resistant tumours. The authors assessed the importance of this using a 3D microfluidic based tumour on chip (ToC) technology, to mimic the tumour microenvironment and recapitulate *in vivo* drug responses. Using ToC, breast cancer cells (MDA-MB-231 and MDA-MB-468) were cocultured with primary ECM-myCAFs isolated from patients in a 3D biomimetic collagen matrix in appropriate ratios to mimic tumours. Addition of ECM-myCAFs significantly enhanced cancer cell survival after chemotherapy treatment (doxorubicin). However, culturing breast cancer cells with the CAF-S4 subset did not improve cell survival after chemotherapy, demonstrating the therapy resistance behaviour is specific to ECM-myCAFs of the CAF-S1 subset. Interestingly, TNBC cells that survived treatment demonstrated proximity to ECM-myCAFs compared to those cells that died, which suggested that priming for chemoresistance may start early in culture. Further analysis comparing gene expression profiles of cancer cells from chemo-resistant ToC experiments and chemo-resistant patients identified the transcript for the apoptosis regulator G0-G1 switch 2 (G0S2) as upregulated in both data sets. Mechanistically, ECM-myCAFs drive activation of SRC kinases within the cancer cells, leading to upregulation of G0S2, and relative resistance to apoptosis. Inhibition of either SRC kinase activity or GOS2 upregulation was sufficient to eliminate the chemo-protective effect offered by ECM-myCAFs. Despite these advances, the authors were unable to isolate the signalling molecules responsible for the paracrine crosstalk, although they speculate that hepatocyte growth factor (HGF) and fibroblast growth factor 2 (FGF2) are candidates. It is noteworthy that CAF-driven paracrine upregulation of GOS2 has been reported previously, although in a different setting; CAFs protect macrophages within pancreatic cancers from FOLFIRINOX-induced death via induction of GOS2 (12). This represents an interesting parallel and it is possible macrophages may also be involved in breast cancer. The new study compellingly demonstrates that increased levels of ECM-myCAFs drive therapy resistance in breast cancer, but it is also interesting to consider that the reduced levels of iCAFs may have a role, through local immunosuppression and immune evasion (4).

Several studies have shown that targeting stromal components may help achieve greater tumour control compared to targeting malignant tumour cells (13,14).

This is because CAFs are more genetically stable compared to tumour cells, which may eventually develop treatment resistance due to genetic instability. However, CAF heterogeneity and plasticity exist, which makes therapeutic interventions challenging. Effective therapies should focus on eliminating specific cancer promoting CAFs, as targeting other CAF subsets may increase tumour aggressiveness. Therefore, for CAF-targeted therapies to become a reality, further detail on the range of CAF subtypes and their specific influences will be needed.

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Footnote

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