Pharmacology & Therapeutics 200 (2019) 55–68

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Stress responses in stromal cells and tumor homeostasis

Ilio Vitale [a,b,c,**], Gwenola Manic [d], Claudia Galassi [e], Lorenzo Galluzzi [f,g,h,i,*]

[a] Department of Biology, University of Rome 'Tor Vergata', Rome, Italy
[b] Italian Institute for Genomic Medicine (IIGM), Turin, Italy
[c] Candiolo Cancer Institute, FPO, IRCCS, Candiolo, Italy
[d] IRCSS, Regina Elena National Cancer Institute, Rome, Italy
[e] Istituto di Patologia Generale, Università Cattolica del Sacro Cuore, Rome, Italy
[f] Department of Radiation Oncology, Weill Cornell Medical College, New York, NY, USA
[g] Sandra and Edward Meyer Cancer Center, New York, NY, USA
[h] Department of Dermatology, Yale School of Medicine, New Haven, CT, USA
[i] Université Paris Descartes/Paris V, Paris, France

ARTICLE INFO

Keywords:
Autophagy
Hypoxia
Immunosuppressive metabolites
Immunotherapy
Mesenchymal stem cells
Oxidative phosphorylation

ABSTRACT

In most (if not all) solid tumors, malignant cells are outnumbered by their non-malignant counterparts, including immune, endothelial and stromal cells. However, while the mechanisms whereby cancer cells adapt to microenvironmental perturbations have been studied in great detail, relatively little is known on stress responses in non-malignant compartments of the tumor microenvironment. Here, we discuss the mechanisms whereby cancer-associated fibroblasts and other cellular components of the tumor stroma react to stress in the context of an intimate crosstalk with malignant, endothelial and immune cells, and how such crosstalk influences disease progression and response to treatment.

Contents

1. Introduction

Non-malignant components of the tumor microenvironment (TME), which include endothelial, immune and stromal cells, numerically exceed their transformed counterparts and play critical roles in all steps of the neoplastic process (Hanahan & Coussens, 2012; Quail & Joyce, 2013).

Cancer-associated fibroblasts (CAFs) constitute the most abundant stromal cell type of the TME (Kalluri, 2016; Shi, Du, Lin, & Wang, 2017) (Box 1). CAFs are particularly enriched in fibrotic neoplasms, such as breast, colorectal, pancreatic and prostate carcinomas (Yamauchi, Barker, Gibbons, & Kurie, 2018), where they can derive from either activation of tissue-resident fibroblasts (*e.g.*, pancreatic stellate cells, PSCs) or differentiation of circulating bone marrow-derived MSCs (BM-MSCs). CAFs can also originate from the transdifferentiation of endothelial cells (via the so-called 'endothelial-to-mesenchymal transition'), epithelial cells (via the so-called 'epithelial-

---

Abbreviations: CAFs, cancer-associated fibroblasts; CSCs, cancer stem cells; CTLs, cytotoxic T lymphocytes; DDR, DNA damage response; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; RCD, regulated cell death; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; TA-MSCs, tumor-associated mesenchymal stem cells; TAMs, tumor-associated macrophages; TME, tumor microenvironment.

* Correspondence to: Lorenzo Galluzzi, PhD, Weill Cornell Medical College, Stich Radiation Oncology, 525 East 68th Street, Box # 169, New York NY 10065.

** Correspondence to: Ilio Vitale, Ph.D., University of Rome "Tor Vergata", Department of Biology, via della Ricerca Scientifica 1, 00133 Rome, Italy.

E-mail addresses: iliovit@gmail.com (I. Vitale), deadoc80@gmail.com (L. Galluzzi).

https://doi.org/10.1016/j.pharmthera.2019.04.004
0163-7258/

Box 1

Stromal cell markers

Several morphological, phenotypic and functional markers have been harnessed to identify (and isolate) stromal cells from the TME. At the microanatomical level, CAFs generally display a spindle-like or stellate morphology, while TA-MSCs are rather heterogeneous (although they can present fibroblastoid features) (Kalluri, 2016; Shi et al., 2017). At the phenotypic level, CAFs express specific cell surface markers including (but not limited to): fibroblast activation protein alpha (FAP), platelet derived growth factor receptor alpha (PDGFRA) and PDGFRB, podoplanin (PDPN), transforming growth factor beta receptor 1 (TGFBR1) and TGFBR2, membrane metalloendopeptidase (MME, best known as CD10), and complement component 5a receptor 2 (C5AR2, best known as GPR77) (Kalluri, 2016). Conversely, CAFs are generally characterized by limited expression of caveolin 1 (CAV1) and CD36, and abundant levels of intracellular proteins involved in cell structure and motility, including actin alpha 2, smooth muscle (ACTA2), desmin (DES), S100 calcium binding protein A4 (S100A4, also known as FSP1), and vimentin (VIM). TA-MSCs express typical MSC markers, including 5'-nucleotidase ecto (5NTE, best known as CD73), Thy-1 cell surface antigen (THY1), endoglin (ENG, best known as CD104), but generally lack CAF biomarkers including FAP, ACTA2, S100A4, PDGFA and VIM, as well as proteins normally expressed by immune and hematopoietic cells, such as CD34 and protein tyrosine phosphatase receptor type C (PTPRC, best known as CD45) (Le Blanc & Mougiakakos, 2012; Shi et al., 2017). At the functional level, activated CAFs can be defined by their secretome, which encompasses: (1) growth factors like VEGFA, PDGFs, FGFs and epidermal growth factor (EGF); (2) cytokines like IL6, SDF1 and TGFB1; (3) metabolites like lactate, alanine and PGE$_2$; (4) ECM components such as type I and II collagen, fibronectin 1 (FN1), periostin (POSTN) and various members of the tenascin family; (5) ECM remodeling enzymes like lysyl oxidases and various metalloproteinases; and (6) other bioactive factors including WNT ligands (X. Chen & Song, 2019; Kalluri, 2016; Shi et al., 2017). That said, most of these markers taken individually are not CAF- or TA-MSC-specific, they are not always co-expressed, and their levels not only vary with tumor type, but also change over space (in different areas of the TME) and time (with disease progression), lending further support to the notion that stromal cells of the TME are highly heterogeneous.

to-mesenchymal transition', EMT), tumor-associated macrophages (TAMs), pericytes, adipocytes, or even malignant cells (Ohlund, Elyada, & Tuveson, 2014; Santi, Kugeratski, & Zanivan, 2018; Shi et al., 2017). The tumor stroma can also contain populations of (poorly characterized) tumor-associated mesenchymal stem cells (TA-MSCs), which derive from BM-MSCs and can potentially generate CAFs (Kalluri, 2016; Shi et al., 2017). Both CAFs and TA-MSCs are embedded in the extracellular matrix (ECM), which they help to synthesize and remodel, and display high degree of phenotypic and functional heterogeneity (Alexander & Cukierman, 2016; Costa, Kieffer, et al., 2018). Such an elevated heterogeneity coupled with a plastic nature and some degree of potency explains the apparently antithetic effects of stromal cells in tumor development and progression that have been reported thus far (Gascard & Tlsty, 2016; Kalluri, 2016; Shi et al., 2017; Valkenburg, de Groot, & Pienta, 2018).

The current view is that stromal cells become activated acutely to support the immunological elimination of pre-malignant lesions, but can switch toward a tumor-supportive state on prolonged activation, hence acquiring the capacity to stimulate the proliferation and dissemination of cancer cells, as well as their ability to evade immune responses (Hanahan & Coussens, 2012; Kalluri, 2016; Klemm & Joyce, 2015; Quail & Joyce, 2013). That said, pro-tumor CAFs have been reported to co-exist with their anti-tumor counterparts, at least in some instances (Brechbuhl et al., 2017; Costa, Kieffer, et al., 2018; Ohlund et al., 2017; Raz et al., 2018). Moreover, at least in specific pre-clinical and clinical settings, CAF depletion appears to accelerate rather than to halt tumor progression, potentially linked to an increased dissemination of cancer cells as a consequence of the partial resolution of local fibrosis (Carstens et al., 2017; Ozdemir et al., 2014; Rhim et al., 2014).

Thus, the stromal cell landscape of solid tumors is highly heterogeneous and dynamic, and hence can vary to considerable degrees depending on disease type and stage, as well as on a plethora of microenvironmental cues (Chen & Song, 2019). These cues include (but potentially are not limited to): (1) metabolic conditions such as nutrient and oxygen limitation (fostered by the harsh metabolic competition between malignant and non-malignant cells in a fibrotic and poorly vascularized TME) or the accumulation of metabolites produced in excess by malignant cells (*e.g.*, lactate) (Bantug, Galluzzi, Kroemer, & Hess, 2018; Chang et al., 2015; Galluzzi, Kepp, Vander Heiden, & Kroemer, 2013); (2) immunomodulatory molecules released by cancer cells and/or tumor-infiltrating immune cells (D. S. Chen & Mellman, 2017; Galluzzi, Chan, Kroemer, Wolchok, & Lopez-Soto, 2018); (3) mechanical forces imposed by the ECM and the elevated hydrostatic pressure (Mohammadi & Sahai, 2018; Scherz-Shouval et al., 2014), and (4) exogenous toxic agents, encompassing pathogen-derived molecules as well as therapeutic interventions (Casey et al., 2015). Similar to their malignant counterparts, stromal cells respond to microenvironmental perturbations with mechanisms aimed at preserving cellular homeostasis or, if this cannot be achieved, promoting the demise (via regulated cell death, RCD) or permanent proliferative arrest (via cellular senescence) of cells irremediably damaged, in both cases along with the emission of signals for the maintenance of microenvironmental homeostasis (Galluzzi, Yamazaki, & Kroemer, 2018). Such cellular and microenvironmental responses to stress often involve changes in ECM as well as intricate paracrine circuitries interconnecting all the cellular compartments of the TME. Ultimately, the mechanisms whereby stromal cells adapt to stress have a major impact on the tumor-immune system co-evolution as they dictate the fate of malignant cells in the course of natural disease progression and response to treatment (Jiang, Hegde, & DeNardo, 2017; Shi et al., 2017; Valkenburg et al., 2018; Vitale et al., 2019).

Here, we outline how stromal cells adapt to stressful conditions, with a particular emphasis on the mechanisms whereby the signals released by stromal cells responding to stress affect cancer cells and tumor-infiltrating immune cells, and how these signals can be hijacked for therapeutic purposes.

1.1. Adaptive response of stromal cells to energetic cues

Stromal cells share with the other cellular compartments of the TME the same metabolic microenvironment and core bioenergetic circuitries, but their metabolic behavior and adaptive response to energetic perturbations are unique.

CAFs and TA-MSCs are recruited to the tumor bed and activated by a variety of stressful conditions, including limited nutrient availability, low oxygen tension (hypoxia), pH deregulation and oxidative stress, often following the release of cytokines such as transforming growth factor beta 1 (TGFB1), platelet derived growth factor (PDGF), and C-X-C motif chemokine ligand 2 (CXCL2), and reactive oxygen species (ROS) from cancer cells (Cadamuro et al., 2013; Chaturvedi, Gilkes, Takano, & Semenza, 2014; Costa, Scholer-Dahirel, & Mechta-Grigoriou, 2014; Gilkes, Semenza, & Wirtz, 2014; LaGory & Giaccia, 2016). Similar to their transformed counterparts, CAFs display elevated degree of metabolic flexibility, implying that they can rapidly adapt to conditions of poor glucose and oxygen availability, and hence they are less prone to undergo RCD in response to nutrient deprivation as compared to other cells of the TME (Yang, Achreja, et al., 2016). In particular, CAFs isolated from breast cancer patients can efficiently recycle metabolic byproducts such as lactate and ammonia as energy sources and nitrogen donors, respectively (Yan et al., 2018). Activated CAFs also resemble cancer cells in that they exhibit high biosynthetic activity and elevated proliferation rates, which they satisfy by robust glucose-driven anabolism coupled to fatty acid-driven mitochondrial respiration (Alexander & Cukierman, 2016; Santolla et al., 2012; Wu, Zhuo, & Wang, 2017). In this setting, increased glucose consumption coupled to extensive lactate secretion (Miller et al., 2017) is enabled by the upregulation of multiple glucose transporters and/or glycolytic enzymes encompassing hexokinase 2 (HK2), phosphoglycerate kinase 1 (PGK1) or lactate dehydrogenase A (LDHA) (Hu, Sun, Zhang, Xiong, & Mi, 2014; Shan et al., 2017; Shangguan et al., 2018; Wang et al., 2010; Wang, Xue, et al., 2016; Wu et al., 2018). The lactate-driven acidification of the TME supports the activation of TA-MSCs, which has been linked to increased stemness and chemoresistance in osteosarcoma cell lines *in vitro* (Avnet et al., 2017). Of note, enhanced glucose metabolism, and in particular increased metabolic flux via glycolysis, gluconeogenesis and the pentose phosphate pathway, has also been associated with the induction of cell senescence (James et al., 2015), which often characterizes the adaptive response of CAFs to genotoxic stress (see below). In cancer cell-fibroblast co-cultures as well as in the pancreatic TME, CAFs respond to microenvironmental perturbations by acquiring a secretive phenotype involving ECM components as well as ECM-remodeling enzymes, ultimately leading to extensive fibrosis (Spivak-Kroizman et al., 2013). Fibrosis limits the availability of nutrients and oxygen, hence setting off a feed-forward circuitry whereby accrued lactate accumulation, glucose deprivation and hypoxia foster the recruitment and activation of additional stromal cells.

Hypoxia has been linked to the rearrangement of core metabolic circuitries in stromal cells (Mitchell & Engelbrecht, 2017). In particular, hypoxia rewires stromal metabolism toward glycolysis via a process dependent on hypoxia inducible factor 1 subunit alpha (HIF1A), a transcription factor that transactivate multiple genes involved in glycolysis when oxygen concentrations fall below a specific threshold (Gonzalez, Xie, & Jiang, 2018). In PDGF-induced CAFs or primary CAFs from melanoma or colon cancer biopsies, decreased isocitrate dehydrogenase 3 (NAD(+)) alpha (IDH3A) promotes glycolysis by stabilizing HIF1A as a consequence of fumarate and succinate accumulation (which inactivate the prolyl hydroxylases normally targeting HIF1A to degradation) (Selak et al., 2005; D. Zhang et al., 2015). In line with an impact for HIF1A activation in CAFs on tumor progression, both chronic hypoxia and the CAF-specific downregulation of egl-9 family hypoxia inducible factor 1 (EGLN1, an enzyme involved in HIF1A degradation best known as PDH2) have been shown to limit metastatic dissemination in an orthotopic breast cancer model (Kuchnio et al., 2015; Madsen et al., 2015). At least in some preclinical and clinical settings, such a tumor-supportive effect depends on the ability of glycolytic CAFs to secrete abundant levels of lactate, which can be taken up by cancer cells to fuel oxidative metabolism (Fiaschi et al., 2012; Romero, Mukherjee, Kenny, Litchfield, & Lengyel, 2015; Sanita et al., 2014; Wu, Fu, et al., 2017). This process, which is commonly known as 'reverse Warburg effect' (Galluzzi, Kepp, & Kroemer, 2012; Pavlides et al., 2009), has been linked, *in vitro*, to HIF1A stabilization in CAFs supported by cancer cell-imposed oxidative stress (Martinez-Outschoorn et al., 2013; Wilde et al., 2017). A similar metabolic cooperation involves CAF-derived pyruvate, in lymphoma models (Sakamoto et al., 2019), and CAF-derived glutamine, in prostate and ovarian cancer models (Mishra et al., 2018; Yang, Achreja, et al., 2016), which can directly feed into the Krebs cycle, as well as ketone bodies (Martinez-Outschoorn, Lisanti, & Sotgia, 2014), which can be harnessed for bioenergetic purposes by cancer cells overexpressing 3-oxoacid CoA-transferase 1 (OXCT1) (Huang, Li, et al., 2016). Moreover, TGFB1-activated CAFs can favor the mobilization of glycogen in cancer cells, although the molecular mechanisms underlying this process remain to be elucidated (Curtis et al., 2019). Along similar lines, *in vitro* experiments and studies from tumor biopsies suggest that CAFs favor glycolysis and the pentose phosphate pathway (hence supporting the anabolic metabolism and antioxidant defenses) by promoting the upregulation of key enzymes in these circuitries (Cruz-Bermudez et al., 2019; Sherman et al., 2017). Although the molecules at play in this setting remain to be characterized, CAF-derived exosomes (perhaps metabolism-relevant microRNAs or RNA species triggering pattern recognition receptor signaling) (Boelens et al., 2014; Nabet et al., 2017; Zhao et al., 2016) and cytokines stand out as potential messengers linking CAFs to cancer cells (La Shu et al., 2018; Zhao et al., 2016; Zhao, Ji, et al., 2017). Interestingly, in some settings CAFs have been reported to drive cancer cells into oxidative phosphorylation rather than glycolysis (Druzhkova et al., 2016). Potentially, this simply reflects the high degree of metabolic heterogeneity of both CAFs and malignant cells (Choi, Kim, Jung, & Koo, 2013).

CAFs also respond to low oxygen tension by overexpressing G protein-coupled estrogen receptor 1 (GPER1), which not only supports the switch of breast CAFs towards glycolysis and fatty acid oxidation (Santolla et al., 2012; Yu et al., 2017), but also endows them with robust tumor-supportive functions including the secretion of pro-angiogenic molecules like vascular endothelial growth factor A (VEGFA) (De Francesco et al., 2013; De Francesco et al., 2017; Ren et al., 2015). Finally, hypoxia contributes to tumor progression by stimulating CAFs to release: (1) immunomodulatory molecules such as CXCL13, as shown, *in vitro* and *in vivo*, in prostate cancer models (Ammirante, Shalapour, Kang, Jamieson, & Karin, 2014), (2) growth factors such as insulin like growth factor 1 (IGF1), as observed in pancreatic tumor samples (Hirakawa et al., 2016), and hepatocyte growth factor (HGF) (Brauer et al., 2013; Kumar et al., 2018), as observed *in vitro* upon co-culturing fibroblasts with breast cancer cells, (3) antioxidants including ornithine and multiple polyamines (Ino et al., 2013), as described in pancreatic tissues, and (4) ECM remodeling enzymes like procollagen-lysine,2-oxoglutarate 5-dioxygenase 2 (PLOD2) (Gilkes, Bajpai, Chaturvedi, Wirtz, & Semenza, 2013), as demonstrated in breast cancer models, *in vitro*. Taken together, these observations delineate metabolic, trophic and immunological circuitries activated by nutritional stress that link CAFs to endothelial cells in support of tumor progression. That said, HIF1A activity in CAFs can also underlie tumor-suppressive effects, at least in specific circumstances. Indeed, the deletion of *HIF1A* from CAFs reportedly accelerates tumor growth in a mouse model of breast cancer (Kim et al., 2012). This latter example lends further support to the notion that CAFs display elevated degrees of phenotypic and functional heterogeneity.

In response to dwindling amino acid levels, CAFs isolated from various tumors acquire the ability to secrete aspartate in direct support of cancer cell proliferation (Bertero et al., 2019), while pancreatic CAFs deposit increased amounts of collagen into the ECM, *de facto* constituting a reservoir of proline for malignant cells (Olivares et al., 2017). Along similar lines, CAFs experiencing nutrient deprivation secrete cytokines including CXCL12 (best known as SDF1) and interleukin 6 (IL6) that mediate antioxidant effects in malignant cells upon the activation of nuclear factor, erythroid 2 like 2 (NFE2L2, best known as NRF2) (Wu, Looi, Subramaniam, Masamune, & Chung, 2016). Likewise, CAFs have been shown to provide cysteine for glutathione synthesis to leukemia cells expressing low levels of the cystine transporter known as 'x_c system' (and hence being unable to synthesize glutathione from cystine) (Zhang et al., 2012).

Importantly, the metabolic circuitries relaying stressed CAFs to cancer cells are often bidirectional. In head and neck squamous cell carcinoma models, while CAF-derived HGF promotes glycolysis in cancer cells, fibroblast growth factor 2 (FGF2) secreted by malignant cells favors lactate uptake and oxidative metabolism in CAFs (D. Kumar et al., 2018). Similarly, CAFs appear to provide cancer cells with alanine (supporting disease progression) in exchange of glutamate (driving oxidative phosphorylation in CAFs) (Bertero et al., 2019). Moreover, breast cancer cells can actively reprogram the metabolism of other cellular components of the TME including CAFs via the exosomal delivery of microRNAs that promote glutamine metabolism (*e.g.*, miR-105) (Yan et al., 2018) and/or limit glucose utilization (*e.g.*, miR-122) (Fong et al., 2015). Along similar lines, melanoma-derived exosomes have been shown to boost glycolysis in cultured CAFs, culminating with extracellular acidification downstream of lactate secretion (La Shu et al., 2018). The precise exosomal mediator of this latter effect, however, remains unknown. Similarly, a hitherto unidentified factor secreted by prostate cancer cells appears to favor extracellular acidification by promoting carbonic anhydrase 9 (CA9) expression on the surface of CAFs, culminating with accelerated disease progression (Fiaschi et al., 2013). Importantly, the net outcome of the abovementioned metabolic interactions is likely to depend on multiple parameters, including type of cancer, stage of the disease and the overall cellular composition of the TME.

Accumulating evidence indicates that macroautophagy – an evolutionary conserved mechanism for lysosomal degradation of dispensable or potentially toxic cytosolic material via double-membraned organelles known as autophagosomes (from here onward referred to as autophagy) (Galluzzi et al., 2017) – is key for CAF activation and survival (Goruppi, Clocchiatti, & Dotto, 2019). Accordingly, CAFs isolated from various tumors display elevated autophagic flux at baseline (Chaudhri et al., 2013; New et al., 2017) and increased levels of autophagy regulators including unc-51 like kinase 3 (ULK3) (Goruppi et al., 2017), most likely in response to the nutrient- and oxygen-poor conditions that characterize the TME. Importantly, autophagic responses in stressed stromal cells also support the survival and proliferation of cancer cells, at least *in vitro* (Sanchez et al., 2011; Zhou et al., 2017). In particular, autophagic PSCs have been shown to provide pancreatic cancer cells with alanine for oxidative metabolism upon intracellular conversion into pyruvate (Sousa et al., 2016). Similar observations have been made in coculture experiments wherein autophagic CAFs provided breast cancer cells with glutamine in support of oxidative phosphorylation and anti-apoptotic signaling (Galluzzi et al., 2018; Ko et al., 2011). Apparently at odds with these observations, downregulation of the autophagic adaptor sequestosome 1 (SQSTM1, best known as p62) has been associated with both CAF activation (Valencia et al., 2014) and accelerated tumor progression as a consequence of increased asparagine supply to cancer cells experiencing glutamine deprivation (Linares et al., 2017). However, this metabolic effect seems independent of the autophagic activity of p62. Altogether, these findings are in line with the increasingly better understood ability of cancer cells to use a variety of exogenous substrates for bioenergetic or biosynthetic purposes, substrates that are often provided by non-malignant cells (including CAFs) via autophagy (Katheder et al., 2017; Poillet-Perez et al., 2018).

In summary, the elevated heterogeneity and metabolic plasticity of stromal cells allow them to survive (and even become activated on) the harsh microenvironmental conditions that characterize most solid tumors, encompassing nutrient limitation, hypoxia, deregulated pH and increased oxidative stress. The adaptation of CAFs to metabolic stress also preserves tumor homeostasis by creating a protective niche that not only shields cancer cells from metabolic stress but also remodels their metabolic profile in support of their biosynthetic and bioenergetic needs (Fig. 1).

1.2. Adaptive response of stromal cells to therapeutic insults

Anticancer therapies, including those aimed at the (re)activation of tumor-targeting immunity, also threaten (most often unintentionally) the survival of stromal cells, *de facto* inducing multiple mechanisms of adaptation that influence therapeutic responses.

Despite increased proliferation rates (which are normally associated with an augmented sensitivity to stress) and evidence of apoptotic priming (*i.e.*, a proteomic profile compatible with an increased propensity for apoptotic cell death) (Lagares et al., 2017; Rizvi et al., 2014), stromal cells display an unusually elevated threshold for RCD activation by treatment. Thus, stromal cells are intrinsically resistant to most conventional therapeutic agents, which is at least in part linked to their autophagic proficiency and their ability to secrete pro-survival factors in response to stress (Chaudhri et al., 2013). Presumably, such a resistance to RCD also evolves over time in response to chronic stress signals from the TME of established tumors, *de facto* sparing CAFs from activation-driven apoptosis (and consequent phagocytic clearance), which seals the fate of normal fibroblasts (*e.g.*, upon wound healing) (Desmouliere, Redard, Darby, & Gabbiani, 1995). Accordingly, CAFs exhibit increased resistance to therapeutic insults as compared to other non-malignant cells of the TME. Thus, CAFs resist treatment with bortezomib (a proteasomal inhibitor commonly employed for multiple myeloma patients) (Garg et al., 2017) along with a TGFB1-driven increase in autophagic flux that ultimately favors chemoresistance in leukemic cells as well (Frassanito et al., 2016). Similar autophagy-dependent cytoprotective responses in CAFs impacting the sensitivity

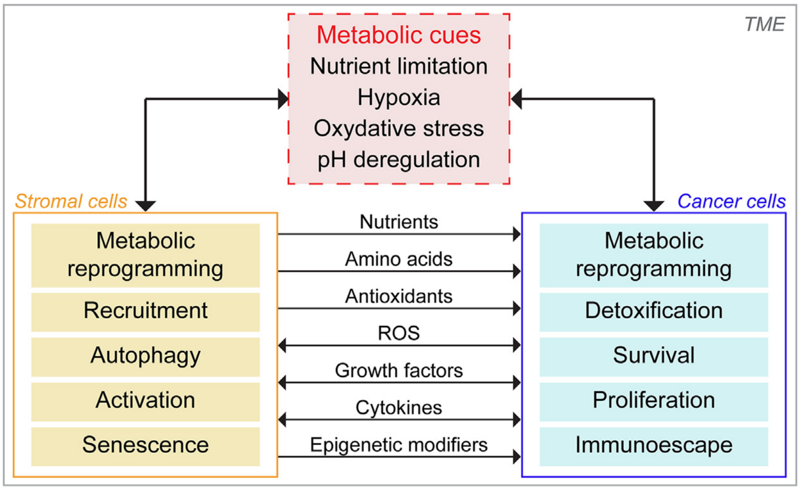


Fig. 1. Metabolic crosstalk between stromal cells and cancer cells in the TME. The tumor microenvironment (TME) of solid neoplasms is generally characterized by relatively harsh metabolic conditions, encompassing nutrient shortage, hypoxia, oxidative stress and pH alterations. All these factors have a direct effect on the metabolic and functional profile of all cellular compartments of the TME, including stromal and malignant cells (both of which exhibit elevated resistance to metabolic challenges). Alongside, metabolic perturbations of the TME enable an intimate, bidirectional crosstalk between stromal and malignant cells whereby the former ultimately support the survival, proliferation and resistance to treatment of the latter. ROS, reactive oxygen species.

of cancer cells to treatment *in vitro* and/or *in vivo* have also been observed in ovarian cancer (Wang, Xue, et al., 2016), multiple myeloma (Yang, Zheng, Zhang, Cao, & Jiang, 2017), colorectal carcinoma (Yang, Xu, Zhu, Zhang, Wu, Wu, et al., 2016), and pancreatic cancer (Zhang et al., 2018). Apparently at odds with these findings, administration of the autophagy inhibitor chloroquine to CAFs reportedly favors the resistance of co-cultured pancreatic cancer cells to gemcitabine *in vitro* (Molejon et al., 2018). That said, chloroquine is not specific for autophagy but inhibits all processes converging on lysosomal degradation (Galluzzi, Bravo-San Pedro, Levine, Green, & Kroemer, 2017), implying that these latter findings may reflect an autophagy-independent function of lysosomes.

The elevated resistance of CAFs to a variety of DNA-damaging agents including radiation therapy (Gorchs et al., 2015; Lotti et al., 2013; Richards et al., 2017; Tommelein et al., 2018) suggests that these cells can mount a proficient cell cycle arrest and DNA damage response (DDR), in thus far resembling cancer stem cells (CSCs, the malignant cell subpopulation responsible for tumor initiation, progression and therapeutic resistance) (Manic et al., 2018; Vitale, Manic, De Maria, Kroemer, & Galluzzi, 2017). Most likely, however, this does not reflect genetic alterations (as in the case of CSCs), but rather epigenetic changes, because CAFs from distinct tumor types are usually described as genetically stable (Hosein et al., 2010; Qiu et al., 2008; Sonnenberg et al., 2008; Wang et al., 2015). Interestingly, CAFs infiltrating breast carcinomas appear to rely (at least in part) on ATR serine/threonine kinase (ATR, a transducer of the cellular response to replication stress) for their survival (Al-Ansari & Aboussekhra, 2014), in spite of reduced ATR expression levels (Al-Ansari & Aboussekhra, 2018) and other alterations in the DDR machinery including low checkpoint kinase 2 (CHEK2) expression (Al-Rakan, Hendrayani, & Aboussekhra, 2016) and, in lung CAFs, defective tumor protein p53 (TP53) signaling (Arandkar et al., 2018). Of note, the activation of TP53 following DNA damage in CAFs isolated from lung cancer biopsies can be relayed to activation of the DDR in adjacent cells that did not experience genotoxic insults (Schmid et al., 2012). The molecular mechanisms underlying this phenomenon, however, remain to be elucidated. Of interest in this setting, lung and pancreatic CAFs responding to genotoxic insults including irradiation and the DNA replication poison gemcitabine (which is commonly used in the clinical management of pancreatic tumors) (Gravett, Trautwein, Stevanovic, Dalgleish, & Copier, 2018) tend to undergo cellular senescence rather than RCD (Hellevik et al., 2012; Toste et al., 2016). Such an induction of cell senescence has been observed in CAFs from distinct tumors, including (but possibly not limited to) ovarian, lung and pancreatic cancer (Capparelli et al., 2012; Hellevik et al., 2012; Pitiyage et al., 2011; Wang, Notta, et al., 2017; Yang et al., 2006). Taken together, these observations indicate that CAFs experiencing DNA-damaging conditions are prone to successfully repair damage or undergo cellular senescence, rather than succumbing to apoptosis driven by the DDR. Further investigations are required to shed light on the molecular bases of such a resistance.

The response of CAF to therapeutic agents involves profound transcriptomic modifications (also occurring in CAF-interacting cancer cells) that (1) rely on the transcriptional activity of multiple nuclear receptors, as observed in CAFs from squamous cell carcinoma biopsies (Chan et al., 2018), and (2) support the establishment of a high apoptotic threshold and resistance to therapy, as observed *in vitro*, in breast CAFs (Marusyk et al., 2016). In particular, activation of specific nuclear receptors in stressed CAFs drives the synthesis and release of biologically active factors that act on cancer cells via paracrine circuitries to support resistance to treatment. Paracrine circuitries of this sort have been described for (1) CAF-derived HGF, underlying the resistance of melanoma cells with B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) mutations to BRAF inhibitors (Straussman et al., 2012; Wilson et al., 2012), lung cancer cells with ALK receptor tyrosine kinase (*ALK*) translocations to ALK inhibitors (Yamada et al., 2012), and breast cancer cells to epidermal growth factor receptor (EGFR) inhibitors (Mueller et al., 2012); (2) CAF-derived FGF2, which supports the resistance of breast cancer cells to hormonotherapy and targeted therapies with phosphoinositide-3-kinase (PI3K) inhibitors (Shee et al., 2018); (3) glial cell derived neurotrophic factor (GDNF), which limits the sensitivity of prostate cancer cells to mitoxantrone, an anthracycline inducing immunogenic cell death, and docetaxel, a microtubular poison (Galluzzi, Buque, Kepp, Zitvogel, & Kroemer, 2017; Huber et al., 2015); and (4) various insulin-like growth factors (IGFs), which drive the resistance of pancreatic cancer cell to gemcitabine (Ireland et al., 2016). Of note, IGF2 is also released by cancer cells responding to monoclonal antibodies specific for insulin like growth factor 1 receptor (IGF1R) (J. S. Lee et al., 2015), a process that indirectly promotes resistance to treatment upon the recruitment of additional CAFs to the tumor bed, at least in colorectal cancer models (Unger et al., 2017).

CAFs also contribute to the resistance of cancer cells to chemotherapy and immunotherapy owing to their ability to secrete ECM components and remodelers. Indeed, a stiff ECM provides malignant cells with a physical barrier against chemotherapeutics and tumor-infiltrating immune cells (see below) (Jacobetz et al., 2013; Miao et al., 2017; Olive et al., 2009; Provenzano et al., 2012; Whatcott et al., 2017). This situation is particularly pronounced in pancreatic tumors, which often display a dense stromal reaction commonly referred to a desmoplastic stroma (Neesse, Algul, Tuveson, & Gress, 2015). In line with the ability of the desmoplastic stroma to support chemoresistance, agents that favor ECM loosening, such as protein tyrosine kinase 2 (PTK2, best known as FAK) inhibitors or pegylated recombinant human hyaluronidase (PEGPH20, a hyaluronic acid-degrading enzyme), have been reported to improve gemcitabine uptake by pancreatic tumors and consequently favor therapeutic responses (Hingorani et al., 2016; Jacobetz et al., 2013; Liang et al., 2017; Provenzano et al., 2012; Whatcott et al., 2017). In this context high levels of intratumoral hyaluronic acid have been suggested to predict the ability of by PEGPH20 to sensitize patients with untreated metastatic pancreatic ductal adenocarcinoma to gemcitabine-based chemotherapy (Hingorani et al., 2018). That said, the desmoplastic stroma also constitutes a barrier against metastatic dissemination (Yamauchi et al., 2018), implying that therapeutic strategies targeting the ECM may ultimately favor distant recurrence. Interestingly, resistance to gemcitabine in pancreatic cancer also involves drug scavenging by stromal cells (Hessmann et al., 2018), as well as the release of transglutaminases by cancer cells, culminating with CAF-dependent ECM remodeling (J. Lee et al., 2016). Moreover, chemotherapy resistance in ovarian and colorectal cancers also arises from inefficient drug delivery due to tumor vasculature deregulation by CAFs (Leung et al., 2018), and to ECM remodeling supported by therapy-driven hypoxia (Rahbari et al., 2016), respectively. Furthermore, changes in the ECM have been linked to increased chemoresistance in cancer cells secondary to the activation of autophagy (Li et al., 2016; Liao et al., 2018) and inhibition of apoptosis via diverse mechanisms (Castells et al., 2013; Hirata et al., 2015; Muerkoster et al., 2008; Seip et al., 2016).

CAFs undergoing senescence in response to DNA damage (as in the context of gemcitabine treatment) or cell cycle blockage acquire the so-called 'senescence-associated secretory phenotype' (SASP), which supports the growth of malignant cells and protects them from therapy (Galluzzi & Vitale, 2018; Guan et al., 2017; Toste et al., 2016). Along similar lines, senescent fibroblasts boost tumor inflammation to support disease recurrence and exacerbate the adverse effects of chemotherapy, as least in the breast cancer setting (Demaria et al., 2017). Mitogen-activated protein kinase 14 (MAPK14, best known as $p38^{MAPK}$) appears to mediate a key role in the acquisition of the SASP by CAFs (Alspach et al., 2014). SASP components that have been linked to chemoresistance in this setting include tumor necrosis factor (TNF) (Acharyya et al., 2012), IL6 (Karakasheva et al., 2018; Qiao et al., 2018; Xu et al., 2018), CXCL8 (J. S. Lee et al., 2015), CXCL13 (Ammirante et al., 2014), serine protease inhibitor Kazal type I (SPINK1) (F. Chen et al., 2018), and serpin family E member 1 (SERPINE1, best known as

PAI-1) (Che et al., 2018). In this setting, TNF favors the activation of the anti-apoptotic transcription factor NF-κB coupled to the recruitment of immunosuppressive cells that favor chemoresistance in breast cancer (Acharyya et al., 2012), IL6 supports esophageal and ovarian cancer cell proliferation by promoting signal transducer and activator of transcription 3 (STAT3) activation (Karakasheva et al., 2018; Qiao et al., 2018; Xu et al., 2018), CXCL8 supports neo-angiogenesis and metastatic dissemination (J. S. Lee et al., 2015), while SERPINE1 inhibits the activation of apoptosis by treatment in esophageal squamous cell carcinoma as a consequence of AKT serine/threonine kinase 1 (AKT1) signaling (Che et al., 2018). Conversely, the pathways activated by CAF-derived CXCL13 and SPINK1 in cancer cells remain obscure. Similar to autophagy, senescence appears to be important also for CAF activation in the course of tumorigenesis, at least in part linked to the downregulation of recombination signal binding protein for immunoglobulin kappa J region (RBPJ, an effector of NOTCH signaling) and either TP53 (Menietti et al., 2016; Procopio et al., 2015) or the stress-responsive transcriptional modulator activating transcription factor 3 (ATF3) (D. E. Kim et al., 2017). Intriguingly, autophagy has been proposed not only to support cellular senescence in multiple settings (Dou et al., 2015; Galluzzi, Bravo-San Pedro, & Kroemer, 2016), but also to modulate RBPJ levels (Goruppi et al., 2018), which suggests the existence of an intimate connection between these two processes in stressed CAFs. Together with promising results from the use of senolytic agents for the treatment of age-associated disorders (Justice et al., 2019), these observations support senescence as potential therapeutic target for cancer therapy.

Additional factors produced by CAFs experiencing therapeutic stress in support of resistance to treatment include (1) Wnt family member 16 (WNT16) and secreted frizzled related protein 2 (SFRP2), two components of the WNT signaling machinery (Galluzzi, Spranger, Fuchs, & Lopez-Soto, 2019) that limit the sensitivity of cancer cells to genotoxic therapies *in vitro* and *in vivo* (Sun et al., 2012; Sun et al., 2016); (2) exosomes, which (by a hitherto unidentified mechanism) activate snail family transcriptional repressor 1 (SNAI1) in pancreatic cancer cells to increase their resistance to gemcitabine (Richards et al., 2017); (3) glutathione and cysteine, which not only can be taken up by prostate cancer cells to strengthen their defense against treatments causing oxidative stress (*e.g.*, radiation therapy) (Cheteh et al., 2017), but also counteract the intracellular accumulation of specific chemotherapeutics (*e.g.*, cisplatin) in lung and ovarian cancer cells (Galluzzi et al., 2013; Wang, Kryczek, et al., 2016).

Recent data suggest that a specific subset of CAFs ($CD10^{+}GPR77^{+}$) drives chemoresistance by specifically promoting the survival of CSCs, at least in the setting of breast cancer (S. Su et al., 2018). Potentially, this process relies on autophagy activation in CAFs, culminating with the release of the non-histone nuclear protein high mobility group box 1 (HMGB1) and consequent Toll-like receptor 4 (TLR4) activation in malignant cells (Zhao, Lin, et al., 2017). CAFs surviving conventional DNA-damaging chemotherapeutics, such as 5-fluorouracil (5-FU) and oxaliplatin, also promote the expansion of colorectal CSCs by releasing IL17A (Lotti et al., 2013) or exosomes (Y. Hu et al., 2015), a process that is exacerbated by hypoxia (as shown in preclinical and clinical settings) (Tang et al., 2018). Of note, differentiated malignant cells have been reported to indirectly stimulate stemness upon the induction of Hedgehog signaling in breast CAFs (Cazet et al., 2018). Whether this circuitry promotes resistance to treatment, however, is unclear. Beyond protecting stromal and malignant cells, CAF-secreted IGFs and SDF1 also drive tumor relapse upon radiotherapy by favoring bioenergetic and behavioral changes in cancer cells surviving treatment (Hirakawa et al., 2016; Tommelein et al., 2018; Wang, Gan, et al., 2017). Of note, in head and neck squamous cancers, tumor repopulation upon radiotherapy also depends on the activation of Hedgehog signaling in both stromal and cancer cells (Gan et al., 2014), pointing to a key role for CSCs in this setting. However, despite encouraging preliminary results (Olive et al., 2009), the abrogation of Hedgehog signaling by smoothened, frizzled class receptor (SMO) inhibitors accelerated tumor development and progression in mouse model of pancreatic cancer (J. J. Lee et al., 2014). Moreover, SMO inhibitors provided limited therapeutic benefits when combined with chemotherapy (in metastatic colorectal or pancreatic cancer patients) or used as maintenance agents (in patients with ovarian cancer) (Berlin et al., 2013; Catenacci et al., 2015; Kaye et al., 2012). This is in line with the role of stromal Hedgehog signaling in restraining rather than supporting oncogenesis (Rhim et al., 2014), limiting enthusiasm on the modulation of the Hedgehog network for anticancer purposes.

Taken together, these observations indicate that stromal cells not only are poorly sensitive to conventional and targeted anticancer therapies, but also respond to these agents by endowing cancer cells with treatment resistance, increased stemness, and superior potential for progression. Accordingly, several strategies to reverse CAF activation have been shown to mediate antineoplastic effects (Box 2).

Box 2
Strategies to reverse CAF activation

Over the past decade, along with the recognition that CAFs play a key role in tumor initiation, progression and resistance to treatment, great interest has been attracted by the possibility to deplete or inactivate CAFs as a means to sensitize malignant lesions to therapy (X. Chen & Song, 2019; Valkenburg et al., 2018). In this context, several strategies have been conceived to drive CAFs into quiescence and/or to limit their capacity to deposit ECM constituents. For instance, both these goals can be achieved by autophagy inhibitors, reflecting the key role of autophagy in CAF activation (Goruppi et al., 2017) as well as in the ability of CAFs to secrete ECM constituents (Endo et al., 2017). However, inhibition of autophagy has also been reported to exacerbate the tumor-supportive functions of CAFs, at least in some settings, by preventing the autophagic degradation of IL33 (Ding et al., 2018). CAF quiescence has also been achieved by perturbing the transcriptional reprogramming of CAFs with calcipotriol (a vitamin D analogue) or all-trans retinoic acid (ATRA), which was accompanied by restored tumor sensitivity to gemcitabine (Carapuca et al., 2016; Sherman et al., 2014), and diminished metastatic dissemination (Chronopoulos et al., 2016; Froeling et al., 2011). Similar results have been obtained with minnelide (a water soluble pro-drug of an active compound from a Chinese herb) in a model of pancreatic cancer, in which CAF quiescence is accompanied by decreased TGFB1 signaling (Dauer et al., 2018). Likewise, preventing therapy-induced CAF activation with low-dose metronomic chemotherapy improved therapeutic efficacy in a preclinical model of breast cancer (T. S. Chan et al., 2016). CAFs are also particularly sensitive to BET inhibitors (which operate as epigenetic modifiers) (Clocchiatti et al., 2018), inhibitors of protein synthesis (limiting ECM deposition) (Duluc et al., 2015), and FAK inhibitors (also influencing ECM deposition) (Jiang et al., 2016; Santos, Jung, Aziz, Kissil, & Pure, 2009). All these interventions drive CAFs into quiescence as they mediate anticancer effects in a variety of preclinical tumor models (Duluc et al., 2015; Huang, Nahar, et al., 2016; Yamamoto et al., 2016). That said, CAFs have been shown to participate in tumor infiltration by CTLs (Kilvaer et al., 2018; Koeck et al., 2017). Moreover, CAF depletion strategies may mediate toxic effects, at least in some settings (Roberts et al., 2013; Tran et al., 2013). Thus, caution should be taken with the development of CAF-targeting strategies for translation to the clinics.

1.3. Impact of stromal cells on anticancer immunity

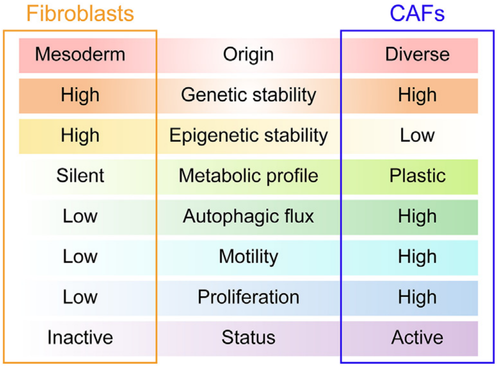
It is now clear that oncogenesis, tumor progression and responses to (immuno)therapy are governed by an intimate crosstalk between malignant cells and non-malignant components of the TME (Jiang et al., 2017; Junttila & de Sauvage, 2013; Turley, Cremasco, & Astarita, 2015).

Stromal and immune cells engage themselves in a bidirectional interaction involving the release of soluble mediators as well as cell-to-cell physical interactions. Thus, pro-inflammatory cytokines released by tumor-infiltrating immune cells (*e.g.*, TNF, IL1B) favor the recruitment of stromal cells to the developing tumors and their activation, as shown in a mouse model of squamous skin carcinogenesis (Erez, Truitt, Olson, Arron, & Hanahan, 2010). In turn, activated CAFs can further aggravate inflammation not only by contributing to TNF and IL1B release, but also by secreting a variety of chemokines that initially sustain the recruitment of immune cells to the tumor bed (*e.g.*, CXCL2, IL6) (Erez et al., 2010; Erez, Glanz, Raz, Avivi, & Barshack, 2013). However, recruited immune cells are generally polarized towards an immunosuppressive phenotype that supports (rather than limits) tumor progression (Kato et al., 2018). Moreover, as CAFs deposit increasing amounts of ECM (Jiang et al., 2017; Klemm & Joyce, 2015), the resulting fibrotic stroma constitutes a physical and functional barrier to tumor infiltration by immune effectors cells (Carstens et al., 2017; Kaur et al., 2019), *de facto* limiting the efficacy of a variety of immunotherapeutic regimens (Elahi-Gedwillo, Carlson, Zettervall, & Provenzano, 2019; Hartmann et al., 2014; Jiang et al., 2016; Zhao et al., 2018).

The functional cooperation between CAFs and TAMs is a crucial determinant of tumor progression (Erez et al., 2010; Hashimoto et al., 2016). Stromal cells promote the recruitment of TAMs to the TME and their polarization toward an anti-inflammatory, tumor-supportive phenotype (so-called ‘M2’) not only by secreting chemoattractants for circulating monocytes such as IL6, SDF1, colony stimulating factor 1 (CSF1), and chitinase 3 like 1 (CHI3L1) (Cho et al., 2018; Cohen et al., 2017; Comito et al., 2014; Jia et al., 2016; Zhang et al., 2017) but also by promoting ECM remodeling (Mazur, Holthoff, Vadali, Kelly, & Post, 2016). Activated CAFs also limit the ability of colony stimulating factor 1 receptor (CSF1R) inhibitors to deplete M2 TAMs or repolarize them toward an immunostimulatory, anticancer phenotype (so-called ‘M1’) by driving granulocytic infiltration of the tumor bed, as shown in murine models of lung cancer and biopsies from non-small cell lung carcinoma patients (Kumar et al., 2017). Stromal cells and their progenitors also recruit myeloid-derived suppressor cells (MDSCs, an immature population of bone marrow-derived myeloid cells that exerts potent immunosuppressive effects) (Allaoui et al., 2016; Mace et al., 2013; Ren et al., 2012; Yang, Lin, et al., 2016; Yen et al., 2013), CD4$^+$CD25$^+$FOXP3$^+$ regulatory T cells (a lymphoid cell population that also exerts potent immunosuppression) (Givel et al., 2018; Kato et al., 2018; Rashedi, Gomez-Aristizabal, Wang, Viswanathan, & Keating, 2017), and can polarize helper T cell responses toward a T$_H$2 profile, which supports (rather than limits) tumor progression (De Monte et al., 2011).

Immunosuppression by stromal cells also involves the inhibition of multiple effectors of the anticancer immune response (Galluzzi, Chan et al., 2018). For instance, CAFs limit the ability of natural killer (NK) cells to mediate anticancer effects by inhibiting the expression of the NK cell-activatory receptor killer cell lectin like receptor K1 (KLRK1, best known as NKG2D) (Lopez-Soto, Gonzalez, Smyth, & Galluzzi, 2017) on their surface and/or expression of its cognate ligands on the surface of malignant cells (Costa, Vene, et al., 2018; Ziani et al., 2017). Along similar lines, stromal cells can inhibit the activity of CD8$^+$ cytotoxic T lymphocytes (CTLs) by secreting immunosuppressive cytokines (*e.g.*, IL10, TGFB1, SDF1) and metabolites (*i.e.*, adenosine) (de Lourdes Mora-Garcia et al., 2016; Feig et al., 2013; Garcia-Rocha et al., 2015; B. Garg et al., 2018; Kerkela et al., 2016; Saldanha-Araujo et al., 2011). The metabolic rewiring of activated CAFs is indeed especially relevant for their ability to quench tumor-targeting CTL-driven immune responses. In particular, stromal cells overconsume glucose, arginine and tryptophan, all of which are required for the optimal expansion of CTLs to mediate robust effectors functions (Bantug et al., 2018; Chang et al., 2015), as a consequence of intense glycolytic metabolism as well as of the elevated expression of indoleamine 2,3-dioxygenase 1 (IDO1) and arginase 1 (ARG1) (J. Y. Chen et al., 2014; Ino et al., 2013; J. Su et al., 2014; Takahashi et al., 2017). Besides depleting CTLs of essential nutrients, this metabolic profile results in the synthesis of actively immunosuppressive molecules including lactate (Comito et al., 2019) and kynurenine (a product of tryptophan metabolism) (Chen et al., 2014; Hsu et al., 2016; Kadle et al., 2018). Moreover, CAFs can inhibit CTL proliferation by secreting nitric oxide (Cremasco et al., 2018) and prostaglandin E$_2$ (Kobayashi, Omori, & Murata, 2018), and directly delete potentially tumor-reacting CTLs by presenting tumor antigens in the context of death signals (Lakins, Ghorani, Munir, Martins, & Shields, 2018). Finally, CAFs not only express high levels of the co-inhibitory ligands CD274 (best known as PD-L1) and programmed cell death 1 ligand 2 (PDCD1LG2, best known as PD-L2) (Chinnadurai, Copland, Patel, & Galipeau, 2014; Davies, Heldring, Kadri, & Le Blanc, 2017; Ebine et al., 2018; Miyoshi et al., 2016; Yang, Liu, et al., 2017), especially in response to therapeutic challenges (Yang, Liu, et al., 2017), but also favor the recruitment of PD-L1-expressing granulocytes to the tumor bed by secreting IL6 (Cheng et al., 2018).

Taken together, these observations exemplify the multipronged immunosuppressive functions of stromal cells. Accordingly, most (if not all) therapeutic strategies based on stromal cell suppression or inactivation (Box 2) reinstate the ability of the host immune system to mediate antineoplastic effects and sensitize tumors to immunotherapy with immune checkpoint blockers (Feig et al., 2013; Mace et al., 2018; Steele et al., 2016; Wang et al., 2014).



Fibroblasts		CAFs
Mesoderm	Origin	Diverse
High	Genetic stability	High
High	Epigenetic stability	Low
Silent	Metabolic profile	Plastic
Low	Autophagic flux	High
Low	Motility	High
Low	Proliferation	High
Inactive	Status	Active

Fig. 2. Side-by-side comparison of CAFs and normal fibroblasts. As compared to their normal counterparts (which derive from the mesoderm), cancer-associated fibroblasts (CAFs, which originate from diverse tissues), exhibit increased epigenetic instability, a plastic metabolic profile generally coupled with increased autophagic proficiency, elevated motility and superior proliferative rates. Such an activated status render CAFs highly resistant to both metabolic and therapeutic challenges.

2. Concluding remarks

Accumulating preclinical evidence indicates that stromal cells populating the TME are considerably different from their normal counterparts (Fig. 2) and particularly resistant to a variety of environmental perturbations, reflecting not only their ability to mount robust responses to stress, but also their elevated phenotypic, metabolic and behavioral plasticity. Importantly, such an intrinsic resistance also favors the survival and adaptation of malignant cells, via metabolic, trophic and immunological circuitries. Thus, stromal cells most often support oncogenesis, tumor progression and resistance to treatment, *de facto* standing out as promising targets for the development of novel anticancer regimens. That said, none of the strategies employed so far to deplete or inactivate CAFs has progressed into clinical drug development (Chen & Song, 2019). Although many reasons can be invoked to explain such a deceit, we surmise that the elevated heterogeneity and plasticity of the stromal compartment of most solid tumors constitute major obstacles against the development of clinically useful stroma-targeting agents. In this context, elucidating the precise molecular mechanisms that underlie the ability of CAFs and TA-MSCs to cope with stress and elude RCD may identify potentially actionable therapeutic targets. Alongside, it will be important to deconvolute the paracrine circuitries that regulate the interaction between stromal cells and other cellular compartments of the TME, and to explore the relevance of precise CAF subpopulations (*e.g.*, PDPN$^+$ CAFs, CD10$^+$GPR77$^+$ CAFs or so-called 'CAFs-S1') (Costa, Kieffer, et al., 2018; Su et al., 2018; Yoshida et al., 2015). Clarifying these aspects of the CAF immunobiology may not only open novel avenues of investigation but also identify previously unexplored CAF-targeting therapeutic strategies.

Disclosures

LG provides remunerated consulting to OmniSEQ (Buffalo, NY, USA), Astra Zeneca (Gaithersburg, MD, USA), VL47 (New York, NY, USA) and the Luke Heller TECPR2 Foundation (Boston, MA, USA), and he is member of the Scientific Advisory Committee of OmniSEQ (Buffalo, NY, USA).

Author contributions

IV and LG conceived the article, prepared the first version of the manuscript and addressed comments from reviewers. GM and CG performed bibliographical searches in support of manuscript preparation. GM prepared display items with inputs and revisions from IV and LG. All authors approved the final version of the article.

Acknowledgements

IV is supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC, IG 2017 grant number 20417), Ministero Italiano della Salute (grant number RF_GR-2011-02351355) and a startup grant from the Italian Institute for Genomic Medicine (Turin, Italy). LG is supported by a Breakthrough Level 2 grant from the US Department of Defense, Breast Cancer Research Program (BRCP) [#BC180476P1], by a startup grant from the Dept. of Radiation Oncology at Weill Cornell Medicine (New York, US), by industrial collaborations with Lytix (Oslo, Norway) and Phosplatin (New York, US), and by donations from Phosplatin (New York, US), the Luke Heller TECPR2 Foundation (Boston, US) and Sotio a.s. (Prague, Czech Republic).

References

Acharyya, S., Oskarsson, T., Vanharanta, S., Malladi, S., Kim, J., Morris, P. G., ... Massague, J. (2012). A CXCL1 paracrine network links cancer chemoresistance and metastasis. *Cell 150*(1), 165–178. https://doi.org/10.1016/j.cell.2012.04.042.

Al-Ansari, M. M., & Aboussekhra, A. (2014). Caffeine mediates sustained inactivation of breast cancer-associated myofibroblasts via up-regulation of tumor suppressor genes. *PLoS ONE 9*(3), e90907. https://doi.org/10.1371/journal.pone.0090907.

Al-Ansari, M. M., & Aboussekhra, A. (2018). ATR suppresses the pro-tumorigenic functions of breast stromal fibroblasts. *Oncotarget 9*(78), 34681–34690. https://doi.org/10.18632/oncotarget.26159.

Alexander, J., & Cukierman, E. (2016). Stromal dynamic reciprocity in cancer: intricacies of fibroblastic-ECM interactions. *Current Opinion in Cell Biology 42*, 80–93. https://doi.org/10.1016/j.ceb.2016.05.002.

Allaoui, R., Bergenfelz, C., Mohlin, S., Hagerling, C., Salari, K., Werb, Z., ... Leandersson, K. (2016). Cancer-associated fibroblast-secreted CXCL16 attracts monocytes to promote stroma activation in triple-negative breast cancers. *Nature Communications 7*, 13050. https://doi.org/10.1038/ncomms13050.

Al-Rakan, M. A., Hendrayani, S. F., & Aboussekhra, A. (2016). CHEK2 represses breast stromal fibroblasts and their paracrine tumor-promoting effects through suppressing SDF-1 and IL-6. *BMC Cancer 16*, 575. https://doi.org/10.1186/s12885-016-2614-5.

Alspach, E., Flanagan, K. C., Luo, X., Ruhland, M. K., Huang, H., Pazolli, E., ... Stewart, S. A. (2014). p38MAPK plays a crucial role in stromal-mediated tumorigenesis. *Cancer Discovery 4*(6), 716–729. https://doi.org/10.1158/2159-8290.CD-13-0743.

Ammirante, M., Shalapour, S., Kang, Y., Jamieson, C. A., & Karin, M. (2014). Tissue injury and hypoxia promote malignant progression of prostate cancer by inducing CXCL13 expression in tumor myofibroblasts. *Proceedings of the National Academy of Sciences of the United States of America 111*(41), 14776–14781. https://doi.org/10.1073/pnas.1416498111.

Arandkar, S., Furth, N., Elisha, Y., Nataraj, N. B., van der Kuip, H., Yarden, Y., ... Oren, M. (2018). Altered p53 functionality in cancer-associated fibroblasts contributes to their cancer-supporting features. *Proceedings of the National Academy of Sciences of the United States of America 115*(25), 6410–6415. https://doi.org/10.1073/pnas.1719076115.

Avnet, S., Di Pompo, G., Chano, T., Errani, C., Ibrahim-Hashim, A., Gillies, R. J., ... Baldini, N. (2017). Cancer-associated mesenchymal stroma fosters the stemness of osteosarcoma cells in response to intratumoral acidosis via NF-kappaB activation. *International Journal of Cancer 140*(6), 1331–1345. https://doi.org/10.1002/ijc.30540.

Bantug, G. R., Galluzzi, L., Kroemer, G., & Hess, C. (2018). The spectrum of T cell metabolism in health and disease. *Nature Reviews. Immunology 18*(1), 19–34. https://doi.org/10.1038/nri.2017.99.

Berlin, J., Bendell, J. C., Hart, L. L., Firdaus, I., Gore, I., Hermann, R. C., ... Low, J. A. (2013). A randomized phase II trial of vismodegib versus placebo with FOLFOX or FOLFIRI and bevacizumab in patients with previously untreated metastatic colorectal cancer. *Clinical Cancer Research 19*(1), 258–267. https://doi.org/10.1158/1078-0432.CCR-12-1800.

Bertero, T., Oldham, W. M., Grasset, E. M., Bourget, I., Boulter, E., Pisano, S., ... Gaggioli, C. (2019). Tumor-Stroma Mechanics Coordinate Amino Acid Availability to Sustain Tumor Growth and Malignancy. *Cell Metabolism 29*(1), 124–140 e110 https://doi.org/10.1016/j.cmet.2018.09.012.

Boelens, M. C., Wu, T. J., Nabet, B. Y., Xu, B., Qiu, Y., Yoon, T., ... Minn, A. J. (2014). Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways. *Cell 159*(3), 499–513. https://doi.org/10.1016/j.cell.2014.09.051.

Brauer, H. A., Makowski, L., Hoadley, K. A., Casbas-Hernandez, P., Lang, L. J., Roman-Perez, E., ... Troester, M. A. (2013). Impact of tumor microenvironment and epithelial phenotypes on metabolism in breast cancer. *Clinical Cancer Research 19*(3), 571–585. https://doi.org/10.1158/1078-0432.CCR-12-2123.

Brechbuhl, H. M., Finlay-Schultz, J., Yamamoto, T. M., Gillen, A. E., Cittelly, D. M., Tan, A. C., ... Kabos, P. (2017). Fibroblast subtypes regulate responsiveness of luminal breast Cancer to Estrogen. *Clinical Cancer Research 23*(7), 1710–1721. https://doi.org/10.1158/1078-0432.CCR-15-2851.

Cadamuro, M., Nardo, G., Indraccolo, S., Dall'olmo, L., Sambado, L., Moserle, L., ... Strazzabosco, M. (2013). Platelet-derived growth factor-D and Rho GTPases regulate recruitment of cancer-associated fibroblasts in cholangiocarcinoma. *Hepatology 58*(3), 1042–1053. https://doi.org/10.1002/hep.26384.

Capparelli, C., Guido, C., Whitaker-Menezes, D., Bonuccelli, G., Balliet, R., Pestell, T. G., ... Lisanti, M. P. (2012). Autophagy and senescence in cancer-associated fibroblasts metabolically supports tumor growth and metastasis via glycolysis and ketone production. *Cell Cycle 11*(12), 2285–2302. https://doi.org/10.4161/cc.20718.

Carapuca, E. F., Gemenetzidis, E., Feig, C., Bapiro, T. E., Williams, M. D., Wilson, A. S., ... Kocher, H. M. (2016). Anti-stromal treatment together with chemotherapy targets multiple signalling pathways in pancreatic adenocarcinoma. *The Journal of Pathology 239*(3), 286–296. https://doi.org/10.1002/path.4727.

Carstens, J. L., Correa de Sampaio, P., Yang, D., Barua, S., Wang, H., Rao, A., ... Kalluri, R. (2017). Spatial computation of intratumoral T cells correlates with survival of patients with pancreatic cancer. *Nature Communications 8*, 15095. https://doi.org/10.1038/ncomms15095.

Casey, S. C., Vaccari, M., Al-Mulla, F., Al-Temaimi, R., Amedei, A., Barcellos-Hoff, M. H., ... Felsher, D. W. (2015). The effect of environmental chemicals on the tumor microenvironment. *Carcinogenesis 36*(Suppl. 1), S160–S183. https://doi.org/10.1093/carcin/bgv035.

Castells, M., Milhas, D., Gandy, C., Thibault, B., Rafii, A., Delord, J. P., & Couderc, B. (2013). Microenvironment mesenchymal cells protect ovarian cancer cell lines from apoptosis by inhibiting XIAP inactivation. *Cell Death & Disease 4*, e887. https://doi.org/10.1038/cddis.2013.384.

Catenacci, D. V., Junttila, M. R., Karrison, T., Bahary, N., Horiba, M. N., Nattam, S. R., ... Kindler, H. L. (2015). Randomized Phase Ib/II Study of Gemcitabine Plus Placebo or Vismodegib, a Hedgehog Pathway Inhibitor, in Patients With Metastatic Pancreatic Cancer. *Journal of Clinical Oncology 33*(36), 4284–4292. https://doi.org/10.1200/JCO.2015.62.8719.

Cazet, A. S., Hui, M. N., Elsworth, B. L., Wu, S. Z., Roden, D., Chan, C. L., ... Swarbrick, A. (2018). Targeting stromal remodeling and cancer stem cell plasticity overcomes chemoresistance in triple negative breast cancer. *Nature Communications 9*(1), 2897. https://doi.org/10.1038/s41467-018-05220-6.

Chan, J. S. K., Sng, M. K., Teo, Z. Q., Chong, H. C., Twang, J. S., & Tan, N. S. (2018). Targeting nuclear receptors in cancer-associated fibroblasts as concurrent therapy to inhibit development of chemoresistant tumors. *Oncogene 37*(2), 160–173. https://doi.org/10.1038/onc.2017.319.

Chan, T. S., Hsu, C. C., Pai, V. C., Liao, W. Y., Huang, S. S., Tan, K. T., ... Tsai, K. K. (2016). Metronomic chemotherapy prevents therapy-induced stromal activation and induction of tumor-initiating cells. *The Journal of Experimental Medicine 213*(13), 2967–2988. https://doi.org/10.1084/jem.20151665.

Chang, C. H., Qiu, J., O'Sullivan, D., Buck, M. D., Noguchi, T., Curtis, J. D., ... Pearce, E. L. (2015). Metabolic Competition in the Tumor Microenvironment Is a Driver of Cancer Progression. *Cell 162*(6), 1229–1241. https://doi.org/10.1016/j.cell.2015.08.016.

Chaturvedi, P., Gilkes, D. M., Takano, N., & Semenza, G. L. (2014). Hypoxia-inducible factor-dependent signaling between triple-negative breast cancer cells and mesenchymal stem cells promotes macrophage recruitment. *Proceedings of the National Academy of Sciences of the United States of America 111*(20), E2120–E2129. https://doi.org/10.1073/pnas.1406655111.

Chaudhri, V. K., Salzler, G. G., Dick, S. A., Buckman, M. S., Sordella, R., Karoly, E. D., ... McGraw, T. E. (2013). Metabolic alterations in lung cancer-associated fibroblasts correlated with increased glycolytic metabolism of the tumor. *Molecular Cancer Research 11*(6), 579–592. https://doi.org/10.1158/1541-7786.MCR-12-0437-T.

Che, Y., Wang, J., Li, Y., Lu, Z., Huang, J., Sun, S., ... He, J. (2018). Cisplatin-activated PAI-1 secretion in the cancer-associated fibroblasts with paracrine effects promoting esophageal squamous cell carcinoma progression and causing chemoresistance. *Cell Death & Disease 9*(7), 759. https://doi.org/10.1038/s41419-018-0808-2.

Chen, D. S., & Mellman, I. (2017). Elements of cancer immunity and the cancer-immune set point. *Nature 541*(7637), 321–330. https://doi.org/10.1038/nature21349.

Chen, F., Long, Q., Fu, D., Zhu, D., Ji, Y., Han, L., ... Sun, Y. (2018). Targeting SPINK1 in the damaged tumour microenvironment alleviates therapeutic resistance. *Nature Communications 9*(1), 4315. https://doi.org/10.1038/s41467-018-06860-4.

Chen, J. Y., Li, C. F., Kuo, C. C., Tsai, K. K., Hou, M. F., & Hung, W. C. (2014). Cancer/stroma interplay via cyclooxygenase-2 and indoleamine 2,3-dioxygenase promotes breast cancer progression. *Breast Cancer Research 16*(4), 410. https://doi.org/10.1186/s13058-014-0410-1.

Chen, X., & Song, E. (2019). Turning foes to friends: targeting cancer-associated fibroblasts. *Nature Reviews. Drug Discovery 18*(2), 99–115. https://doi.org/10.1038/s41573-018-0004-1.

Cheng, Y., Li, H., Deng, Y., Tai, Y., Zeng, K., Zhang, Y., ... Yang, Y. (2018). Cancer-associated fibroblasts induce PDL1+ neutrophils through the IL6-STAT3 pathway that foster immune suppression in hepatocellular carcinoma. *Cell Death & Disease 9*(4), 422. https://doi.org/10.1038/s41419-018-0458-4.

Cheteh, E. H., Augsten, M., Rundqvist, H., Bianchi, J., Sarne, V., Egevad, L., ... Wiman, K. G. (2017). Human cancer-associated fibroblasts enhance glutathione levels and antagonize drug-induced prostate cancer cell death. *Cell Death & Disease 8*(6), e2848. https://doi.org/10.1038/cddis.2017.225.

Chinnadurai, R., Copland, I. B., Patel, S. R., & Galipeau, J. (2014). IDO-independent suppression of T cell effector function by IFN-gamma-licensed human mesenchymal stromal cells. *Journal of Immunology 192*(4), 1491–1501. https://doi.org/10.4049/jimmunol.1301828.

Cho, H., Seo, Y., Loke, K. M., Kim, S. W., Oh, S. M., Kim, J. H., ... Williams, D. R. (2018). Cancer-Stimulated CAFs Enhance Monocyte Differentiation and Protumoral TAM Activation via IL6 and GM-CSF Secretion. *Clinical Cancer Research 24*(21), 5407–5421. https://doi.org/10.1158/1078-0432.CCR-18-0125.

Choi, J., Kim, D. H., Jung, W. H., & Koo, J. S. (2013). Metabolic interaction between cancer cells and stromal cells according to breast cancer molecular subtype. *Breast Cancer Research 15*(5), R78. https://doi.org/10.1186/bcr3472.

Chronopoulos, A., Robinson, B., Sarper, M., Cortes, E., Auernheimer, V., Lachowski, D., ... Del Rio Hernandez, A. (2016). ATRA mechanically reprograms pancreatic stellate cells to suppress matrix remodelling and inhibit cancer cell invasion. *Nature Communications 7*, 12630. https://doi.org/10.1038/ncomms12630.

Clocchiatti, A., Ghosh, S., Procopio, M. G., Mazzeo, L., Bordignon, P., Ostano, P., ... Dotto, G. P. (2018). Androgen receptor functions as transcriptional repressor of cancer-associated fibroblast activation. *The Journal of Clinical Investigation 128*(12), 5531–5548. https://doi.org/10.1172/JCI99159.

Cohen, N., Shani, O., Raz, Y., Sharon, Y., Hoffman, D., Abramovitz, L., & Erez, N. (2017). Fibroblasts drive an immunosuppressive and growth-promoting microenvironment in breast cancer via secretion of Chitinase 3-like 1. *Oncogene 36*(31), 4457–4468. https://doi.org/10.1038/onc.2017.65.

Comito, G., Giannoni, E., Segura, C. P., Barcellos-de-Souza, P., Raspollini, M. R., Baroni, G., & Chiarugi, P. (2014). Cancer-associated fibroblasts and M2-polarized macrophages synergize during prostate carcinoma progression. *Oncogene 33*(19), 2423–2431. https://doi.org/10.1038/onc.2013.191.

Comito, G., Iscaro, A., Bacci, M., Morandi, A., Ippolito, L., Parri, M., ... Chiarugi, P. (2019). Lactate modulates CD4(+) T-cell polarization and induces an immunosuppressive environment, which sustains prostate carcinoma progression via TLR8/miR21 axis. *Oncogene*. https://doi.org/10.1038/s41388-019-0688-7.

Costa, A., Kieffer, Y., Scholer-Dahirel, A., Pelon, F., Bourachot, B., Cardon, M., ... Mechta-Grigoriou, F. (2018). Fibroblast Heterogeneity and Immunosuppressive Environment in Human Breast Cancer. *Cancer Cell 33*(3). https://doi.org/10.1016/j.ccell.2018.01.011 463-479 e410.

Costa, A., Scholer-Dahirel, A., & Mechta-Grigoriou, F. (2014). The role of reactive oxygen species and metabolism on cancer cells and their microenvironment. *Seminars in Cancer Biology 25*, 23–32. https://doi.org/10.1016/j.semcancer.2013.12.007.

Costa, D., Vene, R., Benelli, R., Romairone, E., Scabini, S., Catellani, S., ... Poggi, A. (2018). Targeting the Epidermal Growth Factor Receptor Can Counteract the Inhibition of Natural Killer Cell Function Exerted by Colorectal Tumor-Associated Fibroblasts. *Frontiers in Immunology 9*, 1150. https://doi.org/10.3389/fimmu.2018.01150.

Cremasco, V., Astarita, J. L., Grauel, A. L., Keerthivasan, S., MacIsaac, K., Woodruff, M. C., ... Turley, S. J. (2018). FAP Delineates Heterogeneous and Functionally Divergent Stromal Cells in Immune-Excluded Breast Tumors. *Cancer Immunology Research 6*(12), 1472–1485. https://doi.org/10.1158/2326-6066.CIR-18-0098.

Cruz-Bermudez, A., Laza-Briviesca, R., Vicente-Blanco, R. J., Garcia-Grande, A., Coronado, M. J., Laine-Menendez, S., ... Provencio, M. (2019). Cancer-associated fibroblasts modify lung cancer metabolism involving ROS and TGF-beta signaling. *Free Radical Biology & Medicine 130*, 163–173. https://doi.org/10.1016/j.freeradbiomed.2018.10.450.

Curtis, M., Kenny, H. A., Ashcroft, B., Mukherjee, A., Johnson, A., Zhang, Y., ... Lengyel, E. (2019). Fibroblasts Mobilize Tumor Cell Glycogen to Promote Proliferation and Metastasis. *Cell Metabolism 29*(1), 141–155 e149. https://doi.org/10.1016/j.cmet.2018.08.007.

Dauer, P., Zhao, X., Gupta, V. K., Sharma, N., Kesh, K., Gnamlin, P., ... Saluja, A. (2018). Inactivation of Cancer-Associated-Fibroblasts Disrupts Oncogenic Signaling in Pancreatic Cancer Cells and Promotes Its Regression. *Cancer Research 78*(5), 1321–1333. https://doi.org/10.1158/0008-5472.CAN-17-2320.

Davies, L. C., Heldring, N., Kadri, N., & Le Blanc, K. (2017). Mesenchymal Stromal Cell Secretion of Programmed Death-1 Ligands Regulates T Cell Mediated Immunosuppression. *Stem Cells 35*(3), 766–776. https://doi.org/10.1002/stem.2509.

De Francesco, E. M., Lappano, R., Santolla, M. F., Marsico, S., Caruso, A., & Maggiolini, M. (2013). HIF-1alpha/GPER signaling mediates the expression of VEGF induced by hypoxia in breast cancer associated fibroblasts (CAFs). *Breast Cancer Research 15*(4), R64. https://doi.org/10.1186/bcr3458.

De Francesco, E. M., Sims, A. H., Maggiolini, M., Sotgia, F., Lisanti, M. P., & Clarke, R. B. (2017). GPER mediates the angiocrine actions induced by IGF1 through the HIF-1alpha/VEGF pathway in the breast tumor microenvironment. *Breast Cancer Research 19*(1), 129. https://doi.org/10.1186/s13058-017-0923-5.

De Monte, L., Reni, M., Tassi, E., Clavenna, D., Papa, I., Recalde, H., ... Protti, M. P. (2011). Intratumor T helper type 2 cell infiltrate correlates with cancer-associated fibroblast thymic stromal lymphopoietin production and reduced survival in pancreatic cancer. *The Journal of Experimental Medicine 208*(3), 469–478. https://doi.org/10.1084/jem.20101876.

Demaria, M., O'Leary, M. N., Chang, J., Shao, L., Liu, S., Alimirah, F., ... Campisi, J. (2017). Cellular Senescence Promotes Adverse Effects of Chemotherapy and Cancer Relapse. *Cancer Discovery 7*(2), 165–176. https://doi.org/10.1158/2159-8290.CD-16-0241.

Desmouliere, A., Redard, M., Darby, I., & Gabbiani, G. (1995). Apoptosis mediates the decrease in cellularity during the transition between granulation tissue and scar. *The American Journal of Pathology 146*(1), 56–66.

Ding, L., Ren, J., Zhang, D., Li, Y., Huang, X., Hu, Q., ... Hou, Y. (2018). A novel stromal lncRNA signature reprograms fibroblasts to promote the growth of oral squamous cell carcinoma via LncRNA-CAF/interleukin-33. *Carcinogenesis 39*(3), 397–406. https://doi.org/10.1093/carcin/bgy006.

Dou, Z., Xu, C., Donahue, G., Shimi, T., Pan, J. A., Zhu, J., ... Berger, S. L. (2015). Autophagy mediates degradation of nuclear lamina. *Nature 527*(7576), 105–109. https://doi.org/10.1038/nature15548.

Druzhkova, I. N., Shirmanova, M. V., Lukina, M. M., Dudenkova, V. V., Mishina, N. M., & Zagaynova, E. V. (2016). The metabolic interaction of cancer cells and fibroblasts - coupling between NAD(P)H and FAD, intracellular pH and hydrogen peroxide. *Cell Cycle 15*(9), 1257–1266. https://doi.org/10.1080/15384101.2016.1160974.

Duluc, C., Moatassim-Billah, S., Chalabi-Dchar, M., Perraud, A., Samain, R., Breibach, F., ... Bousquet, C. (2015). Pharmacological targeting of the protein synthesis mTOR/4E-BP1 pathway in cancer-associated fibroblasts abrogates pancreatic tumour chemoresistance. *EMBO Molecular Medicine 7*(6), 735–753. https://doi.org/10.15252/emmm.201404346.

Ebine, K., Kumar, K., Pham, T. N., Shields, M. A., Collier, K. A., Shang, M., ... Munshi, H. G. (2018). Interplay between interferon regulatory factor 1 and BRD4 in the regulation of PD-L1 in pancreatic stellate cells. *Scientific Reports 8*(1), 13225. https://doi.org/10.1038/s41598-018-31658-1.

Elahi-Gedwillo, K. Y., Carlson, M., Zettervall, J., & Provenzano, P. P. (2019). Antifibrotic Therapy Disrupts Stromal Barriers and Modulates the Immune Landscape in Pancreatic Ductal Adenocarcinoma. *Cancer Research 79*(2), 372–386. https://doi.org/10.1158/0008-5472.CAN-18-1334.

Endo, S., Nakata, K., Ohuchida, K., Takesue, S., Nakayama, H., Abe, T., ... Nakamura, M. (2017). Autophagy Is Required for Activation of Pancreatic Stellate Cells, Associated With Pancreatic Cancer Progression and Promotes Growth of Pancreatic Tumors in Mice. *Gastroenterology 152*(6), 1492–1506 e1424. https://doi.org/10.1053/j.gastro.2017.01.010.

Erez, N., Glanz, S., Raz, Y., Avivi, C., & Barshack, I. (2013). Cancer associated fibroblasts express pro-inflammatory factors in human breast and ovarian tumors. *Biochemical and Biophysical Research Communications 437*(3), 397–402. https://doi.org/10.1016/j.bbrc.2013.06.089.

Erez, N., Truitt, M., Olson, P., Arron, S. T., & Hanahan, D. (2010). Cancer-Associated Fibroblasts Are Activated in Incipient Neoplasia to Orchestrate Tumor-Promoting Inflammation in an NF-kappaB-Dependent Manner. *Cancer Cell 17*(2), 135–147. https://doi.org/10.1016/j.ccr.2009.12.041.

Feig, C., Jones, J. O., Kraman, M., Wells, R. J., Deonarine, A., Chan, D. S., ... Fearon, D. T. (2013). Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. *Proceedings of the National Academy of Sciences of the United States of America 110*(50), 20212–20217. https://doi.org/10.1073/pnas.1320318110.

Fiaschi, T., Giannoni, E., Taddei, M. L., Cirri, P., Marini, A., Pintus, G., ... Chiarugi, P. (2013). Carbonic anhydrase IX from cancer-associated fibroblasts drives epithelial-mesenchymal transition in prostate carcinoma cells. *Cell Cycle 12*(11), 1791–1801. https://doi.org/10.4161/cc.24902.

Fiaschi, T., Marini, A., Giannoni, E., Taddei, M. L., Gandellini, P., De Donatis, A., ... Chiarugi, P. (2012). Reciprocal metabolic reprogramming through lactate shuttle coordinately influences tumor-stroma interplay. *Cancer Research 72*(19), 5130–5140. https://doi.org/10.1158/0008-5472.CAN-12-1949.

Fong, M. Y., Zhou, W., Liu, L., Alontaga, A. Y., Chandra, M., Ashby, J., ... Wang, S. E. (2015). Breast-cancer-secreted miR-122 reprograms glucose metabolism in premetastatic niche to promote metastasis. *Nature Cell Biology 17*(2), 183–194. https://doi.org/10.1038/ncb3094.

Frassanito, M. A., De Veirman, K., Desantis, V., Di Marzo, L., Vergara, D., Ruggieri, S., ... Vacca, A. (2016). Halting pro-survival autophagy by TGFbeta inhibition in bone marrow fibroblasts overcomes bortezomib resistance in multiple myeloma patients. *Leukemia 30*(3), 640–648. https://doi.org/10.1038/leu.2015.289.

Froeling, F. E., Feig, C., Chelala, C., Dobson, R., Mein, C. E., Tuveson, D. A., ... Kocher, H. M. (2011). Retinoic acid-induced pancreatic stellate cell quiescence reduces paracrine Wnt-beta-catenin signaling to slow tumor progression. *Gastroenterology 141*(4). https://doi.org/10.1053/j.gastro.2011.06.047 1486-1497, 1497 e1481-1414.

Galluzzi, L., Baehrecke, E. H., Ballabio, A., Boya, P., Bravo-San Pedro, J. M., Cecconi, F., ... Kroemer, G. (2017). Molecular definitions of autophagy and related processes. *The EMBO Journal 36*(13), 1811–1836. https://doi.org/10.15252/embj.201796697.

Galluzzi, L., Bravo-San Pedro, J. M., & Kroemer, G. (2016). Autophagy Mediates Tumor Suppression via Cellular Senescence. *Trends in Cell Biology 26*(1), 1–3. https://doi.org/10.1016/j.tcb.2015.11.001.

Galluzzi, L., Bravo-San Pedro, J. M., Levine, B., Green, D. R., & Kroemer, G. (2017). Pharmacological modulation of autophagy: therapeutic potential and persisting obstacles. *Nature Reviews. Drug Discovery 16*(7), 487–511. https://doi.org/10.1038/nrd.2017.22.

Galluzzi, L., Buque, A., Kepp, O., Zitvogel, L., & Kroemer, G. (2017). Immunogenic cell death in cancer and infectious disease. *Nature Reviews. Immunology 17*(2), 97–111. https://doi.org/10.1038/nri.2016.107.

Galluzzi, L., Chan, T. A., Kroemer, G., Wolchok, J. D., & Lopez-Soto, A. (2018). The hallmarks of successful anticancer immunotherapy. *Science Translational Medicine 10*(459). https://doi.org/10.1126/scitranslmed.aat7807.

Galluzzi, L., Kepp, O., & Kroemer, G. (2012). Reverse Warburg: straight to cancer. *Cell Cycle 11*(6), 1059. https://doi.org/10.4161/cc.11.6.19746.

Galluzzi, L., Kepp, O., Vander Heiden, M. G., & Kroemer, G. (2013). Metabolic targets for cancer therapy. *Nature Reviews. Drug Discovery 12*(11), 829–846. https://doi.org/10.1038/nrd4145.

Galluzzi, L., Marsili, S., Vitale, I., Senovilla, L., Michels, J., Garcia, P., ... Kroemer, G. (2013). Vitamin B6 metabolism influences the intracellular accumulation of cisplatin. *Cell Cycle 12*(3), 417–421. https://doi.org/10.4161/cc.23275.

Galluzzi, L., Spranger, S., Fuchs, E., & Lopez-Soto, A. (2019). WNT Signaling in Cancer Immunosurveillance. *Trends in Cell Biology 29*(1), 44–65. https://doi.org/10.1016/j.tcb.2018.08.005.

Galluzzi, L., & Vitale, I. (2018). Oncogene-induced senescence and tumour control in complex biological systems. *Cell Death and Differentiation 25*(6), 1005–1006. https://doi.org/10.1038/s41418-018-0102-y.

Galluzzi, L., Vitale, I., Aaronson, S. A., Abrams, J. M., Adam, D., Agostinis, P., ... Kroemer, G. (2018). Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death and Differentiation 25*(3), 486–541. https://doi.org/10.1038/s41418-017-0012-4.

Galluzzi, L., Yamazaki, T., & Kroemer, G. (2018). Linking cellular stress responses to systemic homeostasis. *Nature Reviews. Molecular Cell Biology 19*(11), 731–745. https://doi.org/10.1038/s41580-018-0068-0.

Gan, G. N., Eagles, J., Keysar, S. B., Wang, G., Glogowska, M. J., Altunbas, C., ... Jimeno, A. (2014). Hedgehog signaling drives radioresistance and stroma-driven tumor repopulation in head and neck squamous cancers. *Cancer Research 74*(23), 7024–7036. https://doi.org/10.1158/0008-5472.CAN-14-1346.

Garcia-Rocha, R., Moreno-Lafont, M., Mora-Garcia, M. L., Weiss-Steider, B., Montesinos, J. J., Pina-Sanchez, P., & Monroy-Garcia, A. (2015). Mesenchymal stromal cells derived from cervical cancer tumors induce TGF-beta1 expression and IL-10 expression and secretion in the cervical cancer cells, resulting in protection from cytotoxic T cell activity. *Cytokine 76*(2), 382–390. https://doi.org/10.1016/j.cyto.2015.09.001.

Garg, A. D., More, S., Rufo, N., Mece, O., Sassano, M. L., Agostinis, P., ... Galluzzi, L. (2017). Trial watch: immunogenic cell death induction by anticancer chemotherapeutics. *Oncoimmunology 6*(12), e1386829. https://doi.org/10.1080/2162402X.2017.1386829.

Garg, B., Giri, B., Modi, S., Sethi, V., Castro, I., Umland, O., ... Dudeja, V. (2018). NFkappaB in Pancreatic Stellate Cells Reduces Infiltration of Tumors by Cytotoxic T Cells and Killing of Cancer Cells, via Up-regulation of CXCL12. *Gastroenterology 155*(3), 880–891 e888. https://doi.org/10.1053/j.gastro.2018.05.051.

Gascard, P., & Tlsty, T. D. (2016). Carcinoma-associated fibroblasts: orchestrating the composition of malignancy. *Genes & Development 30*(9), 1002–1019. https://doi.org/10.1101/gad.279737.116.

Gilkes, D. M., Bajpai, S., Chaturvedi, P., Wirtz, D., & Semenza, G. L. (2013). Hypoxia-inducible factor 1 (HIF-1) promotes extracellular matrix remodeling under hypoxic conditions by inducing P4HA1, P4HA2, and PLOD2 expression in fibroblasts. *The Journal of Biological Chemistry 288*(15), 10819–10829. https://doi.org/10.1074/jbc.M112.442939.

Gilkes, D. M., Semenza, G. L., & Wirtz, D. (2014). Hypoxia and the extracellular matrix: drivers of tumour metastasis. *Nature Reviews. Cancer 14*(6), 430–439. https://doi.org/10.1038/nrc3726.

Givel, A. M., Kieffer, Y., Scholer-Dahirel, A., Sirven, P., Cardon, M., Pelon, F., ... Mechta-Grigoriou, F. (2018). miR200-regulated CXCL12beta promotes fibroblast heterogeneity and immunosuppression in ovarian cancers. *Nature Communications 9*(1), 1056. https://doi.org/10.1038/s41467-018-03348-z.

Gonzalez, F. J., Xie, C., & Jiang, C. (2018). The role of hypoxia-inducible factors in metabolic diseases. *Nature Reviews. Endocrinology 15*(1), 21–32. https://doi.org/10.1038/s41574-018-0096-z.

Gorchs, L., Hellevik, T., Bruun, J. A., Camilio, K. A., Al-Saad, S., Stuge, T. B., & Martinez-Zubiaurre, I. (2015). Cancer-associated fibroblasts from lung tumors maintain their immunosuppressive abilities after high-dose irradiation. *Frontiers in Oncology 5*, 87. https://doi.org/10.3389/fonc.2015.00087.

Goruppi, S., Clocchiatti, A., & Dotto, G. P. (2019). A role for stromal autophagy in cancer-associated fibroblast activation. *Autophagy*, 1–2. https://doi.org/10.1080/15548627.2019.1569936.

Goruppi, S., Jo, S. H., Laszlo, C., Clocchiatti, A., Neel, V., & Dotto, G. P. (2018). Autophagy Controls CSL/RBPJkappa Stability through a p62/SQSTM1-Dependent Mechanism. *Cell Reports 24*(12), 3108–3114 e3104. https://doi.org/10.1016/j.celrep.2018.08.043.

Goruppi, S., Procopio, M. G., Jo, S., Clocchiatti, A., Neel, V., & Dotto, G. P. (2017). The ULK3 Kinase Is Critical for Convergent Control of Cancer-Associated Fibroblast Activation by CSL and GLI. *Cell Reports 20*(10), 2468–2479. https://doi.org/10.1016/j.celrep.2017.08.048.

Gravett, A. M., Trautwein, N., Stevanovic, S., Dalgleish, A. G., & Copier, J. (2018). Gemcitabine alters the proteasome composition and immunopeptidome of tumour cells. *Oncoimmunology 7*(6), e1438107. https://doi.org/10.1080/2162402X.2018.1438107.

Guan, X., LaPak, K. M., Hennessey, R. C., Yu, C. Y., Shakya, R., Zhang, J., & Burd, C. E. (2017). Stromal Senescence By Prolonged CDK4/6 Inhibition Potentiates Tumor Growth. *Molecular Cancer Research 15*(3), 237–249. https://doi.org/10.1158/1541-7786.MCR-16-0319.

Hanahan, D., & Coussens, L. M. (2012). Accessories to the crime: functions of cells recruited to the tumor microenvironment. *Cancer Cell 21*(3), 309–322. https://doi.org/10.1016/j.ccr.2012.02.022.

Hartmann, N., Giese, N. A., Giese, T., Poschke, I., Offringa, R., Werner, J., & Ryschich, E. (2014). Prevailing role of contact guidance in intrastromal T-cell trapping in human pancreatic cancer. *Clinical Cancer Research 20*(13), 3422–3433. https://doi.org/10.1158/1078-0432.CCR-13-2972.

Hashimoto, O., Yoshida, M., Koma, Y., Yanai, T., Hasegawa, D., Kosaka, Y., ... Yokozaki, H. (2016). Collaboration of cancer-associated fibroblasts and tumour-associated macrophages for neuroblastoma development. *The Journal of Pathology 240*(2), 211–223. https://doi.org/10.1002/path.4769.

Hellevik, T., Pettersen, I., Berg, V., Winberg, J. O., Moe, B. T., Bartnes, K., ... Martinez-Zubiaurre, I. (2012). Cancer-associated fibroblasts from human NSCLC survive ablative doses of radiation but their invasive capacity is reduced. *Radiation Oncology 7*, 59. https://doi.org/10.1186/1748-717X-7-59.

Hessmann, E., Patzak, M. S., Klein, L., Chen, N., Kari, V., Ramu, I., ... Neesse, A. (2018). Fibroblast drug scavenging increases intratumoural gemcitabine accumulation in murine pancreas cancer. *Gut 67*(3), 497–507. https://doi.org/10.1136/gutjnl-2016-311954.

Hingorani, S. R., Harris, W. P., Beck, J. T., Berdov, B. A., Wagner, S. A., Pshevlotsky, E. M., ... Devoe, C. E. (2016). Phase Ib Study of PEGylated Recombinant Human Hyaluronidase and Gemcitabine in Patients with Advanced Pancreatic Cancer. *Clinical Cancer Research 22*(12), 2848–2854. https://doi.org/10.1158/1078-0432.CCR-15-2010.

Hingorani, S. R., Zheng, L., Bullock, A. J., Seery, T. E., Harris, W. P., Sigal, D. S., ... Hendifar, A. E. (2018). HALO 202: Randomized Phase II Study of PEGPH20 Plus Nab-Paclitaxel/Gemcitabine Versus Nab-Paclitaxel/Gemcitabine in Patients With Untreated, Metastatic Pancreatic Ductal Adenocarcinoma. *Journal of Clinical Oncology 36*(4), 359–366. https://doi.org/10.1200/JCO.2017.74.9564.

Hirakawa, T., Yashiro, M., Doi, Y., Kinoshita, H., Morisaki, T., Fukuoka, T., ... Hirakawa, K. (2016). Pancreatic Fibroblasts Stimulate the Motility of Pancreatic Cancer Cells through IGF1/IGF1R Signaling under Hypoxia. *PLoS ONE 11*(8), e0159912. https://doi.org/10.1371/journal.pone.0159912.

Hirata, E., Girotti, M. R., Viros, A., Hooper, S., Spencer-Dene, B., Matsuda, M., ... Sahai, E. (2015). Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin beta1/FAK signaling. *Cancer Cell 27*(4), 574–588. https://doi.org/10.1016/j.ccell.2015.03.008.

Hosein, A. N., Wu, M., Arcand, S. L., Lavallee, S., Hebert, J., Tonin, P. N., & Basik, M. (2010). Breast carcinoma-associated fibroblasts rarely contain p53 mutations or chromosomal aberrations. *Cancer Research 70*(14), 5770–5777. https://doi.org/10.1158/0008-5472.CAN-10-0673.

Hsu, Y. L., Hung, J. Y., Chiang, S. Y., Jian, S. F., Wu, C. Y., Lin, Y. S., ... Kuo, P. L. (2016). Lung cancer-derived galectin-1 contributes to cancer associated fibroblast-mediated cancer progression and immune suppression through TDO2/kynurenine axis. *Oncotarget 7*(19), 27584–27598. https://doi.org/10.18632/oncotarget.8488.

Hu, J. W., Sun, P., Zhang, D. X., Xiong, W. J., & Mi, J. (2014). Hexokinase 2 regulates G1/S checkpoint through CDK2 in cancer-associated fibroblasts. *Cellular Signalling 26*(10), 2210–2216. https://doi.org/10.1016/j.cellsig.2014.04.015.

Hu, Y., Yan, C., Mu, L., Huang, K., Li, X., Tao, D., ... Qin, J. (2015). Fibroblast-Derived Exosomes Contribute to Chemoresistance through Priming Cancer Stem Cells in Colorectal Cancer. *PLoS ONE 10*(5), e0125625. https://doi.org/10.1371/journal.pone.0125625.

Huang, Li, T., Wang, L., Zhang, L., Yan, R., Li, K., ... Zhang, H. (2016). Hepatocellular carcinoma redirects to ketolysis for progression under nutrition deprivation stress. *Cell Research 26*(10), 1112–1130. https://doi.org/10.1038/cr.2016.109.

Huang, Y., Nahar, S., Nakagawa, A., Fernandez-Barrena, M. G., Mertz, J. A., Bryant, B. M., ... Liss, A. S. (2016). Regulation of GLI Underlies a Role for BET Bromodomains in Pancreatic Cancer Growth and the Tumor Microenvironment. *Clinical Cancer Research 22*(16), 4259–4270. https://doi.org/10.1158/1078-0432.CCR-15-2068.

Huber, R. M., Lucas, J. M., Gomez-Sarosi, L. A., Coleman, I., Zhao, S., Coleman, R., & Nelson, P. S. (2015). DNA damage induces GDNF secretion in the tumor microenvironment with paracrine effects promoting prostate cancer treatment resistance. *Oncotarget 6*(4), 2134–2147. https://doi.org/10.18632/oncotarget.3040.

Ino, Y., Yamazaki-Itoh, R., Oguro, S., Shimada, K., Kosuge, T., Zavada, J., ... Hiraoka, N. (2013). Arginase II expressed in cancer-associated fibroblasts indicates tissue hypoxia and predicts poor outcome in patients with pancreatic cancer. *PLoS ONE 8*(2), e55146. https://doi.org/10.1371/journal.pone.0055146.

Ireland, L., Santos, A., Ahmed, M. S., Rainer, C., Nielsen, S. R., Quaranta, V., ... Mielgo, A. (2016). Chemoresistance in Pancreatic Cancer Is Driven by Stroma-Derived Insulin-Like Growth Factors. *Cancer Research 76*(23), 6851–6863. https://doi.org/10.1158/0008-5472.CAN-16-1201.

Jacobetz, M. A., Chan, D. S., Neesse, A., Bapiro, T. E., Cook, N., Frese, K. K., ... Tuveson, D. A. (2013). Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. *Gut 62*(1), 112–120. https://doi.org/10.1136/gutjnl-2012-302529.

James, E. L., Michalek, R. D., Pitiyage, G. N., de Castro, A. M., Vignola, K. S., Jones, J., ... Parkinson, E. K. (2015). Senescent human fibroblasts show increased glycolysis and redox homeostasis with extracellular metabolomes that overlap with those of irreparable DNA damage, aging, and disease. *Journal of Proteome Research 14*(4), 1854–1871. https://doi.org/10.1021/pr501221g.

Jia, X. H., Feng, G. W., Wang, Z. L., Du, Y., Shen, C., Hui, H., ... Tian, J. (2016). Activation of mesenchymal stem cells by macrophages promotes tumor progression through immune suppressive effects. *Oncotarget 7*(15), 20934–20944. https://doi.org/10.18632/oncotarget.8064.

Jiang, H., Hegde, S., & DeNardo, D. G. (2017). Tumor-associated fibrosis as a regulator of tumor immunity and response to immunotherapy. *Cancer Immunology, Immunotherapy 66*(8), 1037–1048. https://doi.org/10.1007/s00262-017-2003-1.

Jiang, H., Hegde, S., Knolhoff, B. L., Zhu, Y., Herndon, J. M., Meyer, M. A., ... DeNardo, D. G. (2016). Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. *Nature Medicine 22*(8), 851–860. https://doi.org/10.1038/nm.4123.

Junttila, M. R., & de Sauvage, F. J. (2013). Influence of tumour micro-environment heterogeneity on therapeutic response. *Nature 501*(7467), 346–354. https://doi.org/10.1038/nature12626.

Justice, J. N., Nambiar, A. M., Tchkonia, T., LeBrasseur, N. K., Pascual, R., Hashmi, S. K., ... Kirkland, J. L. (2019). Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. *EBioMedicine 40*, 554–563. https://doi.org/10.1016/j.ebiom.2018.12.052.

Kadle, R. L., Abdou, S. A., Villarreal-Ponce, A. P., Soares, M. A., Sultan, D. L., David, J. A., ... Ceradini, D. J. (2018). Microenvironmental cues enhance mesenchymal stem cell-mediated immunomodulation and regulatory T-cell expansion. *PLoS ONE 13*(3), e0193178. https://doi.org/10.1371/journal.pone.0193178.

Kalluri, R. (2016). The biology and function of fibroblasts in cancer. *Nature Reviews. Cancer 16*(9), 582–598. https://doi.org/10.1038/nrc.2016.73.

Karakasheva, T. A., Lin, E. W., Tang, Q., Qiao, E., Waldron, T. J., Soni, M., ... Rustgi, A. K. (2018). IL-6 Mediates Cross-Talk between Tumor Cells and Activated Fibroblasts in the Tumor Microenvironment. *Cancer Research 78*(17), 4957–4970. https://doi.org/10.1158/0008-5472.CAN-17-2268.

Katheder, N. S., Khezri, R., O'Farrell, F., Schultz, S. W., Jain, A., Rahman, M. M., ... Rusten, T. E. (2017). Microenvironmental autophagy promotes tumour growth. *Nature 541*(7637), 417–420. https://doi.org/10.1038/nature20815.

Kato, T., Noma, K., Ohara, T., Kashima, H., Katsura, Y., Sato, H., ... Fujiwara, T. (2018). Cancer-Associated Fibroblasts Affect Intratumoral CD8(+) and FoxP3(+) T Cells Via IL6 in the Tumor Microenvironment. *Clinical Cancer Research 24*(19), 4820–4833. https://doi.org/10.1158/1078-0432.CCR-18-0205.

Kaur, A., Ecker, B. L., Douglass, S. M., Kugel, C. H., 3rd, Webster, M. R., Almeida, F. V., ... Weeraratna, A. T. (2019). Remodeling of the Collagen Matrix in Aging Skin Promotes Melanoma Metastasis and Affects Immune Cell Motility. *Cancer Discovery 9*(1), 64–81. https://doi.org/10.1158/2159-8290.CD-18-0193.

Kaye, S. B., Fehrenbacher, L., Holloway, R., Amit, A., Karlan, B., Slomovitz, B., ... Reddy, J. C. (2012). A phase II, randomized, placebo-controlled study of vismodegib as maintenance therapy in patients with ovarian cancer in second or third complete remission. *Clinical Cancer Research 18*(23), 6509–6518. https://doi.org/10.1158/1078-0432.CCR-12-1796.

Kerkela, E., Laitinen, A., Rabina, J., Valkonen, S., Takatalo, M., Larjo, A., ... Laitinen, S. (2016). Adenosinergic Immunosuppression by Human Mesenchymal Stromal Cells Requires Co-Operation with T cells. *Stem Cells 34*(3), 781–790. https://doi.org/10.1002/stem.2280.

Kilvaer, T. K., Rakaee, M., Hellevik, T., Ostman, A., Strell, C., Bremnes, R. M., ... Martinez-Zubiaurre, I. (2018). Tissue analyses reveal a potential immune-adjuvant function of FAP-1 positive fibroblasts in non-small cell lung cancer. *PLoS ONE 13*(2), e0192157. https://doi.org/10.1371/journal.pone.0192157.

Kim, D. E., Procopio, M. G., Ghosh, S., Jo, S. H., Goruppi, S., Magliozzi, F., ... Dotto, G. P. (2017). Convergent roles of ATF3 and CSL in chromatin control of cancer-associated fibroblast activation. *The Journal of Experimental Medicine 214*(8), 2349–2368. https://doi.org/10.1084/jem.20170724.

Kim, J. W., Evans, C., Weidemann, A., Takeda, N., Lee, Y. S., Stockmann, C., ... Johnson, R. S. (2012). Loss of fibroblast HIF-1alpha accelerates tumorigenesis. *Cancer Research 72*(13), 3187–3195. https://doi.org/10.1158/0008-5472.CAN-12-0534.

Klemm, F., & Joyce, J. A. (2015). Microenvironmental regulation of therapeutic response in cancer. *Trends in Cell Biology 25*(4), 198–213. https://doi.org/10.1016/j.tcb.2014.11.006.

Ko, Y. H., Lin, Z., Flomenberg, N., Pestell, R. G., Howell, A., Sotgia, F., ... Martinez-Outschoorn, U. E. (2011). Glutamine fuels a vicious cycle of autophagy in the tumor stroma and oxidative mitochondrial metabolism in epithelial cancer cells: implications for preventing chemotherapy resistance. *Cancer Biology & Therapy 12*(12), 1085–1097. https://doi.org/10.4161/cbt.12.12.18671.

Kobayashi, K., Omori, K., & Murata, T. (2018). Role of prostaglandins in tumor microenvironment. *Cancer Metastasis Reviews*. https://doi.org/10.1007/s10555-018-9740-2.

Koeck, S., Kern, J., Zwierzina, M., Gamerith, G., Lorenz, E., Sopper, S., ... Amann, A. (2017). The influence of stromal cells and tumor-microenvironment-derived cytokines and chemokines on CD3(+)CD8(+) tumor infiltrating lymphocyte subpopulations. *Oncoimmunology 6*(6), e1323617. https://doi.org/10.1080/2162402X.2017.1323617.

Kuchnio, A., Moens, S., Bruning, U., Kuchnio, K., Cruys, B., Thienpont, B., ... Carmeliet, P. (2015). The Cancer Cell Oxygen Sensor PHD2 Promotes Metastasis via Activation of Cancer-Associated Fibroblasts. *Cell Reports 12*(6), 992–1005. https://doi.org/10.1016/j.celrep.2015.07.010.

Kumar, D., New, J., Vishwakarma, V., Joshi, R., Enders, J., Lin, F., ... Thomas, S. M. (2018). Cancer-Associated Fibroblasts Drive Glycolysis in a Targetable Signaling Loop Implicated in Head and Neck Squamous Cell Carcinoma Progression. *Cancer Research 78*(14), 3769–3782. https://doi.org/10.1158/0008-5472.CAN-17-1076.

Kumar, V., Donthireddy, L., Marvel, D., Condamine, T., Wang, F., Lavilla-Alonso, S., ... Gabrilovich, D. I. (2017). Cancer-Associated Fibroblasts Neutralize the Anti-tumor Effect of CSF1 Receptor Blockade by Inducing PMN-MDSC Infiltration of Tumors. *Cancer Cell 32*(5), 654–668 e655. https://doi.org/10.1016/j.ccell.2017.10.005.

La Shu, S., Yang, Y., Allen, C. L., Maguire, O., Minderman, H., Sen, A., ... Ernstoff, M. S. (2018). Metabolic reprogramming of stromal fibroblasts by melanoma exosome microRNA favours a pre-metastatic microenvironment. *Scientific Reports 8*(1), 12905. https://doi.org/10.1038/s41598-018-31323-7.

Lagares, D., Santos, A., Grasberger, P. E., Liu, F., Probst, C. K., Rahimi, R. A., ... Tager, A. M. (2017). Targeted apoptosis of myofibroblasts with the BH3 mimetic ABT-263 reverses established fibrosis. *Science Translational Medicine 9*(420). https://doi.org/10.1126/scitranslmed.aal3765.

LaGory, E. L., & Giaccia, A. J. (2016). The ever-expanding role of HIF in tumour and stromal biology. *Nature Cell Biology 18*(4), 356–365. https://doi.org/10.1038/ncb3330.

Lakins, M. A., Ghorani, E., Munir, H., Martins, C. P., & Shields, J. D. (2018). Cancer-associated fibroblasts induce antigen-specific deletion of CD8 (+) T Cells to protect tumour cells. *Nature Communications 9*(1), 948. https://doi.org/10.1038/s41467-018-03347-0.

Le Blanc, K., & Mougiakakos, D. (2012). Multipotent mesenchymal stromal cells and the innate immune system. *Nature Reviews. Immunology 12*(5), 383–396. https://doi.org/10.1038/nri3209.

Lee, J., Yakubov, B., Ivan, C., Jones, D. R., Caperell-Grant, A., Fishel, M., ... Matei, D. (2016). Tissue Transglutaminase Activates Cancer-Associated Fibroblasts and Contributes to Gemcitabine Resistance in Pancreatic Cancer. *Neoplasia 18*(11), 689–698. https://doi.org/10.1016/j.neo.2016.09.003.

Lee, J. J., Perera, R. M., Wang, H., Wu, D. C., Liu, X. S., Han, S., ... Beachy, P. A. (2014). Stromal response to Hedgehog signaling restrains pancreatic cancer progression. *Proceedings of the National Academy of Sciences of the United States of America 111*(30), E3091–E3100. https://doi.org/10.1073/pnas.1411679111.

Lee, J. S., Kang, J. H., Boo, H. J., Hwang, S. J., Hong, S., Lee, S. C., ... Lee, H. Y. (2015). STAT3-mediated IGF-2 secretion in the tumour microenvironment elicits innate resistance to anti-IGF-1R antibody. *Nature Communications 6*, 8499. https://doi.org/10.1038/ncomms9499.

Leung, C. S., Yeung, T. L., Yip, K. P., Wong, K. K., Ho, S. Y., Mangala, L. S., ... Mok, S. C. (2018). Cancer-associated fibroblasts regulate endothelial adhesion protein LPP to promote ovarian cancer chemoresistance. *The Journal of Clinical Investigation 128*(2), 589–606. https://doi.org/10.1172/JCI95200.

Li, X., Roife, D., Kang, Y., Dai, B., Pratt, M., & Fleming, J. B. (2016). Extracellular lumican augments cytotoxicity of chemotherapy in pancreatic ductal adenocarcinoma cells via autophagy inhibition. *Oncogene 35*(37), 4881–4890. https://doi.org/10.1038/onc.2016.20.

Liang, C., Shi, S., Meng, Q., Liang, D., Ji, S., Zhang, B., ... Yu, X. (2017). Complex roles of the stroma in the intrinsic resistance to gemcitabine in pancreatic cancer: where we are and where we are going. *Experimental & Molecular Medicine 49*(12), e406. https://doi.org/10.1038/emm.2017.255.

Liao, J. K., Zhou, B., Zhuang, X. M., Zhuang, P. L., Zhang, D. M., & Chen, W. L. (2018). Cancer-associated fi broblasts confer cisplatin resistance of tongue cancer via autophagy activation. *Biomedicine & Pharmacotherapy 97*, 1341–1348. https://doi.org/10.1016/j.biopha.2017.11.024.

Linares, J. F., Cordes, T., Duran, A., Reina-Campos, M., Valencia, T., Ahn, C. S., ... Diaz-Meco, M. T. (2017). ATF4-Induced Metabolic Reprograming Is a Synthetic Vulnerability of the p62-Deficient Tumor Stroma. *Cell Metabolism 26*(6), 817–829 e816 https://doi.org/10.1016/j.cmet.2017.09.001.

Lopez-Soto, A., Gonzalez, S., Smyth, M. J., & Galluzzi, L. (2017). Control of Metastasis by NK Cells. *Cancer Cell 32*(2), 135–154. https://doi.org/10.1016/j.ccell.2017.06.009.

Lotti, F., Jarrar, A. M., Pai, R. K., Hitomi, M., Lathia, J., Mace, A., ... Rich, J. N. (2013). Chemotherapy activates cancer-associated fibroblasts to maintain colorectal cancer-initiating cells by IL-17A. *The Journal of Experimental Medicine 210*(13), 2851–2872. https://doi.org/10.1084/jem.20131195.

de Lourdes Mora-Garcia, M., Garcia-Rocha, R., Morales-Ramirez, O., Montesinos, J. J., Weiss-Steider, B., Hernandez-Montes, J., ... Monroy-Garcia, A. (2016). Mesenchymal stromal cells derived from cervical cancer produce high amounts of adenosine to suppress cytotoxic T lymphocyte functions. *Journal of Translational Medicine 14*(1), 302. https://doi.org/10.1186/s12967-016-1057-8.

Mace, T. A., Ameen, Z., Collins, A., Wojcik, S., Mair, M., Young, G. S., ... Lesinski, G. B. (2013). Pancreatic cancer-associated stellate cells promote differentiation of myeloid-derived suppressor cells in a STAT3-dependent manner. *Cancer Research 73*(10), 3007–3018. https://doi.org/10.1158/0008-5472.CAN-12-4601.

Mace, T. A., Shakya, R., Pitarresi, J. R., Swanson, B., McQuinn, C. W., Loftus, S., ... Lesinski, G. B. (2018). IL-6 and PD-L1 antibody blockade combination therapy reduces tumour progression in murine models of pancreatic cancer. *Gut 67*(2), 320–332. https://doi.org/10.1136/gutjnl-2016-311585.

Madsen, C. D., Pedersen, J. T., Venning, F. A., Singh, L. B., Moeendarbary, E., Charras, G., ... Erler, J. T. (2015). Hypoxia and loss of PHD2 inactivate stromal fibroblasts to decrease tumour stiffness and metastasis. *EMBO Reports 16*(10), 1394–1408. https://doi.org/10.15252/embr.201540107.

Manic, G., Signore, M., Sistigu, A., Russo, G., Corradi, F., Siteni, S., ... De Maria, R. (2018). CHK1-targeted therapy to deplete DNA replication-stressed, p53-deficient, hyperdiploid colorectal cancer stem cells. *Gut 67*(5), 903–917. https://doi.org/10.1136/gutjnl-2016-312623.

Martinez-Outschoorn, U. E., Curry, J. M., Ko, Y. H., Lin, Z., Tuluc, M., Cognetti, D., ... Lisanti, M. P. (2013). Oncogenes and inflammation rewire host energy metabolism in the tumor microenvironment: RAS and NFkappaB target stromal MCT4. *Cell Cycle 12*(16), 2580–2597. https://doi.org/10.4161/cc.25510.

Martinez-Outschoorn, U. E., Lisanti, M. P., & Sotgia, F. (2014). Catabolic cancer-associated fibroblasts transfer energy and biomass to anabolic cancer cells, fueling tumor growth. *Seminars in Cancer Biology 25*, 47–60. https://doi.org/10.1016/j.semcancer.2014.01.005.

Marusyk, A., Tabassum, D. P., Janiszewska, M., Place, A. E., Trinh, A., Rozhok, A. I., ... Polyak, K. (2016). Spatial Proximity to Fibroblasts Impacts Molecular Features and

Therapeutic Sensitivity of Breast Cancer Cells Influencing Clinical Outcomes. *Cancer Research 76*(22), 6495–6506. https://doi.org/10.1158/0008-5472.CAN-16-1457.

Mazur, A., Holthoff, E., Vadali, S., Kelly, T., & Post, S. R. (2016). Cleavage of Type I Collagen by fibroblast activation Protein-alpha Enhances Class A Scavenger Receptor Mediated Macrophage Adhesion. *PLoS ONE 11*(3), e0150287. https://doi.org/10.1371/journal.pone.0150287.

Menietti, E., Xu, X., Ostano, P., Joseph, J. M., Lefort, K., & Dotto, G. P. (2016). Negative control of CSL gene transcription by stress/DNA damage response and p53. *Cell Cycle 15*(13), 1767–1778. https://doi.org/10.1080/15384101.2016.1186317.

Miao, L., Liu, Q., Lin, C. M., Luo, C., Wang, Y., Liu, L., ... Huang, L. (2017). Targeting Tumor-Associated Fibroblasts for Therapeutic Delivery in Desmoplastic Tumors. *Cancer Research 77*(3), 719–731. https://doi.org/10.1158/0008-5472.CAN-16-0866.

Miller, A., Nagy, C., Knapp, B., Laengle, J., Ponweiser, E., Groeger, M., ... Haschemi, A. (2017). Exploring Metabolic Configurations of Single Cells within Complex Tissue Microenvironments. *Cell Metabolism 26*(5), 788–800 e786. https://doi.org/10.1016/j.cmet.2017.08.014.

Mishra, R., Haldar, S., Placencio, V., Madhav, A., Rohena-Rivera, K., Agarwal, P., ... Bhowmick, N. A. (2018). Stromal epigenetic alterations drive metabolic and neuroendocrine prostate cancer reprogramming. *The Journal of Clinical Investigation 128*(10), 4472–4484. https://doi.org/10.1172/JCI99397.

Mitchell, M. I., & Engelbrecht, A. M. (2017). Metabolic hijacking: A survival strategy cancer cells exploit? *Critical Reviews in Oncology/Hematology 109*, 1–8. https://doi.org/10.1016/j.critrevonc.2016.11.010.

Miyoshi, H., Kiyasu, J., Kato, T., Yoshida, N., Shimono, J., Yokoyama, S., ... Ohshima, K. (2016). PD-L1 expression on neoplastic or stromal cells is respectively a poor or good prognostic factor for adult T-cell leukemia/lymphoma. *Blood 128*(10), 1374–1381. https://doi.org/10.1182/blood-2016-02-698936.

Mohammadi, H., & Sahai, E. (2018). Mechanisms and impact of altered tumour mechanics. *Nature Cell Biology 20*(7), 766–774. https://doi.org/10.1038/s41556-018-0131-2.

Molejon, M. I., Swayden, M., Fanale, D., Bintz, J., Gayet, O., Soubeyran, P., & Iovanna, J. (2018). Chloroquine plays a cell-dependent role in the response to treatment of pancreatic adenocarcinoma. *Oncotarget 9*(56), 30837–30846. https://doi.org/10.18632/oncotarget.25745.

Mueller, K. L., Madden, J. M., Zoratti, G. L., Kuperwasser, C., List, K., & Boerner, J. L. (2012). Fibroblast-secreted hepatocyte growth factor mediates epidermal growth factor receptor tyrosine kinase inhibitor resistance in triple-negative breast cancers through paracrine activation of Met. *Breast Cancer Research 14*(4), R104. https://doi.org/10.1186/bcr3224.

Muerkoster, S. S., Werbing, V., Koch, D., Sipos, B., Ammerpohl, O., Kalthoff, H., ... Schafer, H. (2008). Role of myofibroblasts in innate chemoresistance of pancreatic carcinoma–epigenetic downregulation of caspases. *International Journal of Cancer 123*(8), 1751–1760. https://doi.org/10.1002/ijc.23703.

Nabet, B. Y., Qiu, Y., Shabason, J. E., Wu, T. J., Yoon, T., Kim, B. C., ... Minn, A. J. (2017). Exosome RNA Unshielding Couples Stromal Activation to Pattern Recognition Receptor Signaling in Cancer. *Cell 170*(2). https://doi.org/10.1016/j.cell.2017.06.031 352-366 e313.

Neesse, A., Algul, H., Tuveson, D. A., & Gress, T. M. (2015). Stromal biology and therapy in pancreatic cancer: a changing paradigm. *Gut 64*(9), 1476–1484. https://doi.org/10.1136/gutjnl-2015-309304.

New, J., Arnold, L., Ananth, M., Alvi, S., Thornton, M., Werner, L., ... Thomas, S. M. (2017). Secretory Autophagy in Cancer-Associated Fibroblasts Promotes Head and Neck Cancer Progression and Offers a Novel Therapeutic Target. *Cancer Research 77*(23), 6679–6691. https://doi.org/10.1158/0008-5472.CAN-17-1077.

Ohlund, D., Elyada, E., & Tuveson, D. (2014). Fibroblast heterogeneity in the cancer wound. *The Journal of Experimental Medicine 211*(8), 1503–1523. https://doi.org/10.1084/jem.20140692.

Ohlund, D., Handly-Santana, A., Biffi, G., Elyada, E., Almeida, A. S., Ponz-Sarvise, M., ... Tuveson, D. A. (2017). Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer. *The Journal of Experimental Medicine 214*(3), 579–596. https://doi.org/10.1084/jem.20162024.

Olivares, O., Mayers, J. R., Gouirand, V., Torrence, M. E., Gicquel, T., Borge, L., ... Vasseur, S. (2017). Collagen-derived proline promotes pancreatic ductal adenocarcinoma cell survival under nutrient limited conditions. *Nature Communications 8*, 16031. https://doi.org/10.1038/ncomms16031.

Olive, K. P., Jacobetz, M. A., Davidson, C. J., Gopinathan, A., McIntyre, D., Honess, D., ... Tuveson, D. A. (2009). Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science 324*(5933), 1457–1461. https://doi.org/10.1126/science.1171362.

Ozdemir, B. C., Pentcheva-Hoang, T., Carstens, J. L., Zheng, X., Wu, C. C., Simpson, T. R., ... Kalluri, R. (2014). Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. *Cancer Cell 25*(6), 719–734. https://doi.org/10.1016/j.ccr.2014.04.005.

Pavlides, S., Whitaker-Menezes, D., Castello-Cros, R., Flomenberg, N., Witkiewicz, A. K., Frank, P. G., ... Lisanti, M. P. (2009). The reverse Warburg effect: aerobic glycolysis in cancer associated fibroblasts and the tumor stroma. *Cell Cycle 8*(23), 3984–4001. https://doi.org/10.4161/cc.8.23.10238.

Pitiyage, G. N., Slijepcevic, P., Gabrani, A., Chianea, Y. G., Lim, K. P., Prime, S. S., ... Parkinson, E. K. (2011). Senescent mesenchymal cells accumulate in human fibrosis by a telomere-independent mechanism and ameliorate fibrosis through matrix metalloproteinases. *The Journal of Pathology 223*(5), 604–617. https://doi.org/10.1002/path.2839.

Poillet-Perez, L., Xie, X., Zhan, L., Yang, Y., Sharp, D. W., Hu, Z. S., ... White, E. (2018). Autophagy maintains tumour growth through circulating arginine. *Nature 563*(7732), 569–573. https://doi.org/10.1038/s41586-018-0697-7.

Procopio, M. G., Laszlo, C., Al Labban, D., Kim, D. E., Bordignon, P., Jo, S. H., ... Dotto, G. P. (2015). Combined CSL and p53 downregulation promotes cancer-associated fibroblast activation. *Nature Cell Biology 17*(9), 1193–1204. https://doi.org/10.1038/ncb3228.

Provenzano, P. P., Cuevas, C., Chang, A. E., Goel, V. K., Von Hoff, D. D., & Hingorani, S. R. (2012). Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. *Cancer Cell 21*(3), 418–429. https://doi.org/10.1016/j.ccr.2012.01.007.

Qiao, Y., Zhang, C., Li, A., Wang, D., Luo, Z., Ping, Y., ... Zhang, Y. (2018). IL6 derived from cancer-associated fibroblasts promotes chemoresistance via CXCR7 in esophageal squamous cell carcinoma. *Oncogene 37*(7), 873–883. https://doi.org/10.1038/onc.2017.387.

Qiu, W., Hu, M., Sridhar, A., Opeskin, K., Fox, S., Shipitsin, M., ... Campbell, I. G. (2008). No evidence of clonal somatic genetic alterations in cancer-associated fibroblasts from human breast and ovarian carcinomas. *Nature Genetics 40*(5), 650–655. https://doi.org/10.1038/ng.117.

Quail, D. F., & Joyce, J. A. (2013). Microenvironmental regulation of tumor progression and metastasis. *Nature Medicine 19*(11), 1423–1437. https://doi.org/10.1038/nm.3394.

Rahbari, N. N., Kedrin, D., Incio, J., Liu, H., Ho, W. W., Nia, H. T., ... Fukumura, D. (2016). Anti-VEGF therapy induces ECM remodeling and mechanical barriers to therapy in colorectal cancer liver metastases. *Science Translational Medicine 8*(360), 360ra135. https://doi.org/10.1126/scitranslmed.aaf5219.

Rashedi, I., Gomez-Aristizabal, A., Wang, X. H., Viswanathan, S., & Keating, A. (2017). TLR3 or TLR4 Activation Enhances Mesenchymal Stromal Cell-Mediated Treg Induction via Notch Signaling. *Stem Cells 35*(1), 265–275. https://doi.org/10.1002/stem.2485.

Raz, Y., Cohen, N., Shani, O., Bell, R. E., Novitskiy, S. V., Abramovitz, L., ... Erez, N. (2018). Bone marrow-derived fibroblasts are a functionally distinct stromal cell population in breast cancer. *The Journal of Experimental Medicine 215*(12), 3075–3093. https://doi.org/10.1084/jem.20180818.

Ren, G., Zhao, X., Wang, Y., Zhang, X., Chen, X., Xu, C., ... Shi, Y. (2012). CCR2-dependent recruitment of macrophages by tumor-educated mesenchymal stromal cells promotes tumor development and is mimicked by TNFalpha. *Cell Stem Cell 11*(6), 812–824. https://doi.org/10.1016/j.stem.2012.08.013.

Ren, J., Guo, H., Wu, H., Tian, T., Dong, D., Zhang, Y., ... Li, Y. (2015). GPER in CAFs regulates hypoxia-driven breast cancer invasion in a CTGF-dependent manner. *Oncology Reports 33*(4), 1929–1937. https://doi.org/10.3892/or.2015.3779.

Rhim, A. D., Oberstein, P. E., Thomas, D. H., Mirek, E. T., Palermo, C. F., Sastra, S. A., ... Stanger, B. Z. (2014). Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma. *Cancer Cell 25*(6), 735–747. https://doi.org/10.1016/j.ccr.2014.04.021.

Richards, K. E., Zeleniak, A. E., Fishel, M. L., Wu, J., Littlepage, L. E., & Hill, R. (2017). Cancer-associated fibroblast exosomes regulate survival and proliferation of pancreatic cancer cells. *Oncogene 36*(13), 1770–1778. https://doi.org/10.1038/onc.2016.353.

Rizvi, S., Mertens, J. C., Bronk, S. F., Hirsova, P., Dai, H., Roberts, L. R., ... Gores, G. J. (2014). Platelet-derived growth factor primes cancer-associated fibroblasts for apoptosis. *The Journal of Biological Chemistry 289*(33), 22835–22849. https://doi.org/10.1074/jbc.M114.563064.

Roberts, E. W., Deonarine, A., Jones, J. O., Denton, A. E., Feig, C., Lyons, S. K., ... Fearon, D. T. (2013). Depletion of stromal cells expressing fibroblast activation protein-alpha from skeletal muscle and bone marrow results in cachexia and anemia. *The Journal of Experimental Medicine 210*(6), 1137–1151. https://doi.org/10.1084/jem.20122344.

Romero, I. L., Mukherjee, A., Kenny, H. A., Litchfield, L. M., & Lengyel, E. (2015). Molecular pathways: trafficking of metabolic resources in the tumor microenvironment. *Clinical Cancer Research 21*(4), 680–686. https://doi.org/10.1158/1078-0432.CCR-14-2198.

Sakamoto, A., Kunou, S., Shimada, K., Tsunoda, M., Aoki, T., Iriyama, C., ... Kiyoi, H. (2019). Pyruvate secreted from patient-derived cancer-associated fibroblasts supports survival of primary lymphoma cells. *Cancer Science 110*(1), 269–278. https://doi.org/10.1111/cas.13873.

Saldanha-Araujo, F., Ferreira, F. I., Palma, P. V., Araujo, A. G., Queiroz, R. H., Covas, D. T., ... Panepucci, R. A. (2011). Mesenchymal stromal cells up-regulate CD39 and increase adenosine production to suppress activated T-lymphocytes. *Stem Cell Research 7*(1), 66–74. https://doi.org/10.1016/j.scr.2011.04.001.

Sanchez, C. G., Penfornis, P., Oskowitz, A. Z., Boonjindasup, A. G., Cai, D. Z., Dhule, S. S., ... Pochampally, R. R. (2011). Activation of autophagy in mesenchymal stem cells provides tumor stromal support. *Carcinogenesis 32*(7), 964–972. https://doi.org/10.1093/carcin/bgr029.

Sanita, P., Capulli, M., Teti, A., Galatioto, G. P., Vicentini, C., Chiarugi, P., ... Angelucci, A. (2014). Tumor-stroma metabolic relationship based on lactate shuttle can sustain prostate cancer progression. *BMC Cancer 14*, 154. https://doi.org/10.1186/1471-2407-14-154.

Santi, A., Kugeratski, F. G., & Zanivan, S. (2018). Cancer associated fibroblasts: the Architects of Stroma Remodeling. *Proteomics 18*(5-6), e1700167. https://doi.org/10.1002/pmic.201700167.

Santolla, M. F., Lappano, R., De Marco, P., Pupo, M., Vivacqua, A., Sisci, D., ... Maggiolini, M. (2012). G protein-coupled estrogen receptor mediates the up-regulation of fatty acid synthase induced by 17beta-estradiol in cancer cells and cancer-associated fibroblasts. *The Journal of Biological Chemistry 287*(52), 43234–43245. https://doi.org/10.1074/jbc.M112.417303.

Santos, A. M., Jung, J., Aziz, N., Kissil, J. L., & Pure, E. (2009). Targeting fibroblast activation protein inhibits tumor stromagenesis and growth in mice. *The Journal of Clinical Investigation 119*(12), 3613–3625. https://doi.org/10.1172/JCI38988.

Scherz-Shouval, R., Santagata, S., Mendillo, M. L., Sholl, L. M., Ben-Aharon, I., Beck, A. H., ... Lindquist, S. (2014). The reprogramming of tumor stroma by HSF1 is a potent enabler of malignancy. *Cell 158*(3), 564–578. https://doi.org/10.1016/j.cell.2014.05.045.

Schmid, J. O., Dong, M., Haubeiss, S., Friedel, G., Bode, S., Grabner, A., ... van der Kuip, H. (2012). Cancer cells cue the p53 response of cancer-associated fibroblasts to cisplatin.

Cancer Research 72(22), 5824–5832. https://doi.org/10.1158/0008-5472.CAN-12-1201.

Seip, K., Fleten, K. G., Barkovskaya, A., Nygaard, V., Haugen, M. H., Engesaeter, B. O., ... Prasmickaite, L. (2016). Fibroblast-induced switching to the mesenchymal-like phenotype and PI3K/mTOR signaling protects melanoma cells from BRAF inhibitors. *Oncotarget 7*(15), 19997–20015. https://doi.org/10.18632/oncotarget.7671.

Selak, M. A., Armour, S. M., MacKenzie, E. D., Boulahbel, H., Watson, D. G., Mansfield, K. D., ... Gottlieb, E. (2005). Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-alpha prolyl hydroxylase. *Cancer Cell 7*(1), 77–85. https://doi.org/10.1016/j.ccr.2004.11.022.

Shan, T., Chen, S., Chen, X., Lin, W. R., Li, W., Ma, J., ... Kang, Y. (2017). Cancer-associated fibroblasts enhance pancreatic cancer cell invasion by remodeling the metabolic conversion mechanism. *Oncology Reports 37*(4), 1971–1979. https://doi.org/10.3892/or.2017.5479.

Shangguan, C., Gan, G., Zhang, J., Wu, J., Miao, Y., Zhang, M., ... Mi, J. (2018). Cancer-associated fibroblasts enhance tumor (18)F-FDG uptake and contribute to the intratumor heterogeneity of PET-CT. *Theranostics 8*(5), 1376–1388. https://doi.org/10.7150/thno.22717.

Shee, K., Yang, W., Hinds, J. W., Hampsch, R. A., Varn, F. S., Traphagen, N. A., ... Miller, T. W. (2018). Therapeutically targeting tumor microenvironment-mediated drug resistance in estrogen receptor-positive breast cancer. *The Journal of Experimental Medicine 215*(3), 895–910. https://doi.org/10.1084/jem.20171818.

Sherman, M. H., Yu, R. T., Engle, D. D., Ding, N., Atkins, A. R., Tiriac, H., ... Evans, R. M. (2014). Vitamin D receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy. *Cell 159*(1), 80–93. https://doi.org/10.1016/j.cell.2014.08.007.

Sherman, M. H., Yu, R. T., Tseng, T. W., Sousa, C. M., Liu, S., Truitt, M. L., ... Evans, R. M. (2017). Stromal cues regulate the pancreatic cancer epigenome and metabolome. *Proceedings of the National Academy of Sciences of the United States of America 114*(5), 1129–1134. https://doi.org/10.1073/pnas.1620164114.

Shi, Y., Du, L., Lin, L., & Wang, Y. (2017). Tumour-associated mesenchymal stem/stromal cells: emerging therapeutic targets. *Nature Reviews. Drug Discovery 16*(1), 35–52. https://doi.org/10.1038/nrd.2016.193.

Sonnenberg, M., van der Kuip, H., Haubeis, S., Fritz, P., Schroth, W., Friedel, G., ... Aulitzky, W. E. (2008). Highly variable response to cytotoxic chemotherapy in carcinoma-associated fibroblasts (CAFs) from lung and breast. *BMC Cancer 8*, 364. https://doi.org/10.1186/1471-2407-8-364.

Sousa, C. M., Biancur, D. E., Wang, X., Halbrook, C. J., Sherman, M. H., Zhang, L., ... Kimmelman, A. C. (2016). Pancreatic stellate cells support tumour metabolism through autophagic alanine secretion. *Nature 536*(7617), 479–483. https://doi.org/10.1038/nature19084.

Spivak-Kroizman, T. R., Hostetter, G., Posner, R., Aziz, M., Hu, C., Demeure, M. J., ... Powis, G. (2013). Hypoxia triggers hedgehog-mediated tumor-stromal interactions in pancreatic cancer. *Cancer Research 73*(11), 3235–3247. https://doi.org/10.1158/0008-5472.CAN-11-1433.

Steele, C. W., Karim, S. A., Leach, J. D. G., Bailey, P., Upstill-Goddard, R., Rishi, L., ... Morton, J. P. (2016). CXCR2 Inhibition Profoundly Suppresses Metastases and Augments Immunotherapy in Pancreatic Ductal Adenocarcinoma. *Cancer Cell 29*(6), 832–845. https://doi.org/10.1016/j.ccell.2016.04.014.

Straussman, R., Morikawa, T., Shee, K., Barzily-Rokni, M., Qian, Z. R., Du, J., ... Golub, T. R. (2012). Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. *Nature 487*(7408), 500–504. https://doi.org/10.1038/nature11183.

Su, J., Chen, X., Huang, Y., Li, W., Li, J., Cao, K., ... Shi, Y. (2014). Phylogenetic distinction of iNOS and IDO function in mesenchymal stem cell-mediated immunosuppression in mammalian species. *Cell Death and Differentiation 21*(3), 388–396. https://doi.org/10.1038/cdd.2013.149.

Su, S., Chen, J., Yao, H., Liu, J., Yu, S., Lao, L., ... Song, E. (2018). CD10(+)GPR77(+) Cancer-Associated Fibroblasts Promote Cancer Formation and Chemoresistance by Sustaining Cancer Stemness. *Cell 172*(4), 841–856 e816. https://doi.org/10.1016/j.cell.2018.01.009.

Sun, Y., Campisi, J., Higano, C., Beer, T. M., Porter, P., Coleman, I., ... Nelson, P. S. (2012). Treatment-induced damage to the tumor microenvironment promotes prostate cancer therapy resistance through WNT16B. *Nature Medicine 18*(9), 1359–1368. https://doi.org/10.1038/nm.2890.

Sun, Y., Zhu, D., Chen, F., Qian, M., Wei, H., Chen, W., & Xu, J. (2016). SFRP2 augments WNT16B signaling to promote therapeutic resistance in the damaged tumor microenvironment. *Oncogene 35*(33), 4321–4334. https://doi.org/10.1038/onc.2015.494.

Takahashi, H., Sakakura, K., Kudo, T., Toyoda, M., Kaira, K., Oyama, T., & Chikamatsu, K. (2017). Cancer-associated fibroblasts promote an immunosuppressive microenvironment through the induction and accumulation of protumoral macrophages. *Oncotarget 8*(5), 8633–8647. https://doi.org/10.18632/oncotarget.14374.

Tang, Y. A., Chen, Y. F., Bao, Y., Mahara, S., Yatim, S., Oguz, G., ... Yu, Q. (2018). Hypoxic tumor microenvironment activates GLI2 via HIF-1alpha and TGF-beta2 to promote chemoresistance in colorectal cancer. *Proceedings of the National Academy of Sciences of the United States of America 115*(26), E5990–E5999. https://doi.org/10.1073/pnas.1801348115.

Tommelein, J., De Vlieghere, E., Verset, L., Melsens, E., Leenders, J., Descamps, B., ... De Wever, O. (2018). Radiotherapy-Activated Cancer-Associated Fibroblasts Promote Tumor Progression through Paracrine IGF1R Activation. *Cancer Research 78*(3), 659–670. https://doi.org/10.1158/0008-5472.CAN-17-0524.

Toste, P. A., Nguyen, A. H., Kadera, B. E., Duong, M., Wu, N., Gawlas, I., ... Donahue, T. R. (2016). Chemotherapy-Induced Inflammatory Gene Signature and Protumorigenic Phenotype in Pancreatic CAFs via Stress-Associated MAPK. *Molecular Cancer Research 14*(5), 437–447. https://doi.org/10.1158/1541-7786.MCR-15-0348.

Tran, E., Chinnasamy, D., Yu, Z., Morgan, R. A., Lee, C. C., Restifo, N. P., & Rosenberg, S. A. (2013). Immune targeting of fibroblast activation protein triggers recognition of multipotent bone marrow stromal cells and cachexia. *The Journal of Experimental Medicine 210*(6), 1125–1135. https://doi.org/10.1084/jem.20130110.

Turley, S. J., Cremasco, V., & Astarita, J. L. (2015). Immunological hallmarks of stromal cells in the tumour microenvironment. *Nature Reviews. Immunology 15*(11), 669–682. https://doi.org/10.1038/nri3902.

Unger, C., Kramer, N., Unterleuthner, D., Scherzer, M., Burian, A., Rudisch, A., ... Dolznig, H. (2017). Stromal-derived IGF2 promotes colon cancer progression via paracrine and autocrine mechanisms. *Oncogene 36*(38), 5341–5355. https://doi.org/10.1038/onc.2017.116.

Valencia, T., Kim, J. Y., Abu-Baker, S., Moscat-Pardos, J., Ahn, C. S., Reina-Campos, M., ... Moscat, J. (2014). Metabolic reprogramming of stromal fibroblasts through p62-mTORC1 signaling promotes inflammation and tumorigenesis. *Cancer Cell 26*(1), 121–135. https://doi.org/10.1016/j.ccr.2014.05.004.

Valkenburg, K. C., de Groot, A. E., & Pienta, K. J. (2018). Targeting the tumour stroma to improve cancer therapy. *Nature Reviews. Clinical Oncology 15*(6), 366–381. https://doi.org/10.1038/s41571-018-0007-1.

Vitale, I., Manic, G., De Maria, R., Kroemer, G., & Galluzzi, L. (2017). DNA Damage in Stem Cells. *Molecular Cell 66*(3), 306–319. https://doi.org/10.1016/j.molcel.2017.04.006.

Vitale, I., Sistigu, A., Manic, G., Rudqvist, N. P., Trajanoski, Z., & Galluzzi, L. (2019). Mutational and Antigenic Landscape in Tumor Progression and Cancer Immunotherapy. *Trends in Cell Biology*. https://doi.org/10.1016/j.tcb.2019.01.003.

Wang, J., Ying, G., Wang, J., Jung, Y., Lu, J., Zhu, J., ... Taichman, R. S. (2010). Characterization of phosphoglycerate kinase-1 expression of stromal cells derived from tumor microenvironment in prostate cancer progression. *Cancer Research 70*(2), 471–480. https://doi.org/10.1158/0008-5472.CAN-09-2863.

Wang, L. C., Lo, A., Scholler, J., Sun, J., Majumdar, R. S., Kapoor, V., ... Albelda, S. M. (2014). Targeting fibroblast activation protein in tumor stroma with chimeric antigen receptor T cells can inhibit tumor growth and augment host immunity without severe toxicity. *Cancer Immunology Research 2*(2), 154–166. https://doi.org/10.1158/2326-6066.CIR-13-0027.

Wang, M., Wu, C. P., Pan, J. Y., Zheng, W. W., Cao, X. J., & Fan, G. K. (2015). Cancer-associated fibroblasts in a human HEp-2 established laryngeal xenografted tumor are not derived from cancer cells through epithelial-mesenchymal transition, phenotypically activated but karyotypically normal. *PLoS ONE 10*(2), e0117405. https://doi.org/10.1371/journal.pone.0117405.

Wang, Q., Xue, L., Zhang, X., Bu, S., Zhu, X., & Lai, D. (2016). Autophagy protects ovarian cancer-associated fibroblasts against oxidative stress. *Cell Cycle 15*(10), 1376–1385. https://doi.org/10.1080/15384101.2016.1170269.

Wang, T., Notta, F., Navab, R., Joseph, J., Ibrahimov, E., Xu, J., ... Tsao, M. S. (2017). Senescent Carcinoma-Associated Fibroblasts Upregulate IL8 to Enhance Prometastatic Phenotypes. *Molecular Cancer Research 15*(1), 3–14. https://doi.org/10.1158/1541-7786.MCR-16-0192.

Wang, W., Kryczek, I., Dostal, L., Lin, H., Tan, L., Zhao, L., ... Zou, W. (2016). Effector T Cells Abrogate Stroma-Mediated Chemoresistance in Ovarian Cancer. *Cell 165*(5), 1092–1105. https://doi.org/10.1016/j.cell.2016.04.009.

Wang, Y., Gan, G., Wang, B., Wu, J., Cao, Y., Zhu, D., ... Mi, J. (2017). Cancer-associated Fibroblasts Promote Irradiated Cancer Cell Recovery Through Autophagy. *EBioMedicine 17*, 45–56. https://doi.org/10.1016/j.ebiom.2017.02.019.

Whatcott, C. J., Ng, S., Barrett, M. T., Hostetter, G., Von Hoff, D. D., & Han, H. (2017). Inhibition of ROCK1 kinase modulates both tumor cells and stromal fibroblasts in pancreatic cancer. *PLoS ONE 12*(8), e0183871. https://doi.org/10.1371/journal.pone.0183871.

Wilde, L., Roche, M., Domingo-Vidal, M., Tanson, K., Philp, N., Curry, J., & Martinez-Outschoorn, U. (2017). Metabolic coupling and the Reverse Warburg Effect in cancer: Implications for novel biomarker and anticancer agent development. *Seminars in Oncology 44*(3), 198–203. https://doi.org/10.1053/j.seminoncol.2017.10.004.

Wilson, T. R., Fridlyand, J., Yan, Y., Penuel, E., Burton, L., Chan, E., ... Settleman, J. (2012). Widespread potential for growth-factor-driven resistance to anticancer kinase inhibitors. *Nature 487*(7408), 505–509. https://doi.org/10.1038/nature11249.

Wu, D., Zhuo, L., & Wang, X. (2017). Metabolic reprogramming of carcinoma-associated fibroblasts and its impact on metabolic heterogeneity of tumors. *Seminars in Cell & Developmental Biology 64*, 125–131. https://doi.org/10.1016/j.semcdb.2016.11.003.

Wu, J., Fu, R., Liu, Z., Li, G., Huang, X., Xue, Y., ... Mi, J. (2017). Cell proliferation downregulated by TGF-beta2-triggered G1/S checkpoint in clinical CAFs. *Cell Cycle 16*(2), 172–178. https://doi.org/10.1080/15384101.2016.1253641.

Wu, J., Hong, Y., Wu, T., Wang, J., Chen, X., Wang, Z., ... Xia, J. (2018). Stromal-epithelial lactate shuttle induced by tumorderived interleukin1beta promotes cell proliferation in oral squamous cell carcinoma. *International Journal of Molecular Medicine 41*(2), 687–696. https://doi.org/10.3892/ijmm.2017.3267.

Wu, Y. S., Looi, C. Y., Subramaniam, K. S., Masamune, A., & Chung, I. (2016). Soluble factors from stellate cells induce pancreatic cancer cell proliferation via Nrf2-activated metabolic reprogramming and ROS detoxification. *Oncotarget 7*(24), 36719–36732. https://doi.org/10.18632/oncotarget.9165.

Xu, S., Yang, Z., Jin, P., Yang, X., Li, X., Wei, X., ... Gao, Q. (2018). Metformin Suppresses Tumor Progression by Inactivating Stromal Fibroblasts in Ovarian Cancer. *Molecular Cancer Therapeutics 17*(6), 1291–1302. https://doi.org/10.1158/1535-7163.MCT-17-0927.

Yamada, T., Takeuchi, S., Nakade, J., Kita, K., Nakagawa, T., Nanjo, S., ... Yano, S. (2012). Paracrine receptor activation by microenvironment triggers bypass survival signals and ALK inhibitor resistance in EML4-ALK lung cancer cells. *Clinical Cancer Research 18*(13), 3592–3602. https://doi.org/10.1158/1078-0432.CCR-11-2972.

Yamamoto, K., Tateishi, K., Kudo, Y., Hoshikawa, M., Tanaka, M., Nakatsuka, T., ... Koike, K. (2016). Stromal remodeling by the BET bromodomain inhibitor JQ1 suppresses the progression of human pancreatic cancer. *Oncotarget 7*(38), 61469–61484. https://doi.org/10.18632/oncotarget.11129.

Yamauchi, M., Barker, T. H., Gibbons, D. L., & Kurie, J. M. (2018). The fibrotic tumor stroma. *The Journal of Clinical Investigation 128*(1), 16–25. https://doi.org/10.1172/JCI93554.

Yan, W., Wu, X., Zhou, W., Fong, M. Y., Cao, M., Liu, J., ... Wang, S. E. (2018). Cancer-cell-secreted exosomal miR-105 promotes tumour growth through the MYC-dependent metabolic reprogramming of stromal cells. *Nature Cell Biology 20*(5), 597–609. https://doi.org/10.1038/s41556-018-0083-6.

Yang, G., Rosen, D. G., Zhang, Z., Bast, R. C., Jr., Mills, G. B., Colacino, J. A., ... Liu, J. (2006). The chemokine growth-regulated oncogene 1 (Gro-1) links RAS signaling to the senescence of stromal fibroblasts and ovarian tumorigenesis. *Proceedings of the National Academy of Sciences of the United States of America 103*(44), 16472–16477. https://doi.org/10.1073/pnas.0605752103.

Yang, H., Zheng, Y., Zhang, Y., Cao, Z., & Jiang, Y. (2017). Mesenchymal stem cells derived from multiple myeloma patients protect against chemotherapy through autophagy-dependent activation of NF-kappaB signaling. *Leukemia Research 60*, 82–88. https://doi.org/10.1016/j.leukres.2017.07.002.

Yang, L., Achreja, A., Yeung, T. L., Mangala, L. S., Jiang, D., Han, C., ... Nagrath, D. (2016). Targeting Stromal Glutamine Synthetase in Tumors Disrupts Tumor Microenvironment-Regulated Cancer Cell Growth. *Cell Metabolism 24*(5), 685–700. https://doi.org/10.1016/j.cmet.2016.10.011.

Yang, M., Liu, P., Wang, K., Glorieux, C., Hu, Y., Wen, S., ... Huang, P. (2017). Chemotherapy induces tumor immune evasion by upregulation of programmed cell death ligand 1 expression in bone marrow stromal cells. *Molecular Oncology 11*(4), 358–372. https://doi.org/10.1002/1878-0261.12032.

Yang, X., Lin, Y., Shi, Y., Li, B., Liu, W., Yin, W., ... He, R. (2016). FAP Promotes Immunosuppression by Cancer-Associated Fibroblasts in the Tumor Microenvironment via STAT3-CCL2 Signaling. *Cancer Research 76*(14), 4124–4135. https://doi.org/10.1158/0008-5472.CAN-15-2973.

Yang, X., Xu, X., Zhu, J., Zhang, S., Wu, Y., Wu, Y., ... Peng, W. (2016). miR-31 affects colorectal cancer cells by inhibiting autophagy in cancer-associated fibroblasts. *Oncotarget 7*(48), 79617–79628. https://doi.org/10.18632/oncotarget.12873.

Yen, B. L., Yen, M. L., Hsu, P. J., Liu, K. J., Wang, C. J., Bai, C. H., & Sytwu, H. K. (2013). Multipotent human mesenchymal stromal cells mediate expansion of myeloid-derived suppressor cells via hepatocyte growth factor/c-met and STAT3. *Stem Cell Reports 1*(2), 139–151. https://doi.org/10.1016/j.stemcr.2013.06.006.

Yoshida, T., Ishii, G., Goto, K., Neri, S., Hashimoto, H., Yoh, K., ... Ochiai, A. (2015). Podoplanin-positive cancer-associated fibroblasts in the tumor microenvironment induce primary resistance to EGFR-TKIs in lung adenocarcinoma with EGFR mutation. *Clinical Cancer Research 21*(3), 642–651. https://doi.org/10.1158/1078-0432.CCR-14-0846.

Yu, T., Yang, G., Hou, Y., Tang, X., Wu, C., Wu, X. A., ... Liu, M. (2017). Cytoplasmic GPER translocation in cancer-associated fibroblasts mediates cAMP/PKA/CREB/glycolytic axis to confer tumor cells with multidrug resistance. *Oncogene 36*(15), 2131–2145. https://doi.org/10.1038/onc.2016.370.

Zhang, A., Qian, Y., Ye, Z., Chen, H., Xie, H., Zhou, L., ... Zheng, S. (2017). Cancer-associated fibroblasts promote M2 polarization of macrophages in pancreatic ductal adenocarcinoma. *Cancer Medicine 6*(2), 463–470. https://doi.org/10.1002/cam4.993.

Zhang, D., Wang, Y., Shi, Z., Liu, J., Sun, P., Hou, X., ... Mi, J. (2015). Metabolic reprogramming of cancer-associated fibroblasts by IDH3alpha downregulation. *Cell Reports 10*(8), 1335–1348. https://doi.org/10.1016/j.celrep.2015.02.006.

Zhang, W., Trachootham, D., Liu, J., Chen, G., Pelicano, H., Garcia-Prieto, C., ... Huang, P. (2012). Stromal control of cystine metabolism promotes cancer cell survival in chronic lymphocytic leukaemia. *Nature Cell Biology 14*(3), 276–286. https://doi.org/10.1038/ncb2432.

Zhang, X., Schonrogge, M., Eichberg, J., Wendt, E. H. U., Kumstel, S., Stenzel, J., ... Zechner, D. (2018). Blocking Autophagy in Cancer-Associated Fibroblasts Supports Chemotherapy of Pancreatic Cancer Cells. *Frontiers in Oncology 8*, 590. https://doi.org/10.3389/fonc.2018.00590.

Zhao, F., Evans, K., Xiao, C., DeVito, N., Theivanthiran, B., Holtzhausen, A., ... Hanks, B. A. (2018). Stromal Fibroblasts Mediate Anti-PD-1 Resistance via MMP-9 and Dictate TGFbeta Inhibitor Sequencing in Melanoma. *Cancer Immunology Research 6*(12), 1459–1471. https://doi.org/10.1158/2326-6066.CIR-18-0086.

Zhao, H., Yang, L., Baddour, J., Achreja, A., Bernard, V., Moss, T., ... Nagrath, D. (2016). Tumor microenvironment derived exosomes pleiotropically modulate cancer cell metabolism. *Elife 5*, e10250. https://doi.org/10.7554/eLife.10250.

Zhao, L., Ji, G., Le, X., Wang, C., Xu, L., Feng, M., ... Zhou, S. (2017). Long Noncoding RNA LINC00092 Acts in Cancer-Associated Fibroblasts to Drive Glycolysis and Progression of Ovarian Cancer. *Cancer Research 77*(6), 1369–1382. https://doi.org/10.1158/0008-5472.CAN-16-1615.

Zhao, X. L., Lin, Y., Jiang, J., Tang, Z., Yang, S., Lu, L., ... Yao, X. H. (2017). High-mobility group box 1 released by autophagic cancer-associated fibroblasts maintains the stemness of luminal breast cancer cells. *The Journal of Pathology 243*(3), 376–389. https://doi.org/10.1002/path.4958.

Zhou, W., Xu, G., Wang, Y., Xu, Z., Liu, X., Xu, X., ... Tian, K. (2017). Oxidative stress induced autophagy in cancer associated fibroblast enhances proliferation and metabolism of colorectal cancer cells. *Cell Cycle 16*(1), 73–81. https://doi.org/10.1080/15384101.2016.1252882.

Ziani, L., Safta-Saadoun, T. B., Gourbeix, J., Cavalcanti, A., Robert, C., Favre, G., ... Thiery, J. (2017). Melanoma-associated fibroblasts decrease tumor cell susceptibility to NK cell-mediated killing through matrix-metalloproteinases secretion. *Oncotarget 8*(12), 19780–19794. https://doi.org/10.18632/oncotarget.15540.