Leveraging microenvironmental synthetic lethalities to treat cancer

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Treatment resistance leads to cancer patient mortality. Therapeutic approaches that employ synthetic lethality to target mutational vulnerabilities in key tumor cell signaling pathways have proven effective in overcoming therapeutic resistance in some cancers. Yet, tumors are organs composed of malignant cells residing within a cellular and noncellular stroma. Tumor evolution and resistance to anticancer treatment are mediated through a dynamic and reciprocal dialogue with the tumor microenvironment (TME). Accordingly, expanding tumor cell synthetic lethality to encompass contextual synthetic lethality has the potential to eradicate tumors by targeting critical TME circuits that promote tumor progression and therapeutic resistance. In this Review, we summarize current knowledge about the TME and discuss its role in treatment. We outline the concept of tumor cell–specific synthetic lethality and describe therapeutic approaches to expand this paradigm to leverage TME synthetic lethality to improve cancer therapy.

Introduction

Solid tumors are organs with a complex organization that fosters tumor cell growth, survival, invasion, and evolution (1, 2). The tumor organ is composed of cancer cells, noncancerous stromal cells (fibroblasts, adipocytes, nerves, and endothelial cells as well as resident and infiltrating immune cells), and an extracellular matrix (ECM) with associated soluble factors that collectively contribute to cancer development, modulate treatment response, and ultimately participate in the evolution of treatment-resistant, metastatic tumors (3, 4). These noncancerous stromal cells and noncellular components are collectively referred to as the tumor microenvironment (TME). The composition and behavior of the TME are dictated by genetic and epigenetic elements of the cancer cells that collaborate through bidirectional communication with the TME to create a functional cancerous tissue. Within the context of this cancerous tissue, therapy-resistant tumors arise through their ability to subvert this dynamism toward their continued survival and regrowth after treatment (5, 6). This tumor organ homeostasis permits the development of drug-resistant, immune-resistant tumors.

Cytotoxic chemotherapy has been used successfully to treat many cancers. However, drug resistance and off-target toxicities remain major challenges that all too often lead to tumor recurrence and patient mortality. These challenges have motivated the search for patient-specific targeted treatments with a lower propensity for drug resistance and fewer off-target toxicities. Tailored therapeutic strategies are matched to a patient's tumor biopsy phenotype and driver mutations. One exciting class of personalized cancer therapy exploits the concept of synthetic lethality, wherein cancer cells with a mutation in a key survival pathway are uniquely sensitive to therapeutic inhibition of a related survival pathway (7). A synthetic lethal therapeutic exploits the relationship between proliferation/viability and survival pathway redundancy; cancer cells achieve proliferation and viability at the expense of losing survival pathway redundancy. Synthetic lethal therapeutics limit off-target toxicity because healthy cells, which lack the tumorigenic mutation, remain insensitive to the therapeutic. Additionally, the high differential sensitivity of cancer cells and noncancer cells to synthetic lethal therapeutics creates a large therapeutic window that could decrease drug dosing and further limit toxicity (8). Despite encouraging success using synthetic lethal cancer therapies, this approach has been limited primarily because only a minority of cancer-associated mutations are understood well enough to identify and develop such targeted treatments. Complicating this issue and contributing to the emergence of treatment resistance is the high heterogeneity of tumors. These heterogeneous cell types are loosely organized into semifunctional tumor tissues with coordinated behavior that lends itself to contextual TME lethality.

Resistance to antitumor treatment can arise either from the emergence of individual tumor cells that harbor mutations that provide survival and proliferative advantages to individual tumor cells or from TME factors that provide context-dependent resistance cues (5). While much work has already been done to understand clonal selection of individual cancer cells, there is an urgent need to better understand how the TME fosters treatment resistance. Indeed, while some cancer cells in therapy-resistant tumors demonstrate tissue-specific treatment resistance, they can exhibit elevated sensitivity when treated as isolated cells. TME factors that promote treatment resistance include hypoxia, the tumor-associated vasculature and ECM, and a protumor immune infiltrate (5, 9). Thus,

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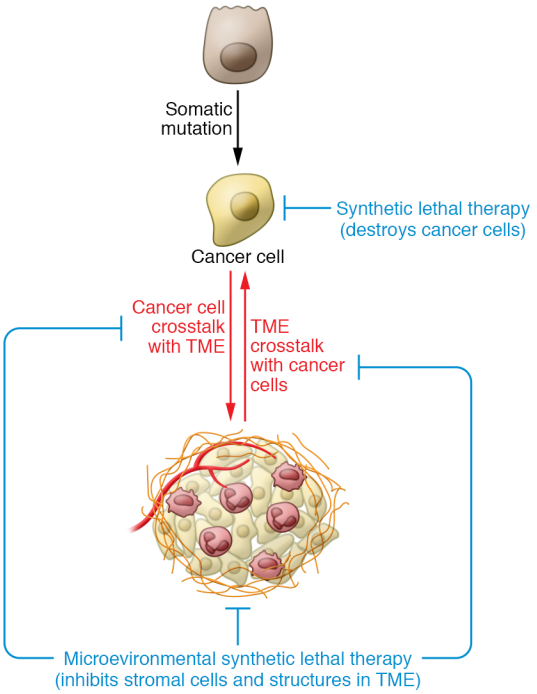

Figure 1. Sensitizing cancer cells with contextually synthetic lethal therapeutics. Cancer develops within a TME to form an organ that engages in bidirectional communication to promote tumor evolution. Contextually synthetic lethal therapies interrupt this system by targeting stromal cells or molecules within the TME to arrest tumor progression and improve treatment responses that ultimately eradicate the cancer. As an example, hypoxia in the TME inhibits DNA damage repair pathways, making hypoxic cancer cells more sensitive poly-ADP ribose polymerase (PARP) inhibitors. In contrast, conventional synthetic lethal therapies target cancer cells based only on mutational vulnerabilities.

analogous to the emergence of cancer cell–specific dependence on specific survival signaling pathways, the tumor organ's growth and survival are exquisitely reliant on key TME factors. Identifying and targeting these critical treatment-stimulated TME growth and survival factors has high potential to improve patient care.

Contextual synthetic lethality, a concept first proposed by Bristow and colleagues, is a nongenetic form of synthetic lethality, where an abnormal structure or function of the TME sensitizes cancer cells to therapy. For example, Bristow and colleagues showed that hypoxic cancer cells, which are deficient in DNA repair, are more sensitive to therapeutic inhibition of DNA damage pathways (10). This example highlights how hypoxia in the TME sensitizes cancer cells to contextually synthetic lethal therapeutics, despite also driving invasive phenotypes and cytotoxic drug resistance (Figure 1). In this Review we describe how cancer cell dependence on tumor-specific TME factors constitutes unique therapeutic vulnerabilities that, if targeted, could synergize with specific tumor cell–targeted therapies to improve cancer patient treatment response and prevent the emergence of treatment-resistant, lethal tumors.

Overview of the tumor microenvironment and drug resistance

Tumors are composed of a population of cancer cells that are genetically, phenotypically, and spatially heterogeneous, and this heterogeneity correlates with drug resistance (11, 12). There are regions of abnormal and poor vascularization in tumors such that some cancer cells experience low nutrient and hypoxic conditions (13, 14). Further, leaky arterial vessels and compressed drainage vessels create a high interstitial pressure that further limits nutrient availability (9). Differential access to nutrients could explain why cancer cell proliferation is spatially heterogeneous as indicated by phospho–histone H3 staining of human breast tumors (luminal A, luminal B, and HER2$^+$ subtypes; ref. 15). Because most cytotoxic chemotherapeutics target dividing cells, cancers with a higher frequency of proliferating cells are generally thought to be more drug sensitive. Indeed, cancer cells grown in three-dimensional spheroids are more resistant to cytotoxic chemotherapeutics, as this culture format typically shows reduced proliferation rates and decreased glycolysis (16, 17). However, in vivo, fast-growing regions of cancer cells within the breast cancer mouse model *MMTV-PyMT*, denoted by greater levels of the phospho–histone H3 proliferation marker, feature increased expression of hypoxia-associated genes and greater resistance to cytotoxic chemotherapy (15).

Cancer cell heterogeneity and drug resistance are also promoted by the ECM, which provides location-specific cues to cancer cells. ECM is categorized into two groups — the basement membrane, which separates the epithelial layer from the mesenchyme, and the interstitial ECM, which forms the bulk of the tissue ECM and provides structural support and is where the stromal cells reside. Invasive epithelial tumors disrupt healthy ECM organization by cleaving and remodeling the basement membrane to invade into the interstitial ECM. As tumors evolve they exhibit substantial interstitial heterogeneity that is most evident at the invasive edge where the ECM is stiffest because of increased levels of reorganized, oriented collagen bundles that project perpendicularly from the tumor core (4, 18–20). ECM composition, organization, and cross-linking are mediated by stromal cells and stimulated by infiltrating immune cells. The cells that populate the TME are specified by the genotype of the tumor cells such that different tumor subtypes develop distinct ECM phenotypes (21, 22). Mesenchymal fibroblasts transdifferentiate into cancer-associated fibroblasts (CAFs) and are the primary cell type that deposit, remodel, and cross-link the interstitial ECM (23). This CAF-instructed ECM provides critical biochemical cues that foster tumor cell growth, survival, and invasion through ligation of ECM receptors including integrins, discoidins, and syndecans (18, 24–27). In particular, laminin, which is a component of the basement membrane, induces β4 integrin signaling and promotes resistance to drug-induced apoptosis (17). A dense, stiffened, and cross-linked ECM can also create a hostile tumor environment by impeding the vasculature to induce hypoxia and restrict drug delivery (28). The ECM also sequesters cytokines, growth factors, and morphogens. These factors are released by CAF-secreted metalloproteins and cathepsins to stimulate tumor cell growth, survival, and invasion and recruit inflammatory cells to the tumor. Importantly, the ECM is highly heterogeneous with respect to its biochemical properties, mechanical features, and associated soluble factors. This hetero-

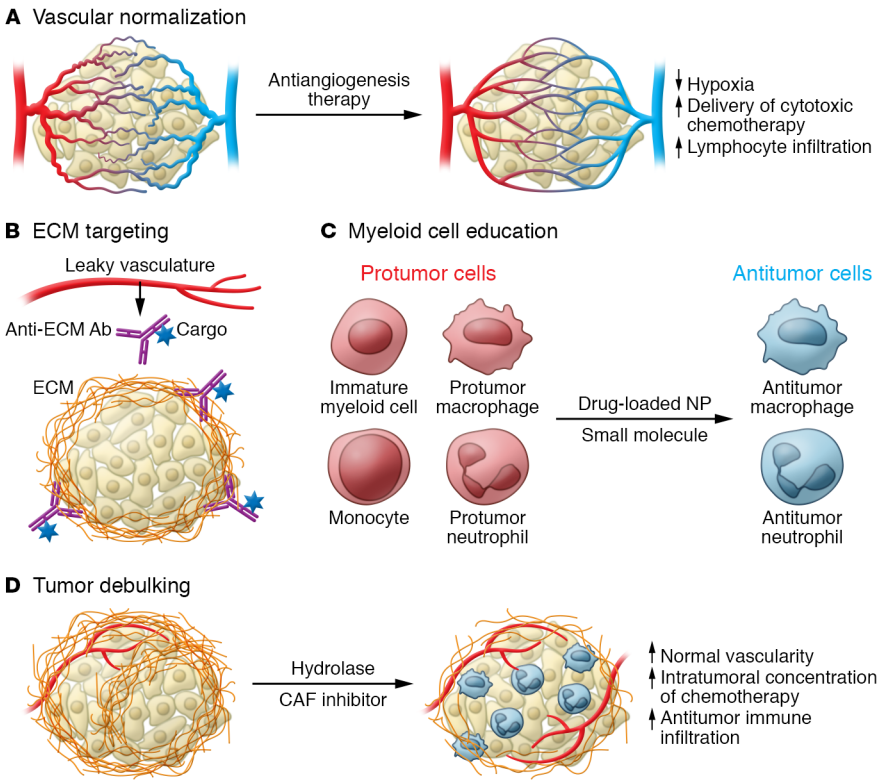

Figure 2. Targeting contextual synthetic lethalities in the TME. (**A**) Low-dose antiangiogenesis therapy normalizes tumor vasculature. (**B**) Leaky vasculature enables affinity targeting of ECM components enriched in tumors. (**C**) Small-molecule drugs educate myeloid cells to antitumor phenotypes by differentiation or repolarization. Nanoparticle (NP) encapsulation improves delivery to phagocytes. (**D**) Enzymatic hydrolysis of ECM or inhibition of CAFs debulks tumor ECM, normalizing tumor structure and vascularity.

The tumor microenvironment inhibits therapeutic response

While chemotherapy, radiation, and surgery are effective mainstream treatments that improve patient survival, all too frequently patients present with recurrent disease that leads to their mortality. Immunotherapies have emerged as treatments with impressive results and cancer patient cures. Unfortunately, not all tumor types are amenable to these therapies, and even in tumor types that show effective remission, some patients do not respond. Although tumor-intrinsic mechanisms drive drug resistance, the TME is now recognized as an additional major contributor to drug resistance. In order to improve therapy for patients not well served by current treatments, a better understanding of how the TME promotes drug resistance is needed.

geneity creates gradients that can markedly modulate tumor cell invasion and metastasis (29). ECM-dense regions within tumors can also present ECM-bound immune-inhibitory cytokines that compromise the efficacy of cytotoxic and immune therapies (30).

A heterogeneous population of immune cell types in tumors contributes to cancer progression and drug resistance. While immune cells have the ability to destroy cancer cells (31), developing tumors can evade the immune system. Spatial heterogeneity within a tumor, which is reflected by tumor subtype (32), contributes to immune suppression by impeding direct interactions between immune cells and cancer cells. Poor tumor vascularity (33) and a dense ECM likely contribute to reduce immune cell infiltration (34). Not surprisingly, tumors with few infiltrating leukocytes or spatially segregated immune infiltrates have poorer outcomes, and these tumors are classified as "immune excluded" and "compartmentalized" (35–37). Indeed, patients whose ER^+ breast tumors demonstrated high lymphocyte spatial heterogeneity when treated with endocrine therapy had higher recurrence rates, emphasizing the importance of immune cell distribution to therapy response (38).

Tumors build their organ and foster drug resistance by coordinating multiple cell types through cell-cell communication. In many healthy tissues, structural cells (epithelial cells, endothelial cells, and fibroblasts) produce cytokines to recruit immune cells (39). Cancer cells subvert this function to produce, or induce stromal cells to produce, cytokines that affect angiogenesis, hematopoiesis, and immune cell recruitment to establish an immunosuppressive microenvironment (40–45). These cytokines also participate in new signaling networks established by aberrant gene expression in malignant cells. For example, CCL2 promotes $CCR2^+$ cancer stem cell self-renewal and promotes tumor growth (46, 47).

Radiation and surgery induce inflammation and tumor-promoting immunity. Radiation and surgery both induce tissue damage that stimulates a wound healing response mediated by local and systemic inflammation (48). This treatment-induced acute inflammation in turn increases risk of local tumor recurrence and promotes metastatic dissemination and progression (49, 50). For instance, following surgery, patients have higher levels of immunosuppressive neutrophils and monocytes that are recruited to the wound (51). Experimental studies have demonstrated that inducing a surgical wound at a site distal to a primary mouse breast tumor promotes tumor growth by stimulating a systemic inflammatory response. Wounding mobilizes immunosuppressive neutrophils and monocytes via increased levels of IL-6, G-CSF, and CCL2 (52). Surgical resection of tumors rapidly returns local and systemic immunity to a healthy state (53), indicating that persisting cancer cells likely play a key role in driving the tumor-promoting inflammatory response. Surgical patients receiving perioperative nonsteroidal antiinflammatory drugs experience lower rates of breast cancer recurrence, which demonstrates that controlling tissue inflammation can improve long-term patient outcomes (52, 54). The degree and nature of tumor inflammation depend on patient-specific factors. For example, triple-negative breast cancer patients with a high neutrophil/lymphocyte ratio after radiation therapy have increased risk of recurrence and decreased survival (55). To harness the inflammatory response to surgery or radiation as a contextual synthetic lethality, polarization of immune cells to antitumor phenotypes could increase infiltration of cytotoxic immune cells in the TME.

Immune response to chemotherapy. Cytotoxic chemotherapy seeks to induce apoptotic cell death in cancer cells. Nevertheless, and unfortunately, heterogeneity in the cancer cell population allows for persistence of drug-resistant cells. A patient's immune response can enhance chemotherapy to eradicate resistant cancer cells (56). Cytotoxic chemotherapy induces apoptotic cells to release their cellular contents, including cytokines and intracellular proteins, that drive local inflammation of innate effector cells (57) and generate cancer-specific neoantigens (56). The chemokine CCL2 is released by cancer cells treated with doxorubicin and attracts $CCR2^+$ monocytes and other myeloid cells involved in antigen presentation to the tumor (58). These antigen-presenting cells present cancer cell peptides by MHC class II and lead to T cell–directed killing of persisting cancer cells (59). In both breast cancer patients and mouse models, a type I interferon response improves efficacy of doxorubicin treatment, which is produced by dying cancer cells and recruited myeloid cells (60). Interestingly, genetic deletion of *Mmp9* also improves doxorubicin treatment, suggesting a link between inflammation, ECM remodeling, and response to chemotherapy (61). Yet, the plasticity of myeloid cells can lead to an immunosuppressive TME that inhibits immune clearance after chemotherapy.

Patients with residual disease after chemotherapy have greater myeloid infiltration (62), suggesting a functional link between inflammation and chemotherapy response (63). In mice, paclitaxel or cisplatin therapy increases recruitment of tumor-promoting macrophages by stimulating the production of CSF-1 by cancer cells. A CSF-1R antagonist improves response to paclitaxel by blocking macrophage recruitment (64). Deletion of *Ccr2* decreases monocyte recruitment to tumors and improves doxorubicin and cisplatin treatment in the *MMTV-PyMT* mouse model. The fact that $CCR2^+$ myeloid cells can both enhance and inhibit immune clearance after cytotoxic chemotherapy suggests that $CCR2^+$ myeloid cells are a heterogeneous population of cells with potential for tumor-promoting and tumor-suppressing activities (61).

Controlling the immune response to chemotherapy may harness immune clearance while limiting immune suppression. New chemotherapy regimens for existing drugs have enhanced efficacy that may in part limit tumor-promoting inflammation. Low-dose metronomic chemotherapy improves therapeutic response by decreasing tumor-promoting inflammation and CAF activation (65–67). Incorporating microenvironmental and inflammatory responses to an adaptive therapy regimen, in which drug dosing is varied as a function of patient response, could further balance the benefits of cytotoxic chemotherapy with the costs of tumor-promoting inflammation (68).

Cancer cells resist immune clearance during immunotherapy. Developing tumors create an immunosuppressive environment that permits their progression. While driver mutations in cancer cells promote carcinogenesis, these mutations also create neoantigens that can be recognized by the immune system for destruction. Cancer cells remodel their cell surface to evade immune destruction, and also secrete factors that create a tolerogenic microenvironment that inhibits immune clearance (69). Immunotherapies that block immune effector checkpoints, especially antibodies blocking PD-1, PD-L1, and CTLA-4 (reviewed in ref. 70), overcome the immunosuppressive TME. Checkpoint therapy has transformed the treatment of cancers, including melanoma, hepatocellular carcinoma, and lung cancer, but has not found success in multiple tumor types (71). Cancers that are recalcitrant to immunotherapy utilize additional mechanisms to inhibit immune surveillance.

Immune destruction of cancer cells requires recognition of changes to the cell surface, relative to healthy cells. All human cells express MHC class I molecules that present intracellular peptides to allow for immune surveillance of mutant or infected cells. While complete loss of MHC class I marks cancer cells for destruction by NK cells (72), downregulation of MHC class I proteins through lysosomal degradation (73) and allelic loss (74, 75) can dampen immune recognition of cancer cells and decrease response to checkpoint inhibitors (73, 76). Further, cancer cells inhibit immune activation by upregulating immune checkpoint proteins including PD-L1 (77), CD47 (78), and CD24 (79). In addition to surface proteins, cancer cells evade immune destruction via a hypersialylated glycocalyx, the outermost layer of protein and glycan polymers that covers all human cells. Sialoglycans directly interact with Siglec receptors on immune cells including T cells (80, 81), NK cells (82–84), and myeloid cells (85). These Siglec receptors have cytosolic immunoreceptor tyrosine-based inhibition motif (ITIM) domains that lead to immune suppression and block cytotoxic reactions toward the hypersialylated cancer cells (86). Immune suppression by cancer cell sialic acids could decrease immunotherapy efficacy. Remodeling of the cancer cell surface to remove sialic acid improves NK cell–mediated cancer cell killing (87) and controls tumor growth in a Siglec-E–dependent manner in a mouse model (85).

Environmental stress promotes drug resistance. In addition to cellular forms of drug resistance, a tumor-promoting metabolite milieu fosters drug resistance. Tumors have increased acidity, higher concentrations of reactive oxygen species, and lower nutrient levels relative to healthy tissue. This harsh microenvironment collectively causes cellular stress in cancer and stromal cells (88). More aggressive tumors express a heat-shock factor 1 (HSF1) transcriptional program in cancer cells and CAFs near necrotic regions (89, 90). Increased glycolysis by cancer cells acidifies the TME by increasing the concentration of lactate, which stimulates differentiation of macrophages into an immunosuppressive state (91). Cancer cells also respond to environmental stress by increasing autophagy levels, which improves cellular viability in nutrient-poor conditions (92). Cancer cells under high environmental stress are more drug resistant. For example, HSF1 positively regulates the expression of drug resistance genes (93–95), and higher levels of autophagy are linked with increased drug resistance (92).

Microenvironmental synthetic lethality for cancer therapy

Synthetic lethal cancer therapies take advantage of differential drug sensitivity of cancer cells relative to healthy cells (8). The first and currently only approved synthetic lethal cancer therapy is poly-ADP ribose polymerase (PARP) inhibitors for *BRCA1*- and *BRCA2*-mutant ovarian cancers (96). PARP, BRCA1, and BRCA2 contribute to DNA repair, making cancer cells carrying *BRCA* mutations more sensitive to PARP inhibitors (97, 98). Interestingly, PARP inhibitors have not been as successful in treating breast cancers with *BRCA* mutations. This lack of success suggests that successful synthetic lethal therapies depend on context outside of the two genes involved in the synthetic lethality (7).

Moving beyond a cancer cell–focused view of synthetic lethal therapy, many new therapies seek to shape the protumor microenvironment to an antitumor phenotype, which in turn leads to cancer cell death. The protumor microenvironment supports tumor viability with abnormal structures and functions that differ from healthy tissue. Analogous to cancer-associated mutations, protumor elements of the TME are unique, and thus tumors are specifically sensitive to targeting of these elements. In this way, therapy targeting the TME uses a principle of nongenetic synthetic lethality. Many key features of the protumor microenvironment are different compared with healthy tissue, opening up microenvironmental synthetic lethal therapy.

Tumor structure and biochemistry create contextual synthetic lethalities. Tumor organs have unique properties that are required for progression. These properties create contextual synthetic lethalities, as healthy organs do not feature these properties and are thus not sensitive to therapeutic inhibition. For example, therapies that target tumorigenic vasculature and ECM could enable immune control and greatly improve patient survival (99).

Inhibiting angiogenesis to normalize vasculature. Tumors need to grow new blood vessels in order to feed rapidly dividing cancer cells (100). Cancer cells rely on glycolysis, as opposed to oxidative phosphorylation, requiring greater nutrient supply and glucose flux (69). Yet many tumors are abnormally and poorly vascularized, which causes nutrient-poor and hypoxic regions within tumors (101). Tumor hypoxia promotes aggressive cancer cell phenotypes and fosters drug resistance (102). However, hypoxic cancer cells are deficient in DNA damage repair (103), representing a contextual synthetic lethality to inhibition of cellular detection of DNA damage. Indeed, hypoxia-induced deficiencies in DNA damage repair sensitize these cells to PARP inhibitors (10, 104). Poor tumor vasculature also causes high interstitial fluid pressure that resists convection of cancer therapeutics from the blood into the core of a tumor (9).

To relieve hypoxia and normalize the abnormal vasculature of tumors, vascular endothelial growth factor (VEGF) antagonists are used to block neoangiogenesis. However, high-dose therapy can lead to complete disruption of tumor vasculature that induces hypoxia, creating a niche for cancer stem cells and immunosuppressive immune cells. Lower-dose therapy that normalizes tumor vasculature has shown greater clinical success (Figure 2A and ref. 13). The success of antiangiogenesis therapy may depend on microenvironmental factors. For example, patients with obesity benefit less from anti-VEGF therapy. In obese mice, anti-VEGF therapy does not inhibit tumor growth due to increased IL-6 and FGF-2 expression in adipocyte and myeloid cells in hypoxic adipocyte-rich regions. Inhibition of IL-6 or FGF-2 improved response to anti-VEGF therapy in obese mice (105).

Tumorigenic ECM presents ligands for localization of therapies. The combination of leaky vasculature and tumor-specific ECM allows for affinity targeting of the TME. In breast cancer, tumors have increased deposition of fibrillar collagen that leads to denser and stiffer tissue and is associated with poorer prognoses (4, 19). Increased stiffness and abnormal structure coupled with leaky vasculature make tumor-associated collagen a unique epitope. For example, affinity targeting of probes to tumor-associated collagen enables diagnostic detection of tumors and micrometastases (106). Further, drug delivery using collagen affinity has shown promise in multiple immuno- and chemotherapeutic drugs in preclinical mouse models (Figure 2B and refs. 107, 108). Tumor localization of IL-2 or IL-12 by linkage to the collagen-binding protein lumican leads to tumor rejection by increasing tumor infiltration of cytotoxic T cells (109). Likewise, multiple immunotherapies (anti–CTLA-4, anti–PD-L1, IL-2, and IL-12) linked to the collagen-binding von Willebrand factor A3 domain selectively localize these protein therapeutics to the TME and lead to tumor rejection in mouse models (110, 111). Thus, leaky vasculature coupled with tumor-specific ECM represents a contextual synthetic lethality for drug localization.

Like collagen, fibrin and fibronectin are also distinct in the TME, opening possibilities for drug delivery (106, 112). Antibody fragments and peptides identified using phage display are selectively enriched in the TME in multiple tumor types in mice (113–116). The L19 antibody, which binds to the cancer-associated extra domain B splice variant of fibronectin, localizes IL-2, IL-12, and TNF to tumors and improves treatment response in glioblastoma multiforme (GBM) in patients in a phase I/II clinical trial. GBM is poorly infiltrated by immune cells, and these immunocytokines enhance immune infiltration and cancer cell death (117).

Manipulating tumor-promoting stromal cell functions. High infiltration of tumor-promoting stromal cell phenotypes could enable contextual synthetic lethalities through polarization of these cells to tumor-suppressing phenotypes. In this section we describe therapies that directly stimulate immune cell polarization and recruitment of cytotoxic effector T cells. In addition, other therapies may have previously unknown immunostimulatory side effects. For example, DNA methyltransferase inhibitors permit expression of tumor antigens and endogenous retrovirus transcripts that drive a cytotoxic immune response, demonstrating how therapies that target the cancer cell epigenome also affect the TME (118). We focus this section on therapies that target myeloid cells and CAFs, and refer the reader to excellent reviews on targeting of lymphoid cells (119, 120).

Phenotypically plastic tumor-associated macrophages can acquire antitumor functions. Tumor-associated macrophages (TAMs) are highly abundant in many cancers, and their high abundance could be therapeutically harnessed as a contextual synthetic lethality if they are polarized to antitumor phenotypes (Figure 2C and ref. 121). Selective modification of monocyte gene expression using the class IIa histone deacetylase (HDAC) inhibitor TMP195 polarizes TAMs to a phagocytic antitumor phenotype that enhances efficacy of carboplatin, paclitaxel, and anti–PD-1 therapies (122). Lysosomal activity may also determine TAM phenotype, as the lysosomal inhibitor chloroquine polarizes macrophages to antitumor phenotypes and enhances T cell control of melanoma tumors in mice (123). Combination therapy of hydroxychloroquine with doxorubicin improves therapeutic efficacy in a non–small cell lung cancer mouse model by reprogramming immunosuppressive TAMs to an antitumor phenotype marked by increased levels of MHC class II and decreased levels of CD206. These reprogramed TAMs increase infiltration of tumor-killing $CD8^+$ T cells (124). Targeting of TAM reprogramming can also be achieved by direct targeting of protumor $CD206^+$ TAMs. The host defense peptide synthetic analog RP-182 binds to the CD206 receptor on tumor-promoting TAMs and activates RAC1/CDC42 signaling. CD206 activation

reprograms TAMs to an antitumor phenotype characterized by increased phagocytosis of cancer cells that results in decreased tumor growth in a pancreatic cancer mouse model (125).

TAMs have a propensity to phagocytose particles in the size range of approximately 0.1–1 μm, acting to endocytose nanoparticle therapeutics. Nanoencapsulation of the TLR7/8 agonist R848 improves macrophage-specific drug delivery and drives TAM expression of genes associated with antitumor activity, which improves survival in mice bearing MC38 xenografts (126). The FDA-approved iron deficiency nanoparticle drug ferumoxytol induces reactive oxygen species–mediated cytotoxic activities in TAMs toward cancer cells that decrease tumor growth and metastatic burden in multiple mouse models (127). As a result of the phagocytic activity of TAMs, they can accumulate nanoencapsulated chemotherapeutics to create a high concentration of cytotoxic drugs within the TME. In the 4T1 breast cancer mouse model, liver metastases are decreased by a nanoencapsulated platinum that accumulates in TAMs (128). This effect was enhanced when tumor-bearing mice were first treated with radiation to increase TAM infiltration (129), a known side effect of radiation therapy (48). Thus, tumors with high TAM infiltration have a contextual synthetic lethality to nanoparticle-based therapies.

Inducing antitumor phenotypes in tumor-mobilized immunosuppressive myeloid cells. Myeloid cells are recruited to the tumor and can support an immunosuppressive microenvironment that is drug resistant. An immature and heterogeneous population of these cells, known as myeloid-derived suppressor cells, serves to inhibit cytotoxic activities of immune effector cells against cancer cells (130). The spectrum of cell types within this population makes depletion difficult. Instead, therapy could be enhanced by targeting repolarization or differentiation of immunosuppressive myeloid cells to antitumor phenotypes (Figure 2C). Control of myeloid polarization can be achieved by manipulation of the differentiation of myeloid progenitors using a bone marrow–homing nanoparticle therapeutic bearing the immunostimulatory muramyl tripeptide. In a mouse model, this nanoparticle therapy increases myelopoiesis, decreases the number of TAMs, and potentiates anti–PD-1 and anti–CTLA-4 therapy (131). Also, β-glucan induces a potent antitumor neutrophil phenotype through epigenetic rewiring during granulopoiesis (132). Outside of the bone marrow, myeloid cells continue to differentiate and polarize. Monocytes are differentiated into antitumor TAMs by a prodrug of 6-diazo-5-oxo-L-norleucine (DON) that blocks glutamine metabolism in myeloid-derived suppressor cells, resulting in decreased tumor growth and metastatic burden in tumor-bearing mice (133). These examples show how the propensity of some tumors to be highly infiltrated by immunosuppressive myeloid cells can thus be turned into a microenvironmental synthetic lethality. Polarizing myeloid cell progenitors to a potent antitumor phenotype, which are then recruited to the tumor, induces an immunostimulatory TME that improves patient outcomes.

Targeting CAFs to remodel ECM. CAFs exist in a unique cell state that could allow for contextual synthetic lethal therapeutic targeting (23). Fibroblast activation protein (FAP) is a CAF marker that is of considerable clinical interest, but has yet to be realized in an approved therapy (134). For example, depletion of FAP$^+$ CAFs using a FAP vaccine decreases collagen density in tumors and improves response to doxorubicin in mice (135). But targeting CAFs for depletion may counterintuitively promote tumor growth in certain contexts, likely owing to FAP expression on other stromal cell types, including cancer-associated pericytes (136). In pancreatic ductal adenocarcinoma (PDAC), which is CAF rich and highly fibrotic, genetic depletion of α-smooth muscle actin–positive (αSMA$^+$) myofibroblasts in a mouse model leads to increased tumor invasion, decreased survival, and increased CTLA-4 expression in tumors. This example shows that CAFs and tumorigenic ECM have multiple tumor-suppressing activities. Combining αSMA$^+$ myofibroblast depletion with gemcitabine treatment does not improve therapeutic response. However, combination of αSMA$^+$ myofibroblast depletion with anti–CTLA-4 therapy improves therapeutic response, showing that the interplay between CAFs and treatment depends on context (137). As another example, while deletion of Sonic hedgehog (*Shh*) in cancer cells decreases the number of CAFs, it also decreases the number of infiltrating immune cells, leading to greater tumor growth in a mouse PDAC model (138). It is likely that the heterogeneity of CAFs within a tumor points to a spectrum of tumor-promoting and -suppressing activities that may be lost by depletion therapies.

Instead of targeting CAF depletion, inhibition of tumor-promoting CAF activities may hold greater promise (Figure 2D). Proliferation of CAFs is inhibited by antagonism of Smoothened of the hedgehog pathway, leading to decreased density of collagen I. Inhibition of CAFs in turn improves therapeutic response to gemcitabine by increasing tumor vascularity and intratumoral concentration of gemcitabine in a PDAC mouse model (139). Combination of a Smoothened antagonist with docetaxel showed promising results in phase I clinical trials when given to triple-negative breast cancer patients with high levels of cancer cell–CAF paracrine hedgehog signaling (140). In the *MMTV-PyMT* model of breast cancer, cancer cells were maintained in a tamoxifen-resistant state by CAFs. Antibody neutralization of cancer cell–derived PDGF-CC blocked PDGFR signaling in CAFs and sensitized these tumors to tamoxifen. These results demonstrate that response to hormone therapy is in part determined by CAF activity (141). Instead of inhibiting CAF function, ECM components can be targeted directly. Debulking hyaluronan with hyaluronidase improves therapeutic response to gemcitabine by enhancing vascularity in a PDAC mouse model (142). In these examples, fibrotic, CAF-rich tumors are vulnerable to chemo- or immune therapy when the tumor ECM is therapeutically normalized. However, this vulnerability must be balanced with potential loss of tumor-suppressive ECM activities.

Conclusion and future directions

The TME plays an important role in tumorigenesis and response to therapy. Clinicians can use therapies that target microenvironmental synthetic lethalities in combination with traditional cytotoxic chemotherapy, surgery, immunotherapy, and radiation to improve survival in patients who currently lack effective treatments. Because these TME-targeted therapies are directed toward protumor microenvironmental features, there are fewer off-target effects and less potential for drug resistance. Treatment of the TME, analogous to targeted therapy, will need to be personalized to treat the specific vulnerabilities of a patient's tumor. Ideally,

TME properties could be discerned with blood measurements of surrogates for tumor inflammation, such as cytokines or circulating immune cell counts. Finally, understanding the evolution of the TME, especially in recurrence, will bring us closer to making cancer a disease that we die with, not from.

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