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Multifaceted cell-cell crosstalk and therapeutic opportunities in the dynamic tumor microenvironment

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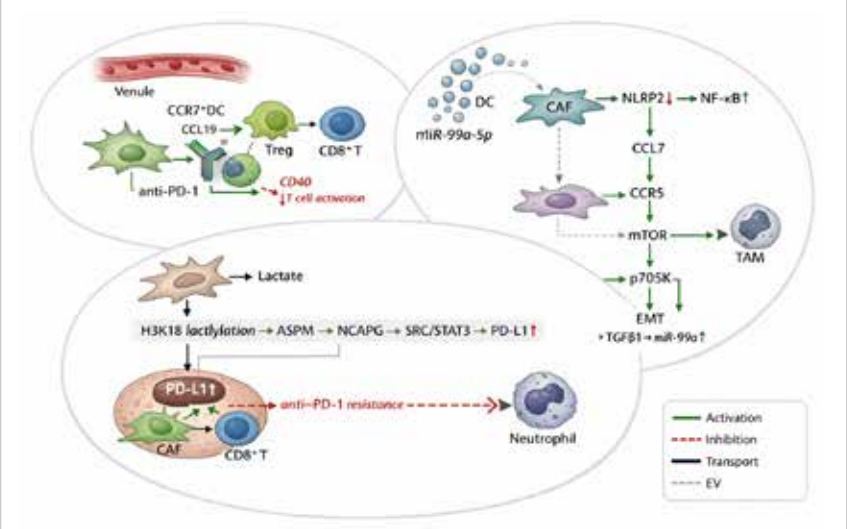

Schematic diagram of cell interactions driving immunosuppression and treatment tolerance in TME.

In the TME, DCs influence CD8⁺ T cell activation through chemokine axes (such as CCR7-CCL19) and Treg pathways, thereby regulating the response to anti-PD-1 therapy. Simultaneously, DC-derived EVs deliver miRNAs that remodel the CAF phenotype, promoting EMT and TAM recruitment/polarization through a series of

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signaling pathways. On the other hand, lactate produced by CAFs induces H3K18 lactylation, activating cascade pathways and upregulating PD-L1, inhibiting $CD8^+$ T cell effects, promoting anti-PD-1 tolerance, and linking it to a neutrophil-associated immunosuppressive phenotype. TME: Tumor microenvironment; DCs: Dendritic cells; Treg: regulatory T cell; EVs: extracellular vesicles; TAM: tumor-associated macrophage; EMT: Epithelial-mesenchymal transition; CAF: cancer-associated fibroblast.

Abstract

The tumor microenvironment (TME) is an ecosystem in which malignant cells co-evolve with immune, stromal, vascular, neural, and microbial components. Rather than acting in isolation, these compartments communicate through ligand-receptor signaling, direct contact, extracellular vesicles, extracellular matrix (ECM) remodeling, and metabolic exchange. This interaction network determines immune surveillance versus immune escape, governs invasion routes such as perivascular and perineural dissemination, and sets the threshold for therapy response and resistance. Single-cell and spatial omics studies emphasize the functionally reversible nature of specific microenvironments, while mechanistic work has exposed actionable coupling between tumor metabolism and myeloid polarization, fibroblast education, platelet-mediated metastatic priming, and vascular barrier functions. This review synthesizes the mechanistic axes of TME crosstalk, emphasize spatial and metabolic logic as organizing principles, discuss methodological strengths and pitfalls, and outline therapeutic strategies that target interactions rather than single cell types.

KEYWORDS

Tumor microenvironment, Cell-cell crosstalk, Immune microenvironment, Cancer-associated fibroblasts, Vascular niche

Introduction

Cancer is no longer viewed as a disease confined to genetically altered malignant cells; it is increasingly recognized as an ecosystem in which tumor progression is governed by dynamic interactions between cancer cells and their surrounding milieu(1). This ecosystem, termed the tumor microenvironment (TME), encompasses not only neoplastic cells but also a heterogeneous assemblage of non-malignant components that co-evolve with the tumor and collectively define its functional boundaries. Beyond infiltrating immune cells—including T lymphocytes, B lymphocytes, natural killer cells, tumor-associated macrophages, dendritic cells, and myeloid-derived suppressor cells—the TME contains stromal populations such as cancer-associated fibroblasts (CAFs), pericytes, endothelial cells, and diverse mesenchymal progenitors(2). These cellular compartments are embedded within a remodeled extracellular matrix (ECM) that provides both structural cues and bioactive signals(3). In parallel, vascular and lymphatic networks regulate nutrient delivery, metabolite clearance, and immune trafficking, thereby shaping spatial gradients of oxygen tension, acidity, and cytokine availability(4). Neural inputs, once considered peripheral to tumor biology, are now appreciated as modulators of inflammation, angiogenesis, and metastatic competence through neurotransmitter-mediated signaling and neurotrophic circuits(5). In selected anatomical sites, resident or invading microorganisms further extend the ecological scope of the TME by influencing epithelial integrity, antigenic tone, and local immunometabolism(6). Together, these elements form an adaptive communication network in which cell–cell crosstalk operates through direct contact, soluble mediators, extracellular vesicles (EVs), and metabolic exchange, ultimately orchestrating immune evasion, therapy resistance, and organ-specific dissemination(7). Defining the TME by its interacting cellular and acellular constituents provides a conceptual framework for dissecting mechanistic principles of intercellular signaling, understanding the spatial

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logic of tissue organization, and identifying translational vulnerabilities that can be exploited for durable cancer control.

The cell-cell crosstalk perspective helps explain intratumoral heterogeneity, because distinct microenvironmental niches impose unequal metabolic constraints, cytokine exposure, and matrix mechanics, thereby steering genetically related clones toward divergent phenotypic states(8). Reciprocal signaling between cancer cells and tumor-associated macrophages, dendritic cells, T lymphocytes, B lymphocytes, natural killer cells, CAFs, endothelial cells, and pericytes can generate spatially confined programs that favor proliferation, quiescence, stem-like plasticity, or stress tolerance(9, 10). These interaction-defined states also provide a mechanistic basis for immune escape. Antigen presentation may be blunted by dysfunctional dendritic cell priming, myeloid-derived suppressor cell expansion, regulatory T cell enrichment, or inhibitory checkpoint engagement, resulting in exclusion or paralysis of cytotoxic T lymphocytes despite ongoing inflammation(11). Therapy resistance frequently arises through non-genetic adaptation supported by paracrine survival cues, ECM remodeling, vascular niche shielding, and metabolic cross-feeding, which together buffer drug-induced stress and sustain minimal residual disease(12). Metastatic competence likewise depends on coordinated dialogues that promote epithelial-to-mesenchymal transition, facilitate intravasation via endothelial reprogramming, and condition pre-metastatic niches through soluble factors or EVs(13). After dissemination, organ-specific stromal signals and local immune education determine dormancy versus outgrowth, creating a substrate for late relapse. Recurrence often reflects the persistence of these protective niches, which preserve therapy-tolerant cells and accelerate evolutionary rebound under renewed selective pressure(14). Therefore, this review aims to systematically elucidate the intercellular communication circuits that constitute the core of heterogeneity, immune escape, drug resistance, metastasis, and recurrence, and how therapeutic approaches can reshape intercellular communication to achieve lasting cancer control.

TME composition and lineage landscapes

Tumor cell subsets

Tumor cells exhibit plasticity across epithelial-mesenchymal transition (EMT)/partial EMT, stress-adapted drug-tolerant states, and stem-like programs. These states are not only intrinsic survival strategies; they actively reshape the TME by changing antigen presentation, cytokine secretion, adhesion programs, and metabolic outputs. In colorectal cancer, tumor-intrinsic metabolic programs were linked to immunosuppressive signaling outputs that preferentially enhance regulatory T cell function via a defined chemokine axis(15). In metastatic breast cancer, single-cell mapping of liver and brain metastases highlights an immunosuppressive landscape associated with poor responsiveness to programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) blockade, implying that tumor states and site-specific microenvironments co-evolve(16). Beyond soluble outputs, tumor cells can be remodeled by vesicular communication. Extracellular vesicle-packaged microRNAs from colorectal cancer cells reprogram fibroblasts into inflammatory cancer-associated fibroblasts that feedback to promote epithelial–mesenchymal transition and metastasis(17). These findings reinforce the idea that “tumor cell programs” cannot be interpreted without mapping their outgoing and incoming interaction edges.

Immune lineages

Immune populations in tumors are best framed by functional state (cytotoxic, exhausted, regulatory, antigen-presenting, suppressive) and microanatomical positioning. A paradigmatic example is the CCR7$^+$ DC subset that clusters around venous vessels, where fibroblast-produced CCL19 positions these cells into perivascular hubs. Regulatory T cells frequently engage these dendritic cells, suppressing CD40 and limiting CD4$^+$ and CD8$^+$ T cell activation; PD-1 blockade increases interleukin-12 production yet can also strengthen a CCL22-dependent regulatory T cell–dendritic cell suppression loop(18). This illustrates that immune checkpoint therapy can simultaneously lift one constraint while reinforcing another, depending on spatial circuit structure.

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Myeloid programs frequently dominate suppressive topology. In hepatocellular carcinoma, single-cell analysis identified an immunosuppressive TREM2-positive macrophage population resembling lipid-associated macrophages that arises from S100A8-positive monocytes, correlates with poor prognosis, recruits suppressive regulatory T cells, and can be reprogrammed via liver X receptor signaling(19). In colorectal liver metastases, tumor-associated macrophage EVs carrying fibrinogen-like 2 promote tumor stemness and neutrophil extracellular trap formation through an FCGR2B-STAT3-interleukin-1β circuit, ultimately dampening PD-1 immunotherapy(20). Natural killer (NK) cell biology adds an additional axis: NK function is shaped by immune, metabolic, innervated, mechanical, and microbial microenvironments, providing a rationale for combining NK-based approaches with niche-rewiring strategies rather than treating NK dysfunction as a solely cell-intrinsic problem(21).

Stromal and vascular cells

CAFs are heterogeneous, with subtype composition associating with clinical outcomes and immunotherapy response, as shown by CAF landscape analyses in epithelial ovarian cancer(22). CAFs also operate as epigenetic and metabolic relays: lactate secreted by CAFs in gastric cancer drives histone H3K18 lactylation in tumor cells, activating an ASPM-NCAPG-SRC/STAT3 pathway that elevates PD-L1 and promotes resistance to anti-PD-1 therapy(23). Vascular cells define oxygenation, trafficking, and niche structure. Pericyte signaling via nitric oxide receptor soluble guanylate cyclase can reshape the vascular niche and microenvironment programs, implicating pericytes as active regulators rather than passive vessel stabilizers(24). Methodologically, vascularized organoids are emerging as tractable platforms for reconstituting these interactions in human-relevant systems(25).

The neuro-tumor-immune axis and related microbiota

Beyond canonical immune-stroma-vasculature axes, certain cancers leverage organ-specific participants. Nerve-tumor interactions, for example, may establish pro-invasive tracks and metabolic support. In perineural invasion-positive distal cholangiocarcinoma, $GFAP^+$ dedifferentiated Schwann cells were implicated in tumor progression via a lactate/HMGB1-associated axis, illustrating that glial-like programs can become functional elements of the tumor niche(26). Microbiome-associated signals—particularly circulating microbial signatures—have been linked to prognosis and immune microenvironment features in non-small cell lung cancer (NSCLC), implying an additional systemic layer of "remote crosstalk" that may track with intratumoral immune states(27). Such findings also demand methodological caution: contamination and batch effects remain non-trivial in low-biomass microbiome analyses.

Core interaction axes and molecular mechanisms

Tumor-immune crosstalk

Tumor-immune interactions are often described through checkpoint ligation, yet mechanistic resolution increasingly points to coupled circuits in which positioning, antigen presentation capacity, and local metabolism jointly determine effective immunity. Perivascular $CCR7^+$ DC hubs provide a concrete example: fibroblast-derived CCL19 guides dendritic cells into venous perivascular niches, creating a privileged site for T cell priming. Regulatory T cells then impose suppression via frequent contacts that downregulate CD40 and blunt $CD4^+$ and $CD8^+$ activation. Notably, anti-PD-1 therapy augments interleukin-12 programs while simultaneously strengthening regulatory T cell-dendritic cell contacts through a CCL22-dependent mechanism, thereby limiting therapeutic efficacy(18). This duality argues for combination strategies that disrupt suppressive contacts or chemokine retention within immune hubs, rather than relying on checkpoint

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blockade alone.

Tumor-intrinsic metabolic programs can translate into immune suppression via chemokine signaling. In colorectal carcinoma, upregulated SIRT1 in tumor cells promotes secretion of CX3CL1, which activates CX3CL1-CX3CR1 signaling to enhance regulatory T cell functionality through transcription factors such as SATB1 and BTG2(15). This mechanism exemplifies a broader principle: metabolic adaptation is not merely a survival strategy under stress; it can serve as a "secretory reprogrammer" that biases local immune composition and functional orientation.

Noncoding RNA programs can operate at the tumor–immune interface with both tumor-intrinsic and immune-extrinsic consequences. Deletion of LINC00673 enhanced the efficacy of PD-1 blockade in colorectal cancer, increasing cytotoxic $CD8^+$ T cell infiltration, reducing exhaustion, improving antigen presentation, and shifting macrophage composition toward less immunosuppressive states. Importantly, LINC00673 also promoted tumor cell migration and immune evasion independently of immune cells, implying parallel tumor-intrinsic and microenvironmental roles(28). Such duality matters clinically because it raises the likelihood that targeting a single node yields multi-compartment benefit.

Myeloid-derived suppressor cells (MDSCs) illustrate another recurrent module: inflammasome-driven interleukin-1β programs can dampen antitumor immunity and promote progression. A nanotherapy strategy using MDSC-targeting peptide–modified gold nanoparticles disrupted NLRP3 inflammasome via interference with NLRP3-NEK7 interactions through reactive oxygen species scavenging, lowering interleukin-1β levels, reducing MDSCs in tumors, and enhancing T cell activation in models sensitive or resistant to PD-1 inhibition(29). Mechanistically, these results highlight that "myeloid suppression" can be approached as a defined biochemical dependency rather than an untargetable phenotype. A critical open question is how frequently these circuits generalize across tumor types versus reflecting context-specific wiring. Resolving this requires spatially grounded causal perturbation, as pure ligand–receptor inference can overcall functional edges when proximity and temporal ordering are not measured.

Tumor-CAF symbiosis

Tumor–CAF interactions are bidirectional and frequently self-reinforcing. A recurring pattern is that tumor-derived signals convert stromal cells into CAF states that then stabilize tumor plasticity, invasion, and therapy resistance. In colorectal cancer, extracellular vesicle-packaged miR-99a-5p from highly metastatic tumor cells reprogrammed fibroblasts by targeting NLRP2 mRNA, activating nuclear factor kappa B (NFκB) signaling, and converting normal fibroblasts into CAFs. These CAFs secrete CCL7, which induces epithelial–mesenchymal transition through a CCR5–mTOR–p70S6K axis, while CAF-derived transforming growth factor β1 (TGFβ1) feeds back to upregulate miR-99a in tumor cells, establishing an miR-99a/TGFβ1 regulatory circuit that sustains inflammatory metastasis niches(17). This is notable for two reasons: it identifies an explicit vesicle-to-stroma causal edge, and it reveals that metastasis-promoting inflammation can be generated locally by tumor–stroma dialogue rather than being imported from systemic inflammation.

CAF-driven immune evasion can also be mediated by metabolic-epigenetic relays. In gastric cancer, CAF-derived lactate promoted H3K18 lactylation, activating ASPM to increase NCAPG levels via altered subcellular transport and deubiquitination, which then engaged SRC/STAT3 signaling to elevate PD-L1 and confer resistance to anti-PD-1 therapy. A small-molecule inhibitor candidate targeting NCAPG was proposed as a therapeutic entry point(23). These findings strengthen the concept that metabolites function as signaling currencies that can rewrite chromatin states, thereby linking CAF metabolism directly to immune checkpoint expression programs. CAF-tumor crosstalk also sustains stemness and chemoresistance in other contexts. In urothelial bladder cancer, CAF-derived miR-146a-5p was implicated in building a niche that promotes cancer stem-like properties and chemoresistance(30). Together with the colorectal and gastric examples above, these studies suggest that CAF signals often converge on tumor state plasticity (stemness, transition programs) and immune escape (PD-L1 upregulation, myeloid recruitment, inflammatory skewing).

Immune-stroma coupling

Immune activity in tumors is constrained not only by inhibitory ligands and cytokines, but also by physical architecture. Mechanical features—matrix density, stiffness, interstitial pressure—can gate immune trafficking and synapse formation, influencing both effector function and therapy delivery.

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Biophysical and mechanobiological considerations for T cell-based immunotherapy argue that tumor and immune cells are mechanosensitive, while standard immunotherapy development often underweights these constraints(31).

Spatial organization is particularly informative. In colon cancer, spatial dynamics and localization of tumor-infiltrating T cell subsets were reported as prognostic, reinforcing that the same immune cell type can reflect distinct functional states depending on whether it resides within tumor epithelium, invasive margins, or stromal compartments(32). This supports a practical clinical implication: immune exclusion is not adequately captured by bulk abundance metrics alone, and spatially defined "access" may be a better predictor of response to therapies that require cell–cell contact.

Perivascular immune niches provide a second example of topology-driven function. $CCR7^+$ DC form perivascular clusters where priming could be efficient, yet this hub is simultaneously vulnerable to regulatory T cell suppression(18). From a systems standpoint, the perivascular niche acts as a controllable bottleneck for immunity—particularly attractive because it integrates chemokine positioning (CCL19), cell-cell contact suppression, and vascular adjacency that could be influenced by vessel normalization strategies.

Pericytes, often overlooked in immunology-centric TME models, can actively shape tumor vascular microenvironments. Pericyte-specific deletion of nitric oxide receptor soluble guanylate cyclase altered pericyte programs and influenced the vascular niche and broader microenvironmental features(24). This suggests that immune access may be modulated not only by endothelial adhesion molecules, but also by perivascular signaling and vessel maturity states.

Metabolic exchange

Metabolic interactions in the TME operate as cross-feeding networks rather than single-cell pathways. A striking example is arginine-derived metabolic interplay in breast cancer: cancer cells acted as the primary arginine source within tumors, driving pro-tumor polarization of tumor-associated macrophages that suppress $CD8^+$ T cell activity. Polyamines produced from arginine metabolism enhanced macrophage polarization through thymine DNA glycosylase-mediated DNA demethylation regulated by p53 signaling. Targeting the arginine-polyamine-thymine DNA glycosylase axis suppressed tumor growth, identifying a tractable metabolic dependency embedded in a cell-cell interaction(33).

Lactate biology illustrates how a "waste product" becomes a signaling mediator. In melanoma, crizotinib was reported to disrupt the CD147-monocarboxylate transporter 1 complex, reducing lactate secretion from tumor cells and lactate uptake by macrophages. This intervention inhibited M2 polarization, remodeled the immune microenvironment, and enhanced responsiveness to immune checkpoint blockade. Mechanistically, lactate induced CXCL13 expression in macrophages through histone lactylation, which was reversed by blocking lactate-driven H3K18 lactylation at the CXCL13 promoter(34). Notably, this study ties together transporter-level metabolic control, macrophage polarization, chemokine expression, and epigenetic modification—suggesting that lactate targeting may yield multifaceted immunologic benefits when executed at the right node. CAF-derived lactate can also drive lactylation programs in tumor cells that elevate PD-L1 and promote resistance to PD-1 blockade(23), emphasizing that lactate is not solely tumor-derived and that "source identity" matters for intervention design. Metabolic crosstalk extends beyond classical metabolites. Tumor-platelet interactions can fuel metastasis, and platelet activation depends on glycolysis; biomimetic membrane-hybridized liposomes were proposed to suppress platelet-tumor crosstalk by reprogramming platelet glycolysis, thereby reducing epithelial-mesenchymal transition and metastatic dissemination in preclinical models(35).

Vascular-immune

The vasculature is both a physical conduit and an immunological regulator. Abnormal vessels create hypoxia, acidosis, and impaired immune trafficking; conversely, vascular normalization can improve perfusion, antigen presentation, and effector infiltration. Synergy between immune checkpoint inhibitors and antiangiogenic agents has been discussed as a strategy to normalize vessels while reducing suppressive myeloid recruitment and improving immune access(36). Mechanistically, vascular adjacency can create immune hubs. $CCR7^+$ DCs localize to venous perivascular niches shaped by fibroblast chemokine production, yet these niches are also sites of regulatory suppression(18). This implies that antiangiogenic therapy might be more effective when designed to (i) stabilize perfusion and (ii) disrupt suppressive perivascular immune circuits, rather than solely pruning

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vessels.

Pericyte signaling adds nuance: soluble guanylate cyclase pathways in pericytes can reshape vascular niche states and microenvironment programs(24). Tumor-specific endothelial phenotypes can also be charted by single-cell profiling in clinical contexts such as clear cell renal cell carcinoma(37), which may guide selection of vascular targets that modulate immune access with less systemic toxicity. A practical clinical gap is how to measure "vascular-immune readiness" beyond microvessel density. Multiplex immunohistochemistry approaches have been used to characterize immune landscapes in hepatocellular carcinoma stratified by glypican-3 expression, addressing why glypican-3-targeted immunotherapies may show limited efficacy and how PD-1/PD-L1 constraints intersect with local immune architecture(38). These pathologic readouts could be integrated with spatial transcriptomics to define actionable vascular–immune phenotypes.

Spatial logic and EV communication

Non-classical communication routes expand the interaction repertoire beyond soluble cytokines and receptor–ligand pairs. EVs can transmit microRNAs, transcripts, and proteins that reprogram recipient cells, as illustrated by tumor EVs converting fibroblasts into inflammatory CAFs or tumor-associated macrophage EVs shaping immunosuppressive invasive fronts(17, 20). EV programs also intersect with hypoxia: in breast cancer, hypoxic conditions increase EV-mediated intercellular communication that can remodel metabolism, promote resistance, and motivate therapeutic engineering of EVs as delivery vehicles(39).

Senescence adds a counterintuitive axis: senescent cells can escape therapy, yet senescence-derived EVs were reported as necessary and sufficient to trigger immune-mediated clearance of senescent cells, thereby limiting recurrence in vivo models(40). This raises a provocative translational idea—augmenting "senescence surveillance" rather than indiscriminately eliminating senescence-associated programs.

Glycosylation represents another layer of immune control. Aberrant tumor glycosylation can create a "glyco-code" that weakens immune surveillance and reduces immunotherapy effectiveness; targeting glycosylation has been proposed as a strategy to enhance immunotherapy(41). Unlike single ligand–receptor checkpoints, glycosylation alters multiple receptors and cell–cell interfaces simultaneously, which could yield broad effects but also increases the risk of off-tumor consequences. Overall, non-classical routes emphasize that interaction networks are multi-modal. Therapeutic translation requires identifying which mode dominates in a given lesion—direct contact versus EV versus metabolic relay—because the optimal intervention class differs accordingly.

Key technologies and model systems to study interactions

Multi-omics analysis

Single-cell RNA sequencing and integration frameworks enable cell state definition, lineage relationships, and candidate ligand–receptor interactions. In intrahepatic cholangiocarcinoma, single-cell and spatial transcriptomics were used to dissect immune-tumor interactions across tumor core, adjacent tissue, and leading-edge areas(42). Similar integrated approaches were applied to relapsed or refractory angioimmunoblastic T cell lymphoma using single-cell RNA sequencing and imaging mass cytometry to compare composition and spatial architecture(43). These studies demonstrate that interaction hypotheses often emerge from multi-omic correlation but require perturbation for causality. Computational methods that incorporate tissue structure can improve inference. Previous research has proposed a heterogeneous graph learning method for spatially resolved transcriptomics, which integrates multimodal signals, gene-gene interactions, and histological regions to better resolve complex cell-cell communication(44). Such approaches help reduce false positives from purely expression-based

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ligand–receptor pairing by adding spatial constraints, though they still require orthogonal validation.

Spatial technologies

Spatial transcriptomics, multiplex immunofluorescence, imaging mass cytometry, and multiplex immunohistochemistry map "who is where," enabling discovery of functional neighborhoods. Spatial analysis of T cell localization in colon cancer highlights prognostic relevance of intraepithelial versus stromal positioning(32). Multiplex immunohistochemistry has been used to profile hepatocellular carcinoma immune landscapes across glypican-3 strata, directly connecting spatial immune organization with target antigen contexts relevant to immunotherapy design(38). Spatial transcriptomics has also been applied in special clinical settings such as esophageal squamous cell carcinoma with human immunodeficiency virus infection, revealing region-specific cellular characteristics(45).

Functional validation platforms

To move from association to mechanism, functional systems that preserve multicellular context are essential. Organoid platforms are increasingly used for personalized testing, yet classical tumor organoids insufficiently model immune and stromal components; reviews outline strategies to create immune microenvironments within organoid systems and to build vascularized organoids that better recapitulate perfusion and vessel-dependent signaling(25, 46). These platforms are particularly suited for validating interaction nodes identified from spatial atlases—such as CAF lactate–lactylation axes or perivascular immune hubs—under controlled perturbation(18, 23).

Translational strategies targeting crosstalk

Relieving immune-suppressive interactions

Therapeutic success often requires breaking the coupling between suppressive niches and exhausted immunity. The $CCR7^{+}$ DC perivascular hub reveals why PD-1 blockade may fail despite increasing immunostimulatory programs: suppression can persist through chemokine-guided positioning and regulatory T cell contacts(18). Translationally, this supports combination designs that pair PD-1 blockade with interventions targeting chemokine retention (for example, disrupting CCL19 positioning or CCL22-dependent reinforcement) or regulatory T cell suppression at immune hubs. In colorectal cancer, LINC00673 deletion synergized with PD-1 blockade by increasing cytotoxic T cell infiltration and improving antigen presentation(28), implying that tumor-intrinsic regulators of immune resistance may be viable combination partners with checkpoint inhibition.

Reprogramming myeloid and CAF compartments

Myeloid reprogramming can be achieved via defined biochemical nodes. NLRP3 inflammasome-driven interleukin-1β production in suppressor populations can be inhibited using targeted nanoparticles that reduce MDSCs and enhance T cell activation even in PD-1-resistant settings(29). In colorectal liver metastases, macrophage EV-driven FGL2-STAT3-interleukin-1β feedback promoted tumor stemness and neutrophil extracellular trap formation; anti–interleukin-1β antibody reduced neutrophil extracellular traps and synergized with PD-1 blockade(20). This offers a clinically interpretable axis because interleukin-1β antibodies already exist, enabling relatively direct translation contingent on biomarker-defined enrichment of the loop. CAF targeting requires subtype-aware approaches. CAF-derived lactate drove lactylation programs that elevated PD-L1 and mediated anti-PD-1 resistance(23). Instead of broad CAF depletion, selective interruption of CAF metabolic outputs or downstream tumor epigenetic responders (ASPM-NCAPG-SRC/STAT3) may preserve stromal homeostatic functions while reducing immune evasion. CAF-mediated stemness and chemoresistance programs in bladder cancer driven by CAF miR-146a-5p further emphasize

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niche precision(30).

Targeting metabolism and hypoxia

Metabolic therapy is most actionable when it targets a cross-feeding dependency rather than a ubiquitous pathway. Cancer cell-derived arginine fueling macrophage polyamine programs that suppress $CD8^+$ T cells provide a defined producer–consumer edge; targeting the arginine–polyamine–thymine DNA glycosylase axis suppressed tumor growth(33). Lactate targeting can also be reframed as a transporter-immune reprogramming intervention: disrupting CD147–monocarboxylate transporter 1 reduced lactate exchange, reversed macrophage histone lactylation programs, and improved checkpoint responsiveness(34). Hypoxia-driven EV signaling adds complexity by enabling long-range metabolic and immune modulation; engineered EVs are proposed as delivery platforms, although off-target distribution and cargo heterogeneity remain translational challenges(39).

ECM/biomechanics and vascular normalization to enhance immune access and delivery

Mechanical constraints can limit immune cell infiltration and synapse formation, while also impairing drug penetration(47). Mechanobiological perspectives argue for incorporating physical parameters into immunotherapy design(31). Vascular–immune combination strategies—immune checkpoint inhibitors with antiangiogenic agents—are proposed to normalize vessels and remodel immune microenvironments(36). Pericyte signaling pathways (soluble guanylate cyclase) may become additional levers for controlling vascular niche states(24).

Biomarkers and patient stratification

Interaction-informed biomarkers can be derived from spatial context (immune hubs, exclusion patterns) and from circulating components (EV cargo, microbial DNA). Circulating microbiome signatures were linked to immune microenvironment features and prognosis in NSCLC(27), while multiplex immunohistochemistry stratified hepatocellular carcinoma immune landscapes by glypican-3 expression, addressing heterogeneity relevant to immunotherapy target selection(38). Future stratification frameworks may combine (i) spatial interaction signatures, (ii) metabolic state markers (lactylation, transporter expression), and (iii) EV or microbial features to predict response and guide rational combinations.

Conclusion

Cell–cell crosstalk in the tumor microenvironment functions as an adaptive control system that governs immune activation, immune evasion, invasion, and treatment response. Mechanistic studies increasingly converge on recurring interaction modules: spatially organized immune hubs subject to reversible suppression, metabolic cross-feeding that rewires myeloid and regulatory T cell function, vesicle-mediated reprogramming that builds inflammatory or suppressive niches, and stromal–epigenetic relays that induce checkpoint expression and therapy resistance. Translational progress will depend on identifying the dominant interaction bottlenecks in individual tumors, pairing perturbations that collapse suppressive loops with therapies that amplify effector immunity, and using spatial and circulating biomarkers to match patients to mechanism-based combinations.

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