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COMMENTARY

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Multidimensional regulation of the tumor microenvironment

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The tumor microenvironment (TME) serves as a central regulatory arena for tumor initiation, progression, and therapeutic response. Rather than being a mere extracellular scaffold, the TME represents a highly complex ecological system composed of diverse cellular populations, secreted factors, metabolic byproducts, and signaling pathways. Accumulating evidence reveals that the TME is governed by an intricate interplay of intrinsic and extrinsic signals, which confer remarkable adaptability and functional plasticity to the tumor milieu.

In this commentary, we highlight five recent high-impact studies that collectively construct a multidimensional, cross-system landscape of TME regulation. These studies encompass themes such as metabolic feedback loops, stress-induced neuro-tumor interactions, chromatin remodeling and treatment sensitivity, drug-induced immunovascular remodeling, and mechanisms of therapy-associated toxicity (Figure 1). Specifically, they exemplify how distinct regulatory axes-from a metabolite-driven immune feedback loop in hepatocellular carcinoma, to a stress-neural circuit modulated by ALKBH5, to an epigenetic control node of H3K9me3 stability, to paradoxical vascular remodeling under HDAC inhibition and its reversal by vascular normalization, and finally to a neutrophil- and CCDC25-dependent pathway driving anthracycline cardiotoxicity-collectively redefine the TME as an active signaling hub rather than a passive background. Together, they reveal that the TME is not merely a passive responder to tumor behavior but functions as an active signaling hub that shapes tumor evolution and therapeutic outcomes. Based on these insights, we emphasize the importance of targeting the TME as an integrative therapeutic strategy and discuss its potential in designing multi-targeted combination treatments.

METABOLIC–IMMUNE LOOP

The study by Kuang's team elucidates a metabolic-immune feedback loop within the TME.[1] In hepatocellular carcinoma (HCC), inflammatory macrophages promote tumor expression of spermidine/spermine N1-acetyltransferase 1 (SAT1), leading to increased extracellular export of N1-acetylspermidine (N1-Ac-Spd) via the polyamine transporter SLC3A2. This metabolite is then taken up by $CCL1^+$ macrophages, activating SRC signaling and driving their pro-inflammatory polarization. The resulting recruitment of $CCR8^+$ regulatory T cells enhance immunosuppression. This process constitutes not a unidirectional immune suppression cascade, but a closed-loop mechanism where tumor metabolism reshapes immune phenotypes, which in turn feedback into the TME. The study reframes the TME from a passive reaction site to an active modulator, introducing the novel concept of extracellular metabolites as signaling effectors and proposing polyamine metabolism-transporter pathways as targets to enhance immune checkpoint blockade (ICB) therapy in HCC.

This metabolite-driven crosstalk illustrates how local biochemical alterations can entrain immune dynamics within the TME, foreshadowing how extrinsic stress signals may similarly impose systemic control over tumor-microenvironmental circuits.

STRESS RESPONSE-NEURAL LOOP

Building on the concept that exogenous signals can rewire the TME, Zheng's group, using a pancreatic cancer model, demonstrated that psychological stress triggers the release of norepinephrine via sympathetic innervation, activating β2-adrenergic receptors (ADRB2) on tumor cells.[2] This downregulates the RNA demethylase ALKBH5, resulting in aberrant methylated RNAs, which are then packaged into extracellular vesicles and transferred to neurons within the TME. These RNAs enhance sympathetic excitability, thereby reinforcing norepinephrine release in a positive feedback loop. This study is the first to delineate neuro-immune-tumor crosstalk at the epigenetic level, underscoring the nervous system as not merely a passive recipient but an active co-conspirator in tumor progression. These findings provide a mechanistic rationale for integrating psychosocial and neuroregulatory interventions into cancer therapy. Notably, the stress-neural circuit converges on an epigenetic node, presaging the broader role of chromatin programs in conditioning TME states and therapy response.

EPIGENETIC REGULATION AND TREATMENT SENSITIVITY

Within the dynamic TME, fluctuating internal and external stimuli must be integrated through epigenetic programs to maintain gene expression and cellular fate. Heterochromatin formation, particularly marked by histone H3K9me3, is critical for transcriptional repression and genomic stability. Kang's team employed genome-wide CRISPR-Cas9 screening and identified the CUL5-ASB7 E3 ubiquitin ligase complex as a negative regulator of H3K9me3.[3] ASB7 is recruited to heterochromatin by HP1 and promotes the degradation of the histone methyltransferase SUV39H1. However, during mitosis, CDK1 phosphorylates ASB7, suppressing its degradation function and thereby stabilizing SUV39H1 to maintain H3K9me3 levels. Dysregulated ASB7 disrupts this balance, leading to H3K9me3 loss, genomic instability, and increased sensitivity to PARP inhibitors. This study highlights how epigenetic regulation in the TME not only governs individual tumor cell behavior but also modulates DNA repair capacity, transcriptional programs, and immune signaling across the microenvironment. As such, it serves as a pivotal entry point for precision therapeutics targeting epigenetic vulnerabilities in the TME.

Although the primary observations are tumor cell-intrinsic, their TME relevance is immediate: H3K9me3 homeostasis governs antigen presentation programs, interferon responsiveness, and the chemokine milieu that orchestrates lymphocyte recruitment. We therefore posit that ASB7-driven chromatin states indirectly calibrate myeloid polarization and T cell trafficking. Testable predictions include altered MHC-I expression, STING pathway engagement, and cytokine/chemokine secretion in co-culture systems with macrophages or CAFs-linking epigenetic vulnerability to microenvironmental control. Such epigenetic plasticity sets the stage for how pharmacologic perturbations can remodel both immune function and tissue architecture.

TME DRUG REMODELING TME

Pharmacologic agents not only exert direct cytotoxic effects on tumor cells but also induce complex remodeling of the TME. Such remodeling can simultaneously enhance immune activation or, conversely, provoke structural barriers or systemic toxicity-underscoring the dual-edged nature of drug-TME interactions. Xu's team, using the iKAP colorectal cancer mouse model integrated with ATAC-seq and scRNA-seq technologies, showed that the histone deacetylase inhibitor (HDACi) chidamide enhances $CD8^+$ T cell effector functions by increasing chromatin accessibility at promoters of cytotoxic genes (e.g., GZMB, IFN-γ, TNF-α), thereby augmenting tumoricidal activity. Paradoxically, HDACi also upregulates VEGFA transcription in tumor-associated macrophages, promoting abnormal angiogenesis and forming a physical barrier that limits T cell infiltration into tumor cores. This immune activation-structural blockade paradox reveals that HDACi induces dual remodeling in the TME. Further studies demonstrated that anti-angiogenic therapy could reverse HDACi-induced vascular abnormalities, restoring T cell infiltration and enhancing immunotherapeutic efficacy. Based on this, the team

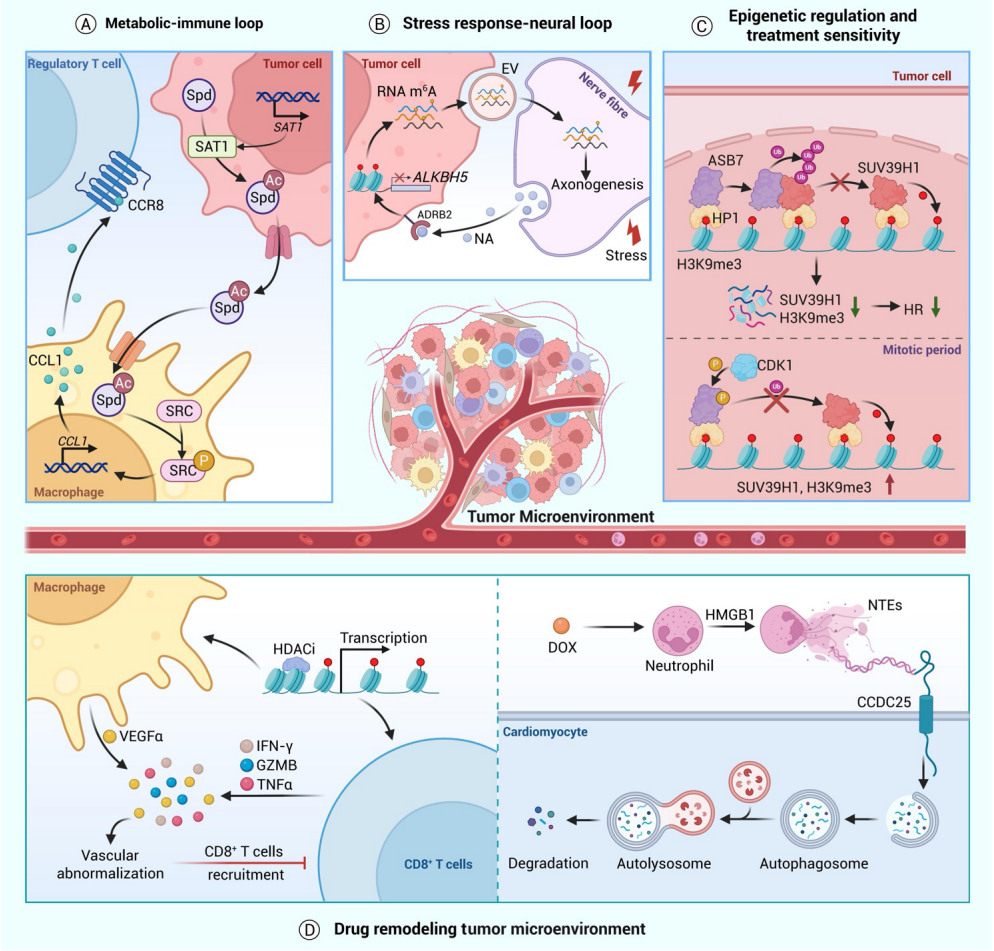

Figure 1. Multidimensional regulation of the tumor microenvironment.

proposed a triple-combination strategy-HDACi, anti-angiogenesis, and ICB therapy-which showed synergistic efficacy in preclinical models, offering a promising path for rational combination therapy in solid tumors.[4]

Separately, Yang's group, in a study published in Nature Cancer, identified a TME-mediated mechanism of chemotherapy-induced toxicity. Anthracyclines such as doxorubicin stimulate neutrophils to release NET-derived DNA (NET-DNA), which is recognized by the transmembrane protein CCDC25 on cardiomyocytes.[5] This triggers ROS accumulation and autophagy cascades, ultimately leading to cardiomyocyte apoptosis. Targeting CCDC25 significantly mitigates cardiac toxicity, offering a potential strategy to dissociate anticancer efficacy from off-target organ damage. This discovery reframes chemotherapy-induced toxicity not solely as a drug-intrinsic problem but as an immunologically mediated consequence within the TME.

CONCLUSION AND PERSPECTIVE

Together, these five studies collectively recontextualize the TME as a dynamic and reprogrammable signaling network. No longer a static backdrop, the TME is shaped by multi-systemic interactions involving metabolic regulation, epigenetic control, immune cell dynamics, and neural stress circuits. Its dynamic, plastic, and responsive properties play a decisive role in tumor trajectory and therapeutic boundaries. Inter-axis crosstalk provides a practical blueprint for combination design: metabolic outputs reprogram myeloid states; stress-neural inputs modulate epigenetic enzymes and neurotransmitter handling; chromatin context sets the ceiling for antigenicity and inflammatory tone; and mechanical compression governs vascular access and immune entry. Furthermore, emerging study suggests that mechanical stress, as a key physical dimension of the TME, can further influence vascular integrity, immune infiltration, and stromal remodeling, thereby shaping both tumor progression and therapeutic responsiveness and offering a promising direction for future investigation.

Future studies should shift from single-target perspectives to systems-level modeling. On one hand, it is crucial to construct integrated models encompassing signals from various pathways and cell types, clarifying the spatiotemporal hierarchies among metabolites, neurotransmitters, chromatin modifiers, and cytokines. On the other hand, therapeutic strategies should evolve from mono-mechanistic interventions to multimodal combinatorial approaches-including immunomodulation, angiogenesis inhibition, metabolic interference, and stress pathway blockade-to achieve comprehensive reprogramming of the TME. These strategies must be supported by sensitive, real-time monitoring technologies to guide dynamic therapeutic adjustments.

The TME is not merely a treatment-responsive context, but a decisive architect of therapeutic outcomes. A deeper understanding of its multidimensional regulatory mechanisms and their clinical exploitability will be central to next-generation anticancer strategies and translational breakthroughs.

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DECLARATION OF INTERESTS

The authors declare no competing interests.