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EDITORIAL

Neurotransmitters in the TME: Can Dopamine and Glutamate Be the Next Cancer Targets?

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ABSTRACT:

Immune and stromal factors are not the only factors that create the tumor microenvironment (TME) because neuromodulatory signals can also change tumor biology. Classical neurotransmitters of the central nervous system, dopamine and glutamate, are becoming known to have an active role in tumor progression, immune modulation, angiogenesis, and metabolic reprogramming of the TME. Dopamine receptors enable dopaminergic to regulate tumor cell proliferation, vascular permeability, and recruitment/activation of immune cells, and glutamatergic to regulate cancer-cell bioenergetics, migration, and excitatory paracrine interactions with stromal cells. Preclinical evidence indicates that receptor heterogeneity, setting-dependent effects, and possible neurotoxicity make it difficult to translate findings from preclinical studies that propose that manipulation of such pathways can sensitize tumors to chemotherapy and immunotherapy. The objective is to summarize existing mechanistic understanding of the roles of dopamine and glutamate in the TME, assess the therapeutic interventions to target the receptors or modulate the metabolism, and outline the main challenges that the biomarker choice, spatial heterogeneity, and safety need to be overcome to develop neuromodulatory oncology. Neurotransmitter network targeting is an exciting, but challenging, area that would add value to the currently available TME-directed therapies and increase the precision of the oncology group.

Keywords: Immunomodulation; Neurotransmitter Agents; Receptors, Dopamine; Receptors, Glutamate; Tumor Microenvironment

The traditional neurotransmitters that are known to be neuronal signaling molecules are now recognized as extra-neural regulators in the tumor microenvironment (TME) [1]. Neuromodulators in small-molecule form may be synthesized, sequestered, or reacted by tumors and related stroma; on the other hand, peripheral nerves and neuroendocrine cells invading tumors provide neurotransmitters and modify physiology in the local area [2]. Dopamine and glutamate are of special focus due to the well-characterized receptor families, different downstream signaling, and extensive effects on cell survival, migration, and immune functioning. It is necessary to know how these neurotransmitters are made, how receptors are distributed between tumor and stromal compartments, and how signaling interacts with the established oncogenic pathways to assess their therapeutic use as therapeutic targets [3].

Sources and Receptor Landscapes in the TME: The dopamine in tumors could be a result of the infiltrating sympathetic nerve fibers, tumor cells producing catecholamines, or systemic circulation. Dopamine activates D1-like receptors (D1, D5) and D2-like receptors (D2, D3, D4) by promoting adenylate cyclase and cAMP synthesis and blocking cAMP, ion channel, and kinase cascade activity, respectively. These receptors are expressed in tumor cells, endothelial cells, and immune populations at varying levels, forming cell-type-specific responses [4]. Cancer cells, stimulated stromal cells, and neuronal releases cause glutamate release. It acts on ionotropic receptors (NMDA, AMPA), which are fast to activate changes in calcium signaling and excitability, and metabotropic glutamate receptors (mGluR1-8), which interact with G-protein coupled pathways to control proliferation and metabolism. The spatial localization and relative level of receptor subtypes dictate whether neurotransmitter signaling induces tumor progression (e.g., proliferation, migration) or suppresses it (e.g., immune activation), and justifies the high-resolution mapping of receptors in tumors [5,6].

Mechanism of Immune Modulation, Angiogenesis, and Metabolism: Glutamate and dopamine adjust the key TME processes in a number of ways. The dopaminergic activation/activation of endothelial junctions can inhibit tumor angiogenesis through the stabilization of endothelial junctions, or enhance vascular permeability based on receptor subtype and context [7]. Certain dopaminergic signaling pathways have been reported to influence myeloid-derived suppressor cell recruitment and cytotoxic T-cell activity in preclinical models [8]. Glutamate signaling facilitates the tumor metabolic reprogramming process by supporting anaplerotic pathways and stimulating antioxidant defences; NMDA receptor-mediated calcium influx can stimulate downstream kinases that facilitate migration and invasion. Macrophage polarization and T-cell activation can be influenced by glutamate in immune cells, and in some cases, it may facilitate immunosuppression through mGluR signaling [9]. Combined with hypoxia, cytokine networks, and ECM remodeling, these neuromodulatory inputs combine to rewire the TME to either tumor tolerance or tumor elimination, based on the ratio of signals.

Therapeutic Opportunities, Attacking Receptors and Metabolism: Certain dopaminergic signaling pathways have been reported to influence myeloid-derived suppressor cell recruitment and cytotoxic T-cell activity in preclinical models. The existing neuropsychiatric drugs could be repurposed to reduce immunosuppression or normalize tumor vasculature by pharmacologic modulation of dopamine receptors (agonists or

antagonists) [10]. There are several modes of glutamate pathway targeting (blocking excitatory receptors - NMDA and AMPA antagonists), or glutamate release or uptake systems, or enzymes in glutaminolysis [11]. The synergistic effect of neuromodulatory agent use in combination with checkpoint inhibitors or antiangiogenics could be achieved by the simultaneous increase of immune infiltration and decreased pro-tumor metabolic support. Notably, the immediate development of clinically approved drugs that target dopamine and glutamate systems increases the possibility of repurposing; however, dose selection and delivery methods (e.g., tumor-specific delivery, prodrugs, or local release) will be necessary to reduce CNS side effects [12].

Clinical Translation Problems: Although promising, neurotransmitter targeting in the TME presents considerable challenges. Receptor heterogeneity among individuals and across tumors makes it complicated to select patients and develop biomarkers. Signaling of neurotransmitters is strongly dependent upon context; different receptors may produce opposite results in different cell types or niches in different microanatomy. With the manipulation of dopaminergic or glutamatergic systems systemically, off-target and the central nervous system are pragmatic issues of concern [13]. Further, conventional preclinical models might not be able to model neuro-tumoral interactions in humans, and more complex models such as organotypic cultures, tumor-on-chip systems, and spatially resolved multi-omics are required to model complexity. Strong pharmacodynamic endpoints and imaging biomarkers will be demanded to show target engagement in the TME and not cause excessive systemic effects [14].

Future Directions: To propel neurotransmitter-targeted oncology, a few priorities are evident, such as: extensive receptor mapping, neurotransmitter gradients with spatial transcriptomics and imaging mass spectrometry, selective ligands or delivery systems that can only activate in tumor tissue, combination trials that combine neurotransmitter modulation with immunotherapy, antiangiogenic or metabolic inhibitors, and integration of CNS-safety endpoints and neurocognitive measurements into early-phase trials [15]. Also, the combination of computational models predicting neurotransmitter flux and receptor responsiveness with data collected in a patient will enhance accuracy in the choice of responsive subgroups. Neurobiological, immuno-oncological, and pharmacological cross-disciplinary partnerships are required to integrate the knowledge gained into useful, safe, and effective therapies [16].

Conclusion: Dopamine and glutamate are attractive, understudied modulators of the tumor microenvironment that have a complex impact on the vasculature, immune landscapes, and metabolic networks. Even though preclinical evidence shows that they are good therapeutic targets, clinical translation must overcome receptor heterogeneity, safety issues, and model constraints. Carefully designed, bio-modulatory approaches that enable the integration of neuromodulatory drugs with current TME-guided treatments might increase the precision oncology arsenal. The TME remodeling through neurotransmitter pathways is a high-risk area at the borderline of neurobiology and cancer therapeutic approaches, and can provide new methods to overcome resistance and enhance patient outcomes.

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