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Review

Novel approaches to clinical trial design in cancer neuroscience

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Summary

The emerging field of cancer neuroscience has revealed profound bidirectional interactions between the nervous system and cancer cells, identifying novel therapeutic vulnerabilities across diverse malignancies. This review examines the unique challenges and strategies for translating these insights into effective therapies. We propose innovative approaches to overcome these barriers through drug repurposing, enhanced biomarker development, and optimized trial designs. Repurposing neuroactive drugs with established safety profiles offers an accelerated path to clinical impact, particularly for targeting glutamatergic, adrenergic, and neurotrophic signaling pathways. Emphasizing mitigation of neurotoxicity and improved patient quality of life will be paramount moving forward. Repurposed agents that show preliminary potential for “dual use” (i.e., simultaneous toxicity mitigation and synergistic anti-tumor effects) are highlighted for special consideration. Master protocols and window-of-opportunity trials provide platforms to rapidly validate mechanisms while addressing patient-centered outcomes. By systematically addressing these foundational elements across disciplines, cancer neuroscience can translate its profound mechanistic insights into meaningful therapeutic advances for patients with treatment-resistant malignancies.

Introduction

The nervous system plays a central role in modulating cellular activities across developmental stages and organ systems, with emerging evidence highlighting its pivotal role in modulating tumor growth, invasion, metastasis, and treatment resistance.[1,2,3] Tumor dependance on the most fundamental neural mechanisms—synaptic plasticity, myelin adaptability, electrochemical gradients, axonal guidance, and others—presents both immense challenges and unique therapeutic opportunities for cancer neuroscience.[2,3,4,5,6,7,8]

Bidirectional communication between neurons and cancer cells facilitates multiple hallmarks of malignancy through distinct yet complementary mechanisms in the central and peripheral nervous systems (CNS and PNS, respectively; for reviews, please see Mancusi and Monje, Winkler et al., Amit et al., Pan and Monje, Amit et al., Pu et al., and Zhang et al.[3,8,9,10,11,12,13]; Figure 1). Glutamatergic neurons promote glioma growth through neuron-to-glioma synapses[14,15,16] and through activity-dependent paracrine secretion of signaling molecules such as neuroligin-3 (NLGN3), brain-derived neurotrophic factor (BDNF), and insulin-like growth factor-1 (IGF-1).[5,17,18,19] Sensory deprivation (visual and olfactory) can prevent glioma formation in the relevant neural circuits of genetically predisposed models,[19,20] and high functional connectivity between the tumor and brain is associated with poorer survival.[21] Similarly, brain metastases exploit neural circuitry by forming “pseudo-tripartite synapses” where cancer cells receive glutamatergic input through N-methyl-D-aspartate receptors (NMDARs), facilitating colonization within the neural microenvironment.[22] In the PNS, sympathetic signaling drives treatment resistance and immune evasion in multiple cancers through β-adrenergic receptors,[23,24,25,26] while sensory nerve-derived calcitonin gene-related peptide (CGRP) fosters immunosuppression in melanoma and head and neck cancers.[27,28] Similarly, parasympathetic innervation exhibits divergent effects, promoting growth in prostate and gastric cancers while suppressing progression in breast and pancreatic tumors.[8,29,30,31] From all angles, neurotrophic factors (e.g., nerve growth factor [NGF], brain-derived neurotrophic factor [BDNF], and glial cell-derived neurotrophic factor [GDNF]) fuel tumorigenesis and perineural invasion (PNI) through feedforward loops, increasing neural inputs to the tumor, that accelerate tumor pathogenesis and cancer progression.[25,32] Glial cells, particularly Schwann cells, promote cancer invasion and modulate the tumor microenvironment (TME) by influencing fibroblasts to adopt more pro-tumor subtypes.[33,34] Extracellular matrix (ECM) stiffening itself can facilitate integrin-mediated mechanotransduction to drive the expression of neurotropic factors (BDNF and NGF) and promote tumor hyperinnervation.[35] Additionally, immune cells within the TME, such as macrophages and T cells, are influenced by neural signals, with neurotransmitters like acetylcholine and neuropeptides modulating immune responses to either suppress anti-tumor immunity or enhance inflammation, further supporting cancer progression.[11,12] Lastly, cell membrane depolarization and ion channel activity stand as crucial final points of convergence for both CNS and PNS interactions,[5,14,36,37,38,39] highlighting the intricate interplay between neural, immune, and tumor components in driving malignancy (Figure 1).

Despite the compelling biological and preclinical evidence, numerous barriers impede the

clinical translation of these insights into effective therapies. The blood-brain barrier (BBB) and blood-nerve barrier restrict delivery of many drugs to cancers within the nervous system, although this may not be as problematic for re-purposed drugs of neurology and psychiatry designed to enter the CNS. Systemic targeting of neural processes important to normal neural cells in the brain and widely distributed in the PNS risks off-tumor toxicities. Perhaps most critically, the absence of validated biomarkers for neural-tumor interactions further complicates patient selection and response assessment.

To overcome these obstacles, a multifaceted approach is required (Figure 2). First, enhanced collaboration across neuroscience, immunology, and oncology is urgently needed to fully characterize the bidirectional communication between tumors and nerves that creates feedforward loops accelerating malignancy. Second, novel biomarkers that capture the complexity of neuron-tumor interactions must be developed to enable precise stratification of patients likely to benefit from neural-targeted interventions. Third, repurposing existing neuroactive drugs with established safety profiles offers an accelerated path to clinical impact (Figure 2B). Fourth, innovative early-phase trial designs such as expanded window-of-opportunity studies and master protocols—including platform, basket, and umbrella designs—provide platforms to rapidly validate mechanisms while minimizing patient risk (Figure 2C). Most importantly, increased emphasis must be placed on addressing patient-centered outcomes—pain, mental health, cognition, addiction, quality of life, and functionality—to ensure that new interventions not only prolong survival but also preserve the dignity, autonomy, and day-to-day well-being of those navigating the burdens of disease. By systematically addressing these foundational elements across disciplines through integrated biomarker discovery and adaptive trial design strategies, the field of cancer neuroscience can translate its profound mechanistic insights into meaningful therapeutic advances for patients with treatment-resistant malignancies.

Section snippets

Biomarker development and monitoring strategies in cancer neuroscience

Effective clinical trial design and evaluation of neuroactive cancer therapeutics rely on robust biomarkers for accurate diagnosis and monitoring of therapeutic responses. Currently, research in the identification of biomarkers for nerve-cancer crosstalk is still in its infancy, limiting our ability to meaningfully stratify patients for clinical trials. Increased emphasis on validating and utilizing promising biomarkers in pilot studies is critical. Incorporating multi-omic approaches and …

Therapeutic repurposing strategies: Targeting neural pathways in cancer

Building on these emerging biomarker and screening platforms, the intricate crosstalk between the nervous system and cancer cells offers a promising frontier for therapeutic innovation.

Targeting this axis through drug repurposing—using existing, regulatory-approved pharmaceuticals for new indications—presents a faster, cost-effective alternative to traditional drug discovery, with the added benefit of established safety profiles, known BBB penetration, and reduced developmental risks.[76] This …

Master protocols: Efficient clinical trial design strategies to expedite drug repurposing in cancer neuroscience

The implementation of master protocols (i.e., umbrella, platform, and basket trials) could eventually revolutionize our approach to cancer neuroscience trials by enabling more efficient patient stratification and rapid evaluation of repurposed treatments. That potential has been demonstrated by GBM AGILE (platform trial), which has screened over 1,300 patients and achieved enrollment rates three to four times higher than conventional GBM trials.[277] With repurposed, low-toxicity drugs, that …

Potential pitfalls and alternatives

Much like targeting the CNS, targeting the PNS for cancer therapies presents distinct challenges. The dispersed distribution of PNS nerves throughout the body, coupled with their vital roles in regulating other systems such as the cardiovascular and gastrointestinal systems,[249,250,251] increases risks of systemic toxicity from interventions aimed at disrupting nerve-tumor crosstalk. Potential side effects, including pain, neuropathy, and autonomic dysfunction, necessitate careful evaluation to …

Conclusion

The emerging field of cancer neuroscience has revealed profound bidirectional interactions between the nervous system and malignant cells, identifying novel therapeutic vulnerabilities across diverse cancer types. As outlined in this review, these insights create exciting opportunities to improve outcomes for patients with treatment-resistant malignancies. However, significant challenges remain in translating these biological discoveries into clinical benefit. Addressing these hurdles demands …

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Declaration of interests

M.M. holds equity in MapLight Therapeutics and Stellaromics Inc. …

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used the large language model service ChatGPT after completion of the final draft to further improve conciseness, grammar, and readability. After using this tool/service, the authors thoroughly reviewed and edited the content as needed and take full responsibility for the content of the publication. …

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