RESEARCH HIGHLIGHT

Peripheral cancer remodeling of central neural system

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Recent work in the field of cancer neuroscience has demonstrated bidirectional interactions between neurons and cancer cells ultimately influencing neural circuit function, tumor growth, and patient survival. In a recent paper published in *Cell Research*, Xu et al. take a novel approach, identifying a secretory factor-induced central nervous system-mediated increase in peripheral autonomic sympathetic activity that drives tumor–immune cell interactions and tumor progression across multiple cancer types.

Since 1938, with the identification of the histopathological colocalization of neurons and brain tumor cells,[1] biologists have suspected that the central nervous system (CNS) participates in CNS tumor biology. Confirming this suspicion, recent studies have delineated a multitude of mechanisms by which this interaction occurs, including via paracrine signaling,[2] systemic and immune cell-mediated interactions,[3] and even direct synaptic connections between neurons and both glial and metastatic neoplastic cells within the CNS.[4,5] At the circuit level, specialized neurons engage in neuronal computations following infiltration by low- and high-grade gliomas.[6] However, CNS circuit remodeling mediated by peripheral cancer without evidence of brain metastasis has many unanswered questions. Xu et al.[7] innovatively apply a top-down approach, using multi-omics across four peripheral cancers to identify secretory factors convergent on a similar neuronal pattern within the CNS (Fig. 1).

First, they observed that peripheral xenografts of murine breast, lung, prostate, and colon cancers not only demonstrated neuronal activity within central brainstem structures, but many activity patterns overlapped across cancer types. Activated CNS structures included cranial nerve nuclei and the paraventricular nucleus of the hypothalamus (PVN), a region responsible for sympathetic output. Next, hypothesizing that this common activity profile could stem from shared secretory factors across cancers, they conducted parallel transcriptomic and proteomic analyses revealing 61 candidate factors expressed by all cancers, of which two, leukemia inhibitory factor (LIF) and galactin-3 (Gal3) were sufficient for inducing the observed brain activity phenotype following intraperitoneal administration.

Xu et al. further demonstrated the necessity of LIF and Gal3 for inducing PVN neuronal activity by generating knockout mice. While knocking out LIF blunted but did not entirely abrogate the conserved activity profile, Gal3 knockout prevented activity in all identified regions. They were able to achieve similar network quiescence by the administration of LIF and Gal3 small-molecule inhibitors to tumor xenografted mice thereby offering overlapping models for the ablation of their target tumor cell-derived cytokines. In both the inhibitor and knockout models, in addition

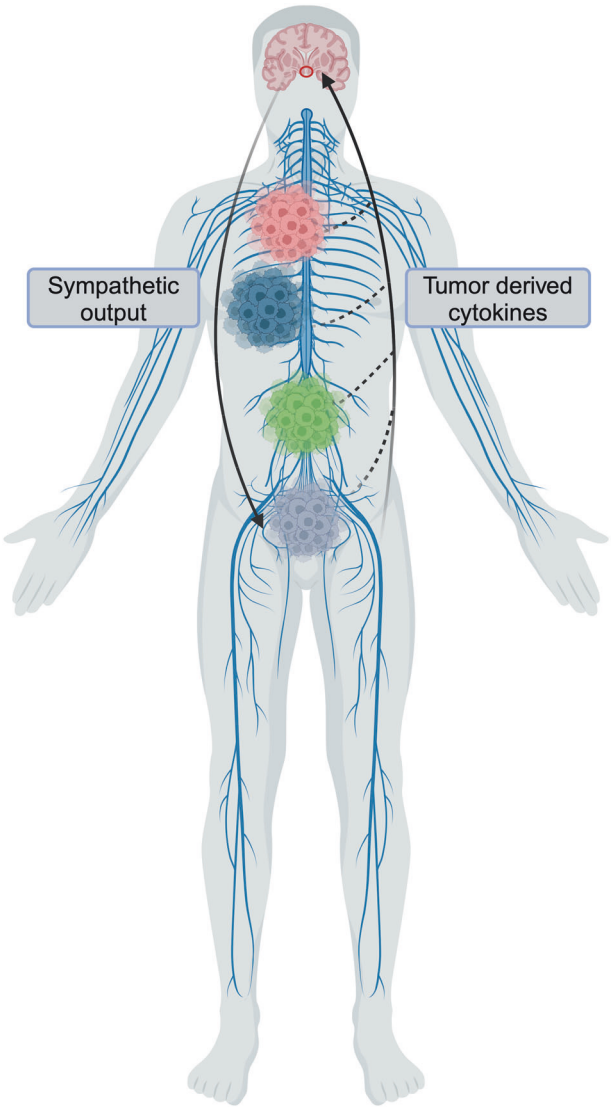

Fig. 1 Redefined model of interactions of peripheral cancers with the CNS. Tumor cells from multiple organs (including breast in pink, lung in blue, colon in green, and prostate in grey) influence the CNS through tumor-derived cytokines with similar features across cancers. Reciprocally, CNS structures within the hypothalamus regulate systemic sympathetic tone. Figure generated with BioRender.com.

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to a rescued brain activity state, mice experienced delayed tumor growth suggesting a role for CNS sympathetic inputs for peripheral malignancy growth.

Following the demonstration that these secreted factors both lead to a convergent brain activity profile and are associated with tumor progression, they hypothesized that this increased rate of tumor growth may stem from a neuroimmune mechanism. Indeed, they uncovered lower counts of myeloid-derived suppressor cells (MDSCs) in the blood and tumor tissue of their knockout mice. Removal of sympathetic inputs from peripheral tissues of tumor model mice also lead to lower MDSC counts. However, doing the same in the knockout mice did not drop MDSC counts further, revealing no additive effect of sympathetic activity with secreting factors LIF and Gal3. The authors posit that this finding suggests that both factors take their action via sympathetic signaling.

Taken together, the authors demonstrate across four peripheral cancer models that paracrine signaling factors Gal3 and LIF activate the PVN, leading to increased sympathetic input into tumor cells and peripheral tissues responsible for MDSC generation, promoting tumor proliferation. Importantly, this discovery is uniquely generalizable across four distinct malignancies thereby representing a common pathway by which solid organ cancers may hijack neuronal systems to drive their own growth.

Notably, sympathetic nerve activity has previously been shown to influence peripheral tumor growth, invasion, and metastatic spread in several tumor types.[8–10] Further, the discovery that the CNS may remotely influence peripheral tumors via the autonomic or peripheral nervous system has previously been demonstrated.[3] However, Xu et al. approach cancer regulation of neuronal systems in the brain from a fresh perspective, searching for conserved strategies that peripheral tumors use to harness the CNS to promote invasion. In doing so, they effectively demonstrate the far-reaching role that the brain plays in cancer found within and beyond itself and raise the possibility of more broadly applicable cancer neuroscience-based therapeutic strategies.

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ADDITIONAL INFORMATION

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