



Mini Review



RUSH3D-HR as a Test Bed for the Tumor-nerve-immune Electrical Axis: From Mesoscale Imaging to Testable Bioelectric Hypotheses

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Abstract

Interactions among tumors, nerves, and immune cells influence cancer progression, but the mechanisms coordinating these compartments remain incompletely understood. Bioelectric signaling has been proposed as an additional coordinating layer, yet direct *in vivo* evidence for a tumor–nerve–immune electrical axis remains limited. In non-tumor models, RUSH3D-HR enables mesoscale *in vivo* imaging of dynamic cellular behaviors, including neutrophil swarming and migrasome dynamics, and has revealed reduced splenic neutrophil swarming following electroacupuncture at Zusanli (ST36). These observations provide dynamic cellular readouts and demonstrate an intervention-associated response; however, the platform does not directly measure membrane voltage, ionic currents, or electric fields, and these findings establish neither electrical coupling nor a specific neural circuit. In this mini review, we examine the proposed axis as a focused, falsifiable complement to broader cancer neuroscience. We distinguish direct observations from mechanistic hypotheses, consider established biochemical explanations involving neurotransmitters and inflammatory mediators, and discuss how context-dependent neural effects, supporting glial cells, opioids, and cancer-induced nerve injury may modify tumor–nerve–immune interactions. We then outline a staged experimental roadmap in tumor models, integrating RUSH3D-HR with voltage and ion reporters, extracellular electrophysiological recordings, and compartment-specific perturbations. This framework prioritizes temporal relationships, identification of candidate signal sources and responding compartments, and causal tests that discriminate electrical contributions from biochemical and systemic effects. Establishing reproducible links between electrical measurements, cellular behavior, and tumor outcomes will be essential for evaluating the axis. Until such evidence is obtained, the tumor–nerve–immune electrical axis should be regarded as a hypothesis-generating experimental program rather than a validated physiological circuit.

Keywords: Tumor-nerve-immune electrical axis; Bioelectricity; RUSH3D-HR; Neutrophil swarming; Migrasome; Voltage imaging; Cancer neuroscience; Intravital imaging.

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Introduction

The tumor microenvironment has been mapped by transcriptomics and proteomics into molecular atlases of remarkable detail, yet these largely static maps cannot resolve the second-to-minute dynamics through which cells exchange ions, alter membrane potential, and release neurotransmitters. We recently proposed the tumor-nerve-immune electrical axis as a hypothesis-generating framework in which bioelectric signals may help coordinate tumor behavior and immune surveillance.¹ The framework is deliberately broader than a single channel or transmitter but narrower than the

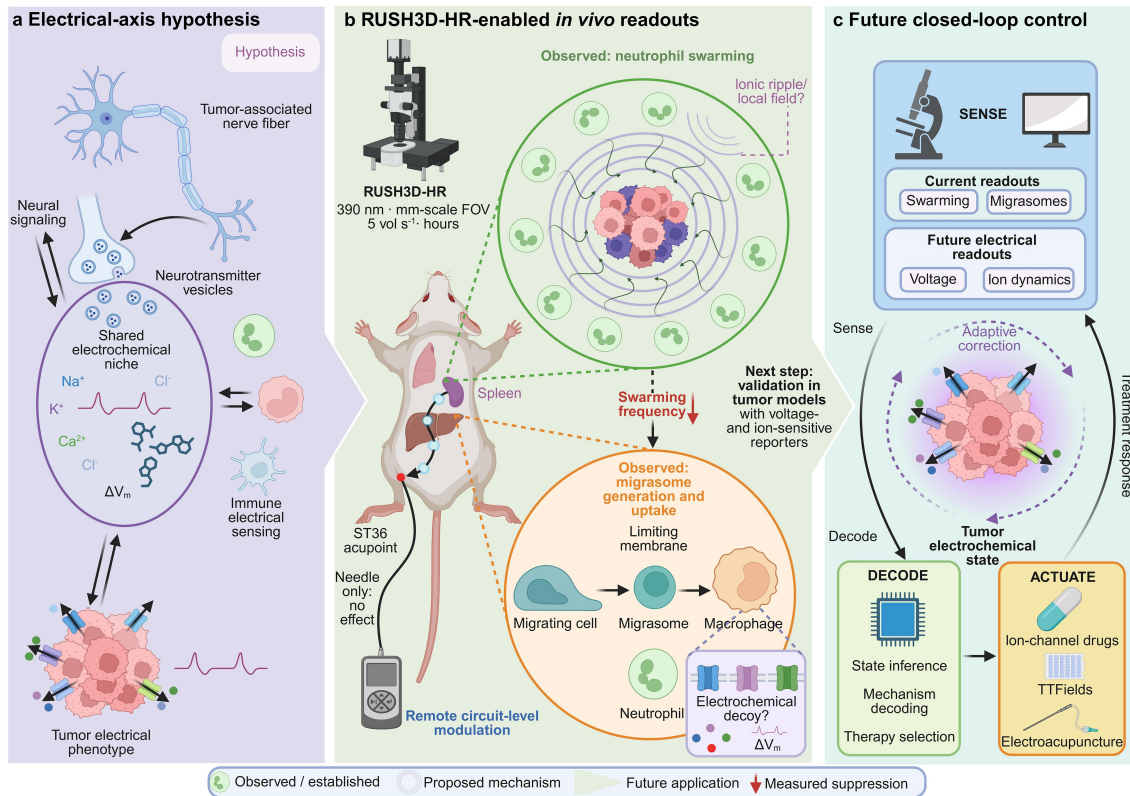


Fig. 1. RUSH3D-HR readouts and testable tumor-nerve-immune electrical-axis hypotheses. (a) Authors' hypothesis (purple): the proposed electrical-axis framework links tumor electrical phenotypes, tumor-associated neural and glial elements, and immune-cell electrical sensing within a shared electrochemical niche. These connections have not been demonstrated by RUSH3D-HR. (b) Observed non-tumor readouts versus proposed mechanisms: RUSH3D-HR directly visualized neutrophil swarming in LPS-inflamed spleen, migrasome generation and uptake during acute liver injury, and reduced splenic swarming after 0.5 mA electroacupuncture at ST36. Purple dashed waves and the migrasome "electrochemical decoy" denote authors' hypotheses; the blue "Remote circuit-level modulation" label is a candidate interpretation, not a measured pathway. Membrane voltage, ionic current, extracellular electric fields, and a mediating neural circuit were not measured. The gray arrow marks the required next step: validation in tumor models with direct electrical and ionic reporters and causal perturbations. (c) Future application (gray/outlined): a prospective sense-decode-actuate loop in which validated imaging and electrical readouts could guide ion-channel pharmacology, tumor-treating fields, or neuromodulation. This panel is a research direction rather than an established clinical system. Created with BioRender.com. Ca^{2+} , calcium; Cl^- , chloride; ΔV_m , change in membrane potential; FOV, field of view; K^+ , potassium; LPS, lipopolysaccharide; Na^+ , sodium; RUSH3D-HR, the high-resolution RUSH3D confocal volumetric mesoscope (RUSH3D denotes real-time, ultra-large-scale, high-resolution three-dimensional imaging); ST36, Zusanli acupuncture point; TTFs, tumor-treating fields.

entire field of cancer neuroscience: it asks whether membrane voltage, transmembrane ion flux, extracellular ionic composition, and electrotonic or synaptic coupling constitute an experimentally separable layer of information across tumor, neural/glial, and immune compartments. The distinction between direct observations and proposed mechanisms used throughout this mini review is summarized in Figure 1.

Recent comprehensive reviews have catalogued peripheral innervation, neural remodeling, neuroimmune signaling, cancer pain, emerging technologies, and translational strategies across tumor types.²⁻¹¹ Rather than duplicating those syntheses or relabeling every neurotransmitter effect as "electrical", the present framework focuses specifically on bioelectric encoding and on the measurements required to establish it. Chemical ligands, mechanical cues, and metabolic states remain central; they may generate, modulate, or be generated by voltage and ion changes. A claim of bioelectric coordination therefore requires more than spatially syn-

chronized cell behavior: it requires direct electrical or ionic readouts, temporally ordered associations, and perturbations that distinguish electrical contributions from established biochemical relays.

Lu *et al.*¹² now provide an important enabling technology. Their RUSH3D-HR confocal volumetric mesoscope combines a numerical aperture of 1.05 with approximately 390 nm lateral resolution across a $2.7 \times 2.0 \times 0.04 \text{ mm}^3$ field of view at five volumes per second, enabling prolonged mesoscale imaging that resolves both subcellular and population dynamics.¹² RUSH3D-HR does not, by itself, measure membrane potential, ionic current, or extracellular electric fields; its contribution is to supply the spatial and temporal scaffold onto which such reporters and probes could be added. Accordingly, this mini review aims to define the framework's specific bioelectric-encoding focus, separate direct RUSH3D-HR observations from mechanistic inference, and outline tumor-model experiments capable of

confirming or falsifying electrical coupling among tumor, neural/glia, and immune compartments.

RUSH3D-HR observations and the central hypothesis

What the platform observes and what it does not

The direct observations reported by Lu *et al.*¹² are compelling but circumscribed. In a lipopolysaccharide (LPS)-inflamed mouse spleen, the platform tracked more than 6,000 neutrophils and resolved transient swarms lasting approximately 20–180 min, with peak migration velocities approaching twice baseline values. In acetaminophen-induced acute liver injury, it visualized migrasome formation on retraction fibers and uptake by neutrophils or macrophages. In the LPS model, electroacupuncture at Zusanli (ST36) was associated with a greater than fivefold reduction in swarming events relative to LPS-only and 0 mA needle controls.¹² These experiments directly establish the cellular dynamics and their association with an intervention. They do not establish a tumor context, electrical coupling between neutrophils, the electrophysiological content of migrasomes, or a neural route linking ST36 stimulation to splenic behavior, because no voltage reporter, ion-selective probe, field electrode, neural recording, or pathway-specific neural manipulation was included.

Testing an electrical contribution to neutrophil swarming

Neutrophil swarming already has a strong biochemical and self-organizing explanation. Leukotriene B4 (LTB4) and CXCL2 amplify recruitment through active receptor-mediated relays; adenosine triphosphate (ATP) sensing, connexin-43-dependent calcium alarm signals, integrins, and calcium-dependent LTB4 production reinforce cluster formation; and receptor desensitization together with NADPH oxidase-dependent negative feedback helps terminate or spatially limit recruitment.^{13–18} An active relay can propagate information faster and farther than passive diffusion of a single pre-existing gradient. The RUSH3D-HR movies are compatible with established mediator relays and do not require an additional electric-field mechanism.

A bioelectric contribution remains a testable, secondary hypothesis. Local ionic changes or coordinated membrane-potential shifts might alter chemotactic sensitivity, polarization, or migration speed, and potassium-channel-dependent bioelectric states can regulate metastatic competence in triple-negative breast cancer.¹⁹ To discriminate this possibility, RUSH3D-HR should be combined with cell-targeted genetically encoded voltage indicators, calcium reporters, extracellular microelectrodes or field-effect sensors, and ion-selective probes. These readouts should be paired in a factorial design with BLT1/CXCR2 blockade, inhibition of ATP or connexin-43 signaling, calcium perturbation, and pharmacological or genetic manipulation of candidate channels such as KCa3.1, Kv1.3, and TRPM2. Viability, basal speed, polarity, and chemotactic competence must be measured to exclude nonspecific motility defects. Evidence for an additional bioelectric layer would require a reproducible voltage or field signature that precedes directional reorientation, predicts swarm recruitment beyond mediator concentrations, and is selectively lost after channel perturbation. If electrical changes disappear when LTB4/CXCL2 or calcium relays are blocked, or consistently follow rather than precede those signals, they would be better interpreted as downstream cor-

relates than as an independent coordinating mechanism.

From non-tumor imaging to cancer

The principal RUSH3D-HR examples are models of sterile or LPS-driven inflammation, not cancer. Cancer studies nonetheless establish that neural and bioelectric interactions are plausible at selected interfaces: autonomic innervation can promote prostate cancer; glioma cells receive AMPA receptor-dependent synaptic input and participate in gap-junction-coupled networks; functional neuron-tumor synapses have been identified in small-cell lung cancer; and GABA-dependent electrical regulation has been linked to melanoma initiation.^{20–24} These findings support specific mechanisms in defined models, but they do not yet validate a universal, integrated tumor-nerve-immune electrical circuit.

Context-dependent and tumor-suppressive neural effects

Neural influence is not uniformly tumor-promoting. Its sign depends on tumor lineage, anatomical site, disease stage, nerve subtype, receptor repertoire, stromal composition, and immune context. In pancreatic ductal adenocarcinoma, vagotomy accelerated tumorigenesis whereas muscarinic stimulation suppressed cancer stemness and myeloid inflammation.²⁵ In melanoma and triple-negative breast cancer models, ablation or desensitization of sensory afferents accelerated tumor growth or vascular leakage, whereas sensory-neuron activation enhanced antitumor T-cell responses and reduced metastatic dissemination.^{26–30} Splenic neural signaling can also restrain myeloid expansion through trefoil factor 2.²⁹ Recent syntheses explicitly emphasize this context dependency.³¹ Conversely, macrophage-derived brain-derived neurotrophic factor can promote axonogenesis and tumor growth in triple-negative breast cancer, illustrating reciprocal immune-to-neural remodeling.³² Thus, “neuronal activity” cannot be treated as a single exposure. Future electrical-axis experiments should stratify adrenergic, cholinergic, and defined sensory populations; report spatial proximity to tumor and immune cells; and test early and late disease separately.

Supporting glial cells as electrochemical gatekeepers

Supporting glial cells add a missing regulatory layer between nerves and the tumor microenvironment. Tumor-activated Schwann cells can undergo c-Jun-dependent reprogramming, form dynamic tracks that physically promote pancreatic cancer invasion, associate with tumor vasculature, and reshape angiogenesis and immune surveillance.^{33–36} Satellite glial cells in peripheral ganglia express diverse ion channels, purinergic receptors, and glutamate-handling programs, consistent with roles in potassium buffering and regulation of neuronal excitability.³⁷ Within the electrical-axis framework, Schwann and satellite glial cells could therefore buffer extracellular K⁺, redistribute ATP or Ca²⁺-linked signals, alter axonal conduction, and set the threshold for neurotransmitter release. These are mechanistically grounded possibilities, not demonstrated tumor phenomena. Direct tests should combine neuron- and glia-specific voltage/calcium reporters with glial perturbation of *KCNJ10*/Kir4.1, connexin-43, purinergic receptors, or c-Jun, while separately quantifying nerve activity, immune-cell state, and tumor behavior.

Cancer-induced nerve injury and electro-immunosuppression

Cancer-induced nerve injury provides a concrete link between

neural integrity and immunotherapy resistance. In cutaneous squamous cell carcinoma, melanoma, and gastric cancer, perineural invasion and myelin disruption were associated with poor response to anti-PD-1 therapy; injured neurons activated an ATF3-dependent program and sustained IL-6 and type I interferon signaling, producing a chronically inflamed, suppressive, and exhausted immune state. Denervation, neuronal *Atf3* deletion, *Ifnar1* loss, or IL-6 receptor blockade restored anti-PD-1 efficacy in experimental settings.³⁸ This mechanism is relevant to “electro-immunosuppression” because nerve injury alters conduction and initiates a neural-to-immune program. Importantly, the demonstrated suppressive effect is mediated through injury-induced cytokine signaling, not through direct proof that an extracellular electric field suppresses immune cells. The electrical-axis model should therefore treat altered electrophysiology as a measurable intermediate to be tested alongside ATF3, IL-6, type I interferon, and immune-exhaustion markers.

Electroacupuncture and migrasomes: defining causal tests

A remote response with an unresolved conduit

The ST36 experiment shows that 0.5 mA electroacupuncture was followed by reduced splenic neutrophil swarming, whereas needle placement at 0 mA was not.¹² The control argues against needle insertion alone under the tested conditions, but it does not establish site specificity, identify a neural circuit, or exclude neuroendocrine, autonomic, vascular, hemodynamic, and systemic inflammatory intermediates. Causal assignment will require non-acupoint and current-matched controls; local anesthetic or peripheral-nerve blockade; selective transection or inhibition of vagal, splenic, or sympathetic pathways; pathway-specific chemogenetic or optogenetic manipulation; neural recording; and measurement or antagonism of catecholamines, glucocorticoids, cytokines, vascular flow, and temperature. A candidate circuit would be supported only if its interruption abolishes the swarming response and its selective activation reproduces it.

From observed migrasome generation and uptake to an electrochemical hypothesis

RUSH3D-HR directly visualized migrasome production and uptake during acute liver injury,¹² and neutrophil-derived migrasomes have established functions in coagulation.³⁹ By contrast, the proposed “electrochemical decoy” is an authors’ hypothesis: migrasome electrophysiology and its ability to reset recipient-cell membrane potential have not been demonstrated. The hypothesis can be tested by profiling migrasome membrane proteins and ionic cargo; measuring donor, vesicle, and recipient voltage or ion concentrations before and after uptake; blocking migrasome biogenesis or engulfment; and using composition-matched liposomes as controls. Rescue with purified, composition-defined migrasomes would be needed to link a measured electrical change to immune behavior. Only after such validation in a tumor model should migrasome dynamics be considered a readout of the proposed axis.

Clinical implications and opioid-related confounding

The translational concepts in Figure 1 are prospective. Vagus

nerve stimulation can modulate human inflammation, tumor-treating fields improve survival in glioblastoma when combined with temozolomide, membrane potential is an emerging pharmacological target, and electrophysiological platforms can decode neuron-glioma interactions.⁴⁰⁻⁴⁴ None of these findings validates neutrophil swarming or migrasome dynamics as clinical cancer biomarkers, and RUSH3D-HR has not yet been deployed as a closed-loop clinical system. Biomarker development will require reproducibility across tumor models, association with independently measured electrical states, incremental predictive value over inflammatory markers, feasible tissue access, and prospective correlation with treatment response.

Opioids are also important because they are widely used for cancer pain and can directly modify the signals under study.^{45,46} Classical mu-, delta-, and kappa-opioid receptors couple to Gi/o proteins, open G-protein-gated inwardly rectifying K⁺ channels, inhibit voltage-gated Ca²⁺ channels, hyperpolarize neurons, and reduce transmitter release; opioid receptors are also reported on subsets of immune and glial cells.⁴⁵ Opioid exposure could therefore change neural firing, extracellular ion handling, calcium-dependent immune signaling, and inflammatory tone. Evidence linking opioid class or dose to tumor progression and antitumor immunity remains heterogeneous and sometimes conflicting.^{46,47} Opioid identity, dose, route, timing, analgesic efficacy, and pain severity should consequently be prespecified covariates in tumor-electrophysiology studies rather than treated as a uniform therapeutic effect.

Experimental roadmap for tumor models

A staged roadmap can move the framework from analogy to causal testing. First, use orthotopic or genetically engineered tumor models with defined innervation—for example, glioma for direct synaptic input and pancreatic, prostate, melanoma, or head-and-neck models for peripheral neural interactions. Label tumor cells, selected immune populations, axons, and supporting glial cells with spectrally separable reporters, and establish whether the 40-micrometer imaging depth captures the relevant neuroimmune niche.

Second, add direct electrical and ionic measurements. RUSH3D-HR-compatible genetically encoded voltage and calcium indicators should be calibrated against patch-clamp or microelectrode-array measurements; extracellular K⁺, pH, ATP, and field signals should be measured with orthogonal probes. Time-lagged analyses should test whether electrical events precede, predict, and spatially organize cellular behaviors after controlling for chemokine concentration, perfusion, oxygenation, and motion.

Third, establish causality with compartment-specific perturbation and rescue. Candidate channels or receptors should be altered separately in tumor, neural, glial, and immune cells. Neural blockade or activation should be crossed with chemokine-receptor, calcium, and ion-channel perturbations in factorial experiments. A convincing mechanism should show loss of the electrical signature and phenotype after targeted perturbation, restoration by a mechanism-matched rescue, and preservation of general cell viability and motility.

Finally, translation should proceed only after replication across models. Human tumor slices or innervated organoids can test

conservation, while clinical studies should compare electrical or imaging readouts with established pathological and immune biomarkers. A closed-loop “sense-decode-actuate” platform is a long-term engineering objective, not a current clinical capability.

Limitations

Several constraints delimit the present framework. First, the RUSH3D-HR observations highlighted here were obtained in LPS-inflamed spleen and acute liver injury, not in tumors, and the platform did not directly measure voltage, current, extracellular fields, or neural activity. Second, spatial or temporal covariation among reporters would remain correlational unless supported by cell-specific perturbation, pathway blockade, and rescue. Voltage and ion reporters can be confounded by motion, pH, expression level, sensor kinetics, photophysics, and tissue scattering, whereas invasive electrodes sample limited regions and may perturb the microenvironment. Third, biochemical, mechanical, metabolic, and electrical processes are tightly coupled; separating an independent electrical contribution may be impossible in some contexts and should not be assumed. Fourth, neural effects vary with tumor type, nerve subtype, glial state, disease stage, pain, medication exposure, and immune composition, limiting generalization from any single model. Fifth, RUSH3D-HR has a relatively shallow axial imaging range and requires fluorescent labeling, which constrain access to deep or clinically sampled tissues. Finally, swarming frequency, migrasome dynamics, and closed-loop intervention remain unvalidated as cancer biomarkers or therapies. These limitations make the framework falsifiable but currently preclude claims that an integrated tumor-nerve-immune electrical axis has been visualized or clinically addressed.

Conclusions

RUSH3D-HR does not yet visualize the tumor-nerve-immune electrical axis; it visualizes cellular dynamics at the scale needed to begin testing it. The strongest current conclusion is that the platform can resolve neutrophil swarming, migrasome generation and uptake, and an electroacupuncture-associated change in swarming in non-tumor inflammatory models. The electrical-axis hypothesis will gain support only if direct voltage, ionic, or field signals precede and predict these behaviors and if compartment-specific perturbations distinguish them from established chemokine, lipid, calcium, neural, endocrine, and vascular mechanisms. If those criteria are not met, the observed dynamics should be explained by the established alternatives. Applied with this evidentiary discipline and extended to relevant tumor models, the framework can serve not as a declaration of a completed circuit, but as a rigorous experimental program for discovering when bioelectric encoding adds explanatory and therapeutic value.

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Conflict of interest

Wei-Lin Jin is an Editorial Board Member of *Oncology Advances*. He was not involved in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process was delegated to an independent editor. The other authors declare no competing interests.

Author contributions

Conceptualization (PYZ, MZJ, WLJ), investigation (PYZ), visualization (PYZ), funding acquisition (WLJ), supervision (MZJ, WLJ), drafting the manuscript (PYZ), and critical revision of the manuscript (PYZ, MZJ, WLJ). All authors have read and approved the final manuscript.

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