The neural stem cell-NSCLC axis: Molecular drivers, microenvironment crosstalk and emerging therapies (Review)

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Abstract. Non-small cell lung cancer (NSCLC), as the main type of lung cancer, is characterized by high heterogeneity and a complex tumor microenvironment (TME), which are key factors contributing to therapeutic resistance, recurrence and metastasis. In recent years, the interaction between neural stem cells (NSCs) and NSCLC, known as the 'NSC-NSCLC axis', has gradually become a research hotspot at the intersection of tumor biology and cancer neuroscience. The present review summarizes the extensive overlap between NSCs and NSCLC stem cells in terms of molecular markers and signaling pathways, and discusses the possible mechanisms through which NSCLC cells 'hijack' NSC programs to enhance stemness, therapeutic resistance and metastatic potential. The present review further discusses how the TME actively recruits NSCs and drives their functional reprogramming, thereby promoting tumor progression through the paracrine secretion of neurotrophic factors, the induction of angiogenesis, remodeling of the immune microenvironment and the formation of synapse-like connections. In addition, the regulatory networks of neurotransmitters, neurotrophic factors and neuropeptides in NSCLC are reviewed, with particular emphasis on evaluating the potential and challenges of emerging therapies targeting neurotransmitter receptors, perineural invasion, neuroendocrine differentiation and brain metastasis. Unlike previous reviews that focused predominantly on a single mechanism or flux, the present review adopts an integrated perspective of the 'neural stem cell-non-small cell lung cancer axis' to link three tiers: Molecular hijacking, microenvironment remodeling and clinical translation. The present review further highlights translational research priorities, including targeting neurotransmitter receptors, perineural invasion, neuroendocrine transformation and brain metastasis. Additionally, it is proposed that single-cell and spatial omics are poised to advance this field from phenomenological description toward precise subtyping, providing a novel therapeutic strategy for NSCLC shifting from 'tumor eradication' to 'reprogramming the tumor microecology'.

Contents

1. Introduction

Non-small cell lung cancer (NSCLC) is the primary histological type of lung cancer, accounting for ~85% of all lung cancer cases. Its subtypes include adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma (1-3). NSCLC exhibits marked molecular heterogeneity and a complex tumor microenvironment, both of which contribute to tumor stemness, metastatic potential and therapeutic resistance (4,5). Although significant progress has been made in surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy, the majority of patients are diagnosed at advanced stages, with the 5-year survival rate still <25%. Issues, such as drug resistance and recurrence urgently require innovative therapies (6,7). Neural stem cells (NSCs) are a type of progenitor cells with self-renewal capacity and multi-lineage differentiation potential, residing in the central nervous system of adult mammals (8). Under physiological conditions, NSCs undergo

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asymmetric division to produce neurons and glial cells (9), maintaining adult neurogenesis, supporting learning, memory and nerve injury repair, thus endowing the nervous system with high plasticity and regenerative potential (10).

In recent years, the crosstalk between NSCs and tumor cells has gradually emerged as a critical perspective for unraveling the mechanisms underlying tumor initiation and progression (11,12). Although the tumor microenvironment (TME) is commonly recognized as a sophisticated ecosystem composed of tumor cells, immune cells, fibroblasts and extracellular matrix, the pivotal roles of neural components and stem-like properties of tumor cells within this ecosystem have long been overlooked. Accumulating evidence currently demonstrates that NSCLC cells express a variety of NSC markers and activate relevant signaling pathways to exhibit 'NSC-like behaviors (13). Moreover, neurogenic factors, neurotransmitters and direct cell-cell contact can profoundly modulate the proliferation, stemness maintenance, invasion and metastasis capacities of tumor cells (14-16). This emerging research niche has been conceptualized as the 'NSC-NSCLC axis'. Within this framework, NSCLC cells augment cancer stemness and therapeutic resistance by hijacking multiple core signaling cascades of neural stem cells; nerve fibers residing in the TME remodel the immune microenvironment and facilitate angiogenesis via the secretion of neurotrophic factors. Intriguingly, tumors can reciprocally regulate peripheral neurons and potential NSC-like cell populations, thereby establishing a bidirectional regulatory loop. Nevertheless, the precise molecular mechanisms and therapeutic targets in this field remain incompletely characterized.

Therefore, analyzing the key molecular drivers of the 'NSCs-NSCLC axis', the associated microenvironment crosstalk networks and their functions in malignant progression will help uncover novel biological targets and provide innovative insights for the precise diagnosis and treatment of NSCLC. The present review aimed to summarize the latest research advances in this field and provide perspectives on potential therapeutic strategies (Fig. 1).

2. Biological features and molecular regulatory networks of neural stem cells

NSCs are the main population of endogenous adult stem cells in the central nervous system, primarily residing in the subventricular zone and the subgranular zone of the hippocampal dentate gyrus (17). Under pathological conditions, NSCs can also be derived from reactive astrocytes or neural crest-derived progenitor cells (18,19). Their core characteristics involve the long-term maintenance of a dynamic balance between 'self-renewal' and 'multi-lineage differentiation' potential (20,21). This balance is regulated by a set of highly conserved molecular markers, such as Nestin, SOX2, Musashi-1, CD133, along with core signaling pathways such as Notch, Wnt/β-catenin, Shh and BMP (22,23). Notably, these molecules and pathways are also highly active in cancer stem cells (CSCs). This 'molecular homology' is not coincidental, but rather reflects the evolutionary co-option of developmental programs by tumor cells (24). For example, the Notch signaling pathway regulates cell fate determination in normal NSCs, whereas in NSCLC CSCs, it is frequently constitutively activated, thereby promoting stemness maintenance and chemotherapeutic resistance (4). However, the majority of existing studies remain largely descriptive of this overlap (24,25). The crosstalk among distinct signaling pathways within specific TME contexts, as well as their spatiotemporal dynamics, remains poorly understood, representing a critical area for future mechanistic investigation.

In the TME, NSCs can be actively recruited. Chemokines and growth factors, including SDF-1α/CXCL12, SCF, IL-6 and TGF-β secreted by tumor cells and tumor-associated macrophages bind to surface receptors, such as CXCR4 and c-Kit on NSCs, subsequently activating the PI3K/Akt, MAPK and JAK/STAT3 signaling pathways to drive the directional migration of NSCs toward tumor lesions (26-28). In addition, the hypoxic microenvironment upregulates VEGF expression via HIF-1α, which cooperates with exosome-carried miR-21 to further facilitate the homing and survival of NSCs (29). These mechanisms lay a cellular foundation for the subsequent functional aberrance of NSCs within the TME. After entering the TME, the intrinsic normal differentiation program of NSCs is hijacked. Tumor cell-derived Notch ligands (Jagged1/DLL4) persistently activate intracellular Notch signaling in NSCs to repress cell differentiation (30); miR-21 and miR-210 encapsulated in tumor-derived exosomes remodel the survival and metabolic phenotypes of NSCs by targeting PTEN and inhibiting mitochondrial metabolism, respectively (31); furthermore, hypoxia upregulates the levels of pluripotency factors, including Oct4 and Nanog in a HIF-1α-dependent manner, arresting the differentiation of NSCs into mature neural cells (32). Collectively, these regulatory mechanisms endow NSCs with a pro-tumorigenic phenotype

3. Hijacking of NSC molecular programs by NSCLC stem cells

NSCLC CSCs achieve the functional hijacking of the NSC programs by aberrantly activating core molecular signatures and signaling networks that highly overlap with those of NSCs, exhibiting significant 'NSC-like behavior (33). This 'co-option of homologous programs' not only endows NSCLC CSCs with extreme stemness, therapeutic resistance and metastatic potential, but also provides a molecular basis for the tumor cells to efficiently recruit and utilize authentic NSCs within the TME.

A summary of the functional divergence of certain shared markers and their clinical significance is provided in Table I (34-73). Taking SOX2 as an example, in normal NSCs, it forms a positive feedback loop with other factors (such as Nestin and TLX) to maintain stemness homeostasis (34). However, in NSCLC CSCs, SOX2 often collaborates with ASCL1 to induce neuroendocrine differentiation (35), and interacts with various factors such as miRNAs, lncRNAs, STAT3 and Wnt/β-catenin to drive tumor progression and drug resistance (36,37), becoming an independent predictor of a poor prognosis (40). Notably, discrepancies exist among studies regarding the reported functions of these markers, which may arise from tumor heterogeneity, differences in model systems (such as cell lines, organoids and *in vivo* models),and the complexity of microenvironmental signals. For example, CD133 expression is associated with multiple

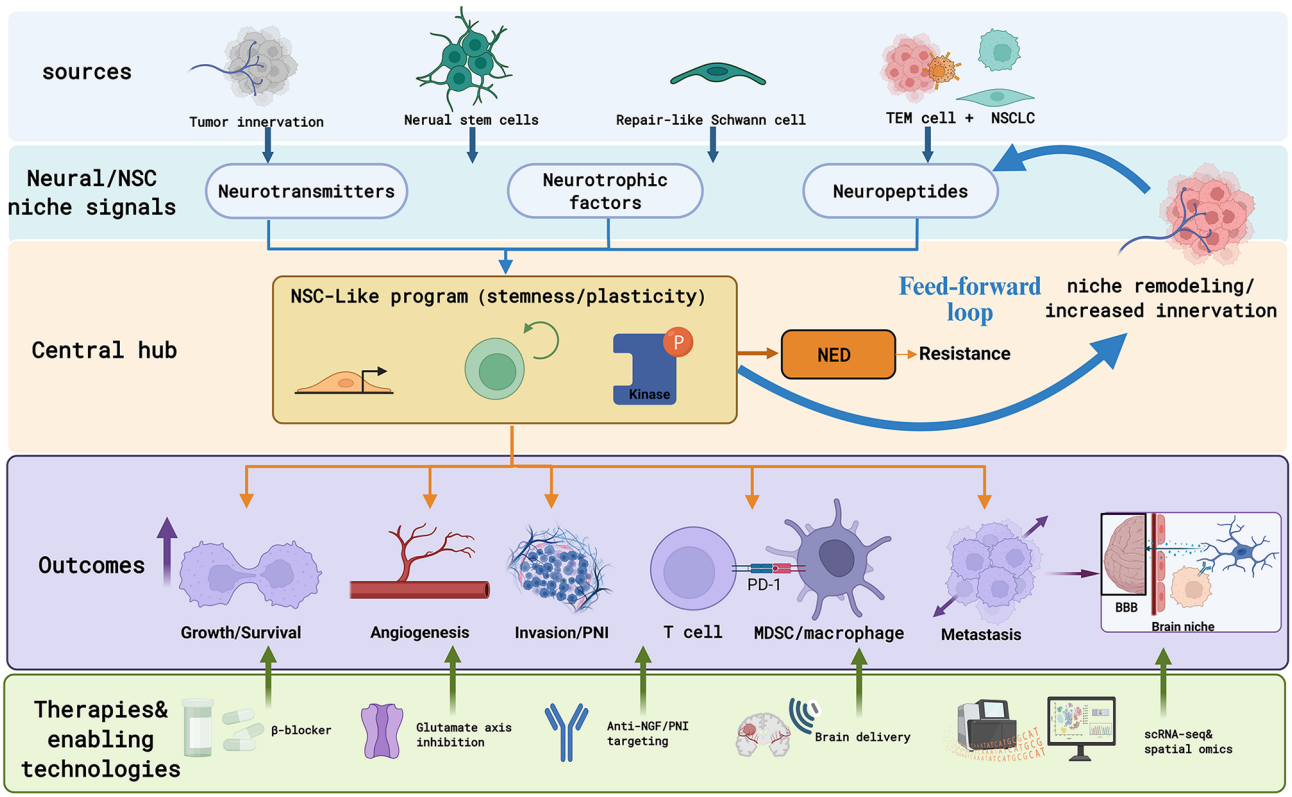

Figure 1. Schematic illustration of the mechanisms and intervention strategies by which neural and NSC microenvironmental signaling regulates malignant progression. Neurogenic signals derived from upstream tumor innervation and neural stem cells activate NSC-like programs in tumor cells, thereby inducing neuroendocrine differentiation and resistance. These signals further remodel the tumor microenvironment through feed-forward loops, promoting tumor growth, invasion, and metastasis. The lower panel illustrates potential therapeutic strategies and technological approaches targeting different stages of this process. NSC, neural stem cell; NGF, nerve growth factor; PNI, perineural invasion; MDSC, myeloid-derived suppressor cell.

pro-tumor characteristics: It can maintain stemness by activating the Src/PI3K/mTOR pathway (49); under hypoxic conditions, $CD133^+$ cells enhance adaptability by stabilizing HIF1α/2α (50). Furthermore, this subpopulation exhibits a strong potential for initiating brain metastasis (53,54). However, the expression and function of CD133 are not fixed and may be dynamically regulated by microenvironmental factors such as hypoxia and inflammation. Therefore, future research should not be limited to descriptive correlations of markers, but should also delve into their upstream regulatory mechanisms and downstream effect networks in specific clinical subtypes or microenvironmental contexts.

Notably, the hijacking of neural programs is not confined to stemness and therapeutic resistance, but extends directly to metastasis. Several of the shared markers and pathways co-opted by NSCLC CSCs are mechanistically linked to invasive and metastatic behavior. $CD133^+$ subpopulations represent the strongest initiators of brain metastasis (53,54), and Nestin serves as an independent risk factor for brain and bone metastasis in lung adenocarcinoma by forming complexes with vimentin/Snail/Slug to drive epithelial-mesenchymal transition (58-60). Moreover, as detailed below, functionally reprogrammed NSCs further promote metastasis by secreting VEGF to induce angiogenesis and releasing MMP-2/9 to degrade the extracellular matrix, thereby paving the way for the invasion and metastatic dissemination of CSCs. This metastatic dimension is further reinforced at the level of neural signaling and of the brain-metastatic niche, as discussed in the corresponding sections. In this sense, the same neural-program hijacking that sustains stemness and resistance also drives the metastatic potential of NSCLC.

After entering the TME, the normal differentiation program of NSCs is hijacked, which in turn acts reciprocally on NSCLC CSCs to form a malignant amplification loop. Tumor-cell-secreted Notch ligands (Jagged1/DLL4) can persistently activate intracellular Notch signaling in NSCs and inhibit their differentiation (74); miR-21 and miR-210 derived from tumor exosomes remodel the survival and metabolic phenotypes of NSCs by targeting PTEN and suppressing mitochondrial metabolism, respectively (31,75); the hypoxic microenvironment upregulates pluripotency factors, such as Oct4 and Nanog via HIF-1α, thereby blocking the differentiation of NSCs into mature neural cells (76). Following functional aberrance, these NSCs secrete neurotrophic factors, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) in a paracrine manner to activate PI3K/Akt,MAPK/ERK and other signaling cascades in NSCLC CSCs, elevating the expression of stemness markers and conferring chemoresistance (77,78). Furthermore, NSCs produce VEGF to facilitate angiogenesis and release MMP-2/9 to degrade the extracellular matrix, paving the way for the invasion and metastasis of CSCs (79). A subset of NSCs can further differentiate into neuron-like cells that form synapse-like junctions with tumor cells to supply sustained neurotrophic support (80). Collectively, the aforementioned mechanisms constitute the

Table I. functional divergence of core markers shared between neural stem cells and NSCLC stem cells.

Marker	Main function in normal NSCs (Refs.)	Functional divergence in NSCLC CSCs (Refs.)	Clinical prognostic significance (Refs.)
SOX2	Maintains the balance between self-renewal and differentiation inhibition; forms a positive feedback loop with Nestin and TLX (34).	Collaborates with ASCL1 to induce neuroendocrine differentiation (NED) (35); interacts with miRNA, lncRNA, STAT3, and Wnt/β-catenin to regulate tumor progression (36,37).	Promotes therapeutic resistance and recurrence (38,39); an independent predictor of a poor prognosis (40,41).
Musashi-1	RNA-binding protein (42); deactivates and translocates to the nucleus upon phosphorylation, precisely regulating exit from stemness (43).	Loss of phosphorylation deactivation mechanism, continuously inhibits PTEN, p53, leading to anti-apoptosis and multi-drug resistance (44-46).	Independent predictor of a poor prognosis.
CD133	Maintains cell polarity and low ROS microenvironment (47); marks long-term repopulating stem cells (48).	Activates Src/PI3K/mTOR (49), stabilizes HIF-1α/2α (50), upregulates ABCG2/ABCB1 (51), driving drug efflux, hypoxia adaptation, EMT, and vasculogenic mimicry (52).	CD133+ subpopulation exhibits the strongest tumorigenicity, drug resistance, and brain metastasis initiation (53,54).
Nestin	Dynamic intermediate filament, ensures asymmetric division polarity (55,56); marker of proliferative activity (51).	Forms complexes with vimentin/Snail/Slug to drive typical EMT (58,59).	Independent risk factor for brain and bone metastasis in lung adenocarcinoma (60); increases risk of metastasis.
ALDH1A1	Almost silent in adulthood.	Highly activated to clear chemotherapeutic aldehyde metabolites (55), maintains high ROS tolerance (56).	Increases the risk of postoperative recurrence (57).
Lgr5	Extremely low or not expressed in adulthood	Amplifies Wnt signaling by binding to RSPOs, RNF43/ZNRF3, maintaining extreme self-renewal and dormancy-reactivation cycles (58,59).	Independent risk factor (60)
CD44	Almost not expressed in. adulthood	Collaborates with HA, MMP-9 and EGFR, confers strong matrix invasion and vasculogenic mimicry abilities (60-64).	Correlates positively with T stage, lymph node metastasis, and radioresistance (65).
ASCL1	Promotes NSC differentiation into neurons (66).	Forms a pathological synergistic loop with SOX2, inducing NED^{+} high-stemness phenotype; a core driver of SCLC transformation following EGFR-TKI resistance (67).	Potential biomarker for predicting SCLC transformation (1).

ROS, reactive oxygen species; EMT, epithelial-mesenchymal transition; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor.

molecular basis underlying the bidirectional crosstalk between NSCs and NSCLC CSCs.

4. Neural signaling regulatory networks in non-small cell lung cancer

NSCLC is not a disease process driven solely by genetic mutations. An increasing body of evidence suggests that, under sustained neural input, tumor cells can undergo alterations in receptor expression profiles and reprogram downstream signal transduction, thereby converting external neural stimuli into a broad spectrum of biological effects, including enhanced proliferation and survival, invasion and metastasis, angiogenesis, immune suppression and therapeutic resistance (81,82). These neural signals include neurotransmitters, neurotrophic factors and neuropeptides. It should be emphasized, however, that substantial heterogeneity exists among studies with respect to experimental models, exposure paradigms and endpoint definitions. As a result, the magnitude and even the direction of the effects attributed to a given 'neural signal' are not always consistent across different investigations. Accordingly, this section is structured based on the relevance of each signaling axis to NSCLC and the relative contribution of direct versus indirect effects, thereby clarifying which findings are

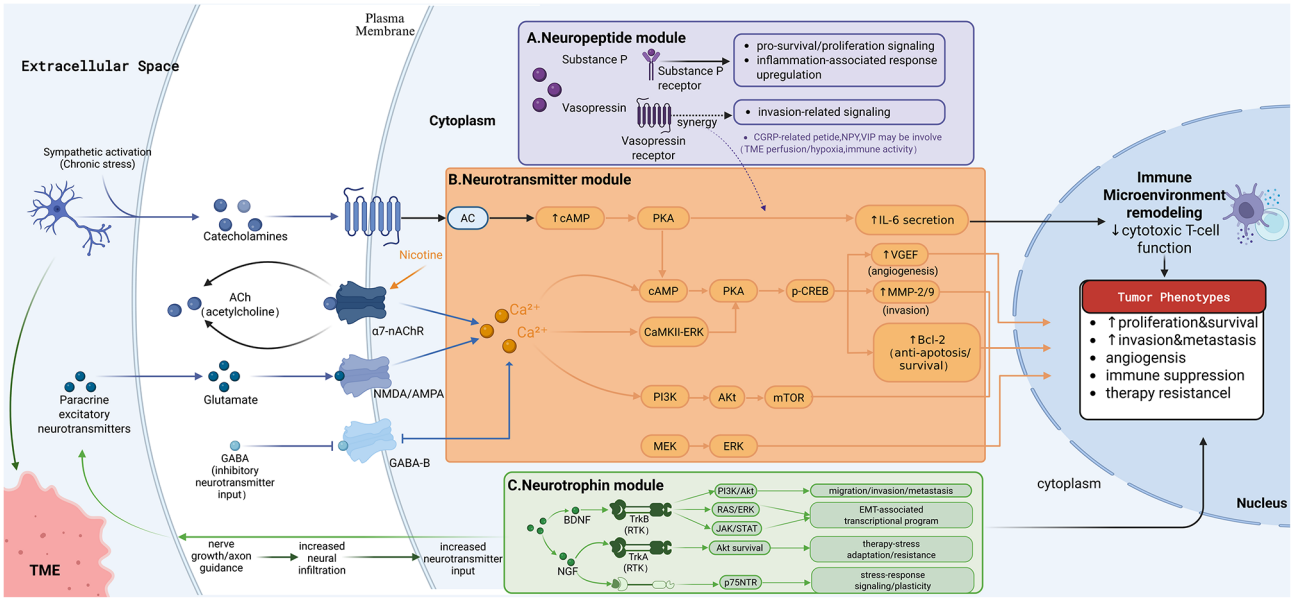

Figure 2. Schematic illustration of the mechanisms by which neural signals regulate tumor cell signaling pathways and tumor phenotypes. The diagram is organized into three color-coded modules:n (A) The neuropeptide module, (B) the neurotransmitter module, and (C) the neurotrophin module. Through their respective receptors, these signals activate downstream cascades such as cAMP-PKA, CaMKII-ERK and PI3K-AKT-mTOR, and act cooperatively to remodel the immune microenvironment, ultimately driving tumor proliferation/survival, invasion and metastasis, angiogenesis, immune suppression, and therapeutic resistance. TME, tumor microenvironment.

approaching consensus and which should be interpreted as preliminary or suggestive (Fig. 2).

Neurotransmitter signaling pathways. Among the currently available studies on NSCLC, neurotransmitters exhibit the most direct associations (83-85). Evidence indicates that NSCLC cells are not merely passively exposed to the surrounding neurochemical milieu, but are frequently subjected to sustained and dynamic neurotransmitter input (86). For example, under chronic stress conditions, sympathetic excitation increases the release of catecholamines, while excitatory neurotransmitters, such as glutamate may also be present in the TME via paracrine mechanisms (87). Notably, NSCLC cells may even establish autocrine loops, autonomously synthesizing acetylcholine (ACh), thereby conferring a local 'autocrine growth factor-like' effect within the tumor niche (88). Corresponding to these diverse sources of neurotransmitters, NSCLC cells often upregulate and exploit multiple classes of neurotransmitter receptors to accomplish signal sensing and transduction. These include β2-adrenergic receptor, nicotinic and muscarinic acetylcholine receptors (particularly α7-nAChR), as well as NMDA/AMPA and GABA-B receptors. The activation of these receptors converts external neural stimuli into changes in second messengers, such as cAMP or Ca^{2+}, which are subsequently propagated through key oncogenic pathways including PI3K/AKT/mTOR, MEK/ERK and CaMKII-ERK, thereby driving malignant biological behaviors such as proliferation and survival, angiogenesis, invasion and migration, and immune suppression (Fig. 2B).

Catecholamine signaling provides a relatively well-characterized example of neurotransmitter-mediated regulation in NSCLC. Upon binding to β2-adrenergic receptors on NSCLC cells, catecholamines stimulate adenylate cyclase, leading to elevated intracellular cAMP levels and the activation of PKA. Activated PKA phosphorylates CREB, inducing the upregulation of VEGF, MMP-2/9 and Bcl-2, which respectively promote angiogenesis, enhance invasive capacity and increase resistance to apoptosis (89). In parallel, this signaling axis can stimulate the secretion of inflammatory cytokines, such as IL-6 (90), thereby remodeling the immune microenvironment and attenuating cytotoxic T-cell activity, resulting in a more pronounced immunosuppressive tumor phenotype. By contrast, cholinergic signaling in NSCLC more commonly manifests as a sustained driver of tumor growth and survival. Research indicates show that NSCLC cells are capable of synthesizing and releasing ACh. The immediate targets of ACh are cholinergic receptors on the cell membrane, including both nicotinic and muscarinic acetylcholine receptors, among which the α7-nAChR is most frequently implicated in NSCLC research. Upon binding to α7-nAChR, ACh triggers the earliest and most reproducible event:receptor-mediated ion channel opening and Ca^{2+} influx (86). This Ca^{2+} entry subsequently mobilizes multiple canonical cancer-associated signaling modules. For example, Ca^{2+}-dependent nodes, such as CaMKII can participate in signal amplification and couple with ERK activation, while the PI3K/Akt/mTOR and MEK/ERK pathways are also commonly observed to be upregulated downstream of α7-nAChR activation (91). In this context, nicotine, acting as a high-affinity agonist of nAChRs, can markedly amplify cholinergic signaling, thereby promoting aberrant clonal expansion and enhancing phenotypes related to anti-apoptosis and resistance to therapy (92).

Taken together, neurotransmitters represent the most direct and environmentally sensitive class of neural inputs in NSCLC. Through specific receptors, they translate host systemic factors and local neural activity within the tumor into executable intracellular events, such as cAMP or Ca^{2+}, which are then integrated through classical oncogenic modules, such

as PI3K/AKT/mTOR and MEK/ERK to remodel proliferation and survival, invasion and migration, angiogenesis and the immune microenvironment (93,94). Key questions for future investigation include the following: First, the relative temporal and spatial contributions of different neurotransmitter sources to disease progression. Second, whether receptor expression profiles are predictable and stratifiable in the context of tumor heterogeneity. Third, whether neurotransmitter signaling represents merely a correlate of treatment response or a causal driver of therapeutic resistance in the setting of targeted therapy and immunotherapy.

Neurotrophic factor signaling pathways. Neurotrophic factors constitute a central hub in tumor-nerve interactions in NSCLC. Their sources are diverse, including neurons, Schwann cells (SCs), tumor cells and stromal cells (95). These factors activate downstream signaling pathways through receptors, helping tumor cells survive under stress conditions, such as detachment from the matrix, hypoxia and treatment pressure. Studies indicate that neuronal factors not only participate in regulating tumor angiogenesis and microenvironmental remodeling (96), but also that NGF signaling is closely related to the initiation and progression of tumor-associated inflammation (97). Further exploration has revealed the multi-layered mechanisms and translational prospects of the 'neuro-immune-tumor' axis in tumors such as gliomas (98). Notably, neurotrophic factors inherently promote neuronal growth and axonal guidance (99), which may drive nerve fiber infiltration and the increase of neuro-related structures within tumors, thereby enhancing the input of neurotransmitters, such as catecholamines and acetylcholine. This suggests that there may be a positive feedback loop of mutual reinforcement between tumors and neural components, where tumors are more likely to survive and spread under the support of neurotrophic factors and neural components, driven by neurotrophic factors, become further enriched. The enhanced neural input continuously stimulates the tumor and promotes its progression. In terms of the existing evidence in NSCLC, BDNF and NGF are the most discussed neurotrophic factors; however, their predominant roles are not identical. BDNF is more commonly associated with migration, invasion, metastasis and phenotype changes, translating external or tumor-derived stimuli into stronger motility and dissemination capabilities. By contrast, NGF is more often used to explain adaptive survival under therapeutic stress, and its correspondence with the increase in neural components within tumors is clearer, rendering it more likely to be incorporated into the framework of tumor-neuron mutual reinforcement. Collectively, the BDNF-TrkB and NGF-TrkA/p75NTR axes constitute the core of neurotrophin signaling in NSCLC (Fig. 2C).

Within BDNF-related mechanisms, binding of BDNF to TrkB activates receptor tyrosine kinase signaling and elicits multiple downstream pathways (100). Research has provided relatively consistent evidence that the PI3K-AKT axis represents a major component of this signaling, being closely associated with enhanced cellular survival under adverse conditions (101). Additional studies suggest the involvement of RAS-ERK-related pathways, which are linked to migration- and invasion-associated transcriptional programs, as well as cytoskeletal remodeling (102). In certain experimental models, outputs related to JAK-STAT signaling have also been observed (103). Taken together, the functional outcomes of these signaling pathways place the BDNF-TrkB axis predominantly within a pro-migratory, pro-invasive and pro-metastatic framework, with established links to transcriptional regulatory networks associated with epithelial-mesenchymal transition. In this sense, the BDNF axis can be viewed as a signaling conduit that translates extrinsic or tumor-derived cues into enhanced cellular motility and dissemination capacity.

In NGF-related mechanisms, the binding of NGF to TrkA similarly triggers receptor tyrosine kinase signaling, with research indicating that one of its key outputs remains the AKT-associated survival pathway, which can be linked to the tolerance of tumor cells to chemotherapy and other stresses (104). Unlike TrkA, p75NTR does not rely on intrinsic kinase activity, but instead modulates stress-responsive pathways through the formation of complexes with distinct intracellular binding proteins, thereby contributing to cellular state plasticity and stress tolerance (105). In NSCLC, a key implication of the NGF axis is that it points in two directions simultaneously: On the one hand, toward intrinsic tumor cell survival and therapeutic adaptation, and on the other hand, toward the correspondence between its neurotrophic growth-promoting effects and increased intratumoral neural structures. From this perspective, NGF is better viewed as mediating a bidirectional association: NGF-related signaling enables tumor cells to better withstand therapeutic pressure, while simultaneously facilitating the expansion of neural components within the tumor. The resulting increase in neural inputs subsequently provides sustained exogenous stimulation via neurotransmitter release, thereby reinforcing and perpetuating this process.

Neuropeptide signaling pathways. The role of neuropeptides in NSCLC resembles that of neurotrophic factors, but is better conceptualized as a signal amplifier that converts neural activity into tumor behavior. By binding to receptors on tumor cells or microenvironmental components, neuropeptides translate external neural inputs into signaling responses within the tumor (106,107). Overall, neuropeptides are typically invoked to explain three categories of phenomena. First, they facilitate tumor cell survival and tolerance under hypoxic conditions, and conditions of nutrient fluctuations or therapeutic stress. Second, they alter cell adhesion and motility, thereby promoting migration and invasion and associated with an increased risk of metastasis. Third, they remodel the TME by influencing vascular status, inflammatory responses and immune cell function, ultimately affecting tumor growth rate and treatment responsiveness. As these effects often occur in parallel, neuropeptides function less as singular growth factors and more as regulatory links between neural input and tumor progression (108) (Fig. 2A). Precisely as their actions are distributed and highly context-dependent, the critical challenge in neuropeptide research is not the continued expansion of their catalog, but the identification of signaling axes supported by causal evidence and druggability, which can be prioritized for translational development.

From the perspective of translational potential and research depth, substance P is the most worthy of priority discussion. Closely associated with sensory nerves, substance P can be

detected within the TME (109). After its receptor is activated, intracellular pro-survival and pro-proliferative pathways are enhanced, often accompanied by the upregulation of inflammation-related responses (110). In some studies, blocking this receptor has been associated with reduced cell growth or increased therapy-induced cell death, thus being repeatedly discussed as a potential intervention target (111). However, much of the existing evidence remains confined to functional associations observed in *in vitro* systems or specific models. The critical next step is to determine whether this axis truly determines treatment response differences in well-stratified NSCLC population, and whether blocking it could generate reproducible benefits in the context of immunotherapy or chemoradiotherapy, rather than merely a 'universal effect' of inhibiting proliferation.

Another commonly discussed axis involves neurotensin and its receptor. In certain NSCLC specimens, receptor expression is higher and associated with greater invasiveness (112). This pathway is considered to activate growth- and migration-related signaling and may synergize with common growth factor receptor pathways, thus rendering the tumor more likely to maintain proliferation and acquire stronger migratory and invasive abilities (113).Additionally, other neuropeptides, such as calcitonin gene-related peptide, neuropeptide Y and vasoactive intestinal peptide have also been suggested to be involved in regulation, primarily from a microenvironment perspective, such as influencing perfusion and hypoxia or modulating immune activity (108). Overall, neuropeptide research should shift from 'which neuropeptides are involved' to 'which axes are most capable of determining clinically relevant phenotypes and are most amenable to pharmacological targeting'. Within the current evidence framework, the substance P receptor axis and the neurotensin receptor axis have higher priority and are closer to a feasible translational intervention path.

5. Neural-stem cell interaction in the TME of NSCLC

In NSCLC, the 'neural-stem cell crosstalk' is not merely regulated via paracrine signaling mediated by neurotransmitters, neurotrophic factors or neuropeptides; instead, it is predominantly manifested as niche remodeling driven by nerve fiber infiltration and glial cell recruitment (114). Neural signals deliver not only transient stimulatory cues, but may also reshape the TME into a neutralized microenvironment that favors the survival, migration and therapeutic escape of CSCs by altering local tissue architecture and cellular composition (115,116).

Notably, intratumoral nerve fibers are heterogeneously distributed and preferentially enriched at invasive fronts, perivascular regions and sites with prominent stromal remodeling, implying their synergistic interplay with invasive pathways (117). Accordingly, perineural invasion (PNI) enables tumor cells to spread along nerve tracts and gain survival privileges, which is associated with elevated risks of local recurrence and distant metastasis. Moreover, PNI provides pathological evidence for spatially focused neural input: Nerve tracts function as anatomically structured migratory conduits on the one hand, and confer localized survival benefits via continuous, short-range signaling and nutritional supply on the other. In other words, PNI should no longer be regarded solely as a passive consequence of advanced tumor progression; it serves as a pathologically accessible research model to verify whether neural-associated signaling pathways actively facilitate tumor invasion and metastasis.

Furthermore, the core feature of neural invasion/PNI lies not in the simple upregulation of soluble transmitters, but in the transformation of neural input from intermittent to persistent stimulation. Direct juxtaposition between nerve fibers and tumor cells or NSC-like cells establishes stable local concentration gradients, which endows CSC subsets with high receptor expression with persistent selective advantages and shifts intratumoral heterogeneity toward the emergence of neural-dependent clones (118).

6. Role of Schwann cells in NSCLC

In addition to neuronal axons, SCs represent another key cellular component of the peripheral nervous system whose role in the neural microenvironment of NSCLC may have been substantially underestimated. Under physiological conditions, SCs exhibit a pronounced injury-response and repair capacity: Following nerve injury, they can dedifferentiate into a 'repair-like' state characterized by enhanced migratory ability, the secretion of multiple growth factors and chemokines, and active remodeling of the extracellular matrix to support axonal regeneration (119,120). As the TME and chronic inflammation share substantial signaling similarities with 'tissue injury', it is plausible that tumors co-opt the SC repair program, positioning SCs as a potential hub linking neural input to the maintenance of tumor phenotypes, including stemness-associated states (121,122).

It should be emphasized that, to date, the NSCLC field lacks direct experimental studies centered on 'SC-tumor interactions'. Accordingly, the following discussion is primarily intended to propose transferable and testable mechanistic frameworks based on evidence from other solid tumors, rather than to draw definitive conclusions for NSCLC. Existing studies nonetheless provide at least two lines of evidence that are highly relevant to NSCLC (93,94). First, in melanoma models, tumors have been shown to reprogram surrounding SCs into a repair-like state and activate 12/15-LOX (Alox15) and COX2-associated eicosanoid pathways, thereby increasing the production of immunosuppressive lipid mediators, such as PGE2. These mediators subsequently suppress T-cell activation via EP4 signaling on T-cells. By analogy, if similar repair-like SCs are present in the peritumoral regions of NSCLC, they may contribute to the formation of an immunosuppressive niche through a '12/15-LOX/COX2-PGE2-EP4' axis (93). Second, in pancreatic ductal adenocarcinoma, cancer cells can induce the c-Jun-dependent injury-repair-like reprogramming of non-myelinating SCs, leading to the formation of dynamic 'tumor-activated Schwann cell tracks' (TASTs) that provide both physical paths and mechanical support for tumor cell migration and local invasion (94). Correspondingly, in NSCLC subpopulations exhibiting neural infiltration or PNI phenotypes, whether SCs display c-Jun activation and form TAST-like structures, and whether such structures spatially colocalize with the invasive front, represents a question of high priority for experimental validation.

Beyond their roles in immunity and invasion, SCs are also key sources of neurotrophic signals. SCs can produce neurotrophic factors, such as NGF, BDNF and GDNF, which may enhance tumor cell survival and stress tolerance on the one hand (123), while promoting further growth and the branching of nerve fibers on the other hand (124). Together, these effects may reinforce intratumoral neural input. Moreover, dedifferentiated repair-like SCs can participate in matrix remodeling and alterations in adhesion molecule networks, facilitating tumor cell migration along neural or stromal tracks and thereby providing structural conditions for PNI and the formation of invasive fronts (125,126). When tumor cells are chronically exposed to a combination of neurotrophic factors, inflammatory mediators and hypoxia within SC-enriched regions, they are more likely to sustain the functional activity of proteins, such as SOX2 and Nestin, and to acquire enhanced resistance under therapeutic pressure (127,128).

Therefore, the significance of discussing SCs in NSCLC extends beyond merely 'identifying an additional cell type'. Rather, SCs provide a more explanatory and potentially actionable upstream framework for understanding why neural-related signals can form localized, high-intensity and sustained inputs within tumors, and how such persistent inputs establish more coherent causal links with key phenotypes, such as immunosuppression, invasion and metastasis, and therapeutic resistance. On this basis, validation studies focusing on SC spatial localization, repair-like markers and key signaling axes may help advance 'neural-related phenomena' from correlative observations toward mechanistically tractable targets.

Across the NSCs-NSCLC axis, inflammation emerges as an integral intermediary rather than an incidental feature. Neural signaling and inflammatory responses are tightly intertwined at multiple nodes discussed throughout the present review. NGF signaling is closely associated with the initiation and progression of tumor-associated inflammation (97); catecholamine/β2-adrenergic signaling stimulates the secretion of inflammatory cytokines, such as IL-6, thereby remodeling the immune microenvironment and attenuating cytotoxic T-cell activity (90); the activation of the substance P receptor is frequently accompanied by upregulation of inflammation-related responses (110) and repair-like Schwann cells generate immunosuppressive lipid mediators, such as PGE2 via the 12/15-LOX/COX2-EP4 axis (93). Inflammatory mediators act as key intermediaries linking neural input to immune remodeling, stemness maintenance, and therapeutic resistance.

7. Current clinical therapeutic strategies targeting the NSC-NSCLC axis

An improved understanding of the NSCs-NSCLC axis is reshaping contemporary paradigms of cancer therapy. Accumulating evidence suggests that neural signals not only directly promote tumor growth, but may also function as an upstream regulatory layer driving multiple malignant phenotypes, including immunosuppression, the maintenance of stemness, metastatic colonization and the evolution of therapeutic resistance. For example, Cao (129) proposed the concept of 'neural stemness' as a basal state underlying cellular tumorigenesis and differentiation potential, providing a theoretical framework for tumor stemness maintenance. Cerv antes-Villagrana *et al* (130) demonstrated that tumor-induced neurogenesis and immune evasion may represent actionable targets for innovative anti-cancer therapies. As regards metastatic colonization, Ouyang *et al* (131) revealed that the neuropeptide precursor, neural growth factor-inducible gene (VGF), can remodel the microenvironment through paracrine loops to promote liver metastasis of uveal melanoma, implying that analogous mechanisms may also operate in NSCLC. By contrast, Rotow and Bivona (132) focused directly on NSCLC and comprehensively reviewed multiple resistance mechanisms, including those mediated by neural signaling. Collectively, these findings indicate that interventions targeting neural inputs possess multifaceted clinical value. Such strategies may not only directly suppress tumor cell proliferation and invasion, but may also enhance the efficacy of immune checkpoint inhibitors (ICIs) by relieving neural-associated immunosuppression, while additionally contributing to cancer pain control and an improved quality of life. Current translational efforts mainly advance along five directions: Receptor antagonism, intervention against PNI, targeting neuroendocrine programs, neural adaptation in brain metastases, and strategies for delivery and biomarker development (Fig. 3).

Therapeutic strategies targeting neurotransmitter receptors. Based on the growing understanding of neurotransmitter signaling in NSCLC, clinical studies have begun to explore therapeutic strategies targeting these systems. Clinical evidence to date is mainly derived from retrospective and observational studies. Among these, studies examining the impact of non-selective β-adrenergic receptor blockers (β-blockers) on patient survival have yielded notable progress. For example, a scoping review published in 2024 summarized current evidence and reported that the addition of β-blockers to standard lung cancer therapies was associated with an improved overall survival (OS) and recurrence-free survival, and a reduced incidence of metastasis (133). However, findings in this field are not entirely consistent, and more detailed subgroup analyses reveal a more complex image. A large meta-analysis published in 2021, encompassing >30,000 patients, demonstrated that β-blocker use was not universally associated with a significant improvement in OS among patients with lung cancer (134). Nevertheless, survival benefits were observed in specific subpopulations, such as patients with stage III disease or those who did not undergo surgical resection. Notably, the analysis highlighted that the use of non-selective β-blockers was associated with a worse OS (hazard ratio, 1.14), suggesting that distinct β-blocker subtypes may exert divergent biological effects (134).

In contrast to these clinical observations, preclinical and mechanistic studies provide the biological rationale for this strategy. Mechanistic analyses have further indicated that blockade of β-adrenergic signaling can reduce the recruitment of myeloid-derived suppressor cells, downregulate PD-L1 expression and enhance $CD8^+$ T-cell cytotoxic activity, thereby providing a clear biological rationale for its combination with ICIs (135). Accordingly, prospective clinical trials can be designed to evaluate the efficacy and safety of propranolol in combination with immunotherapy in NSCLC and other solid tumors, with the aim of enhancing immunotherapeutic

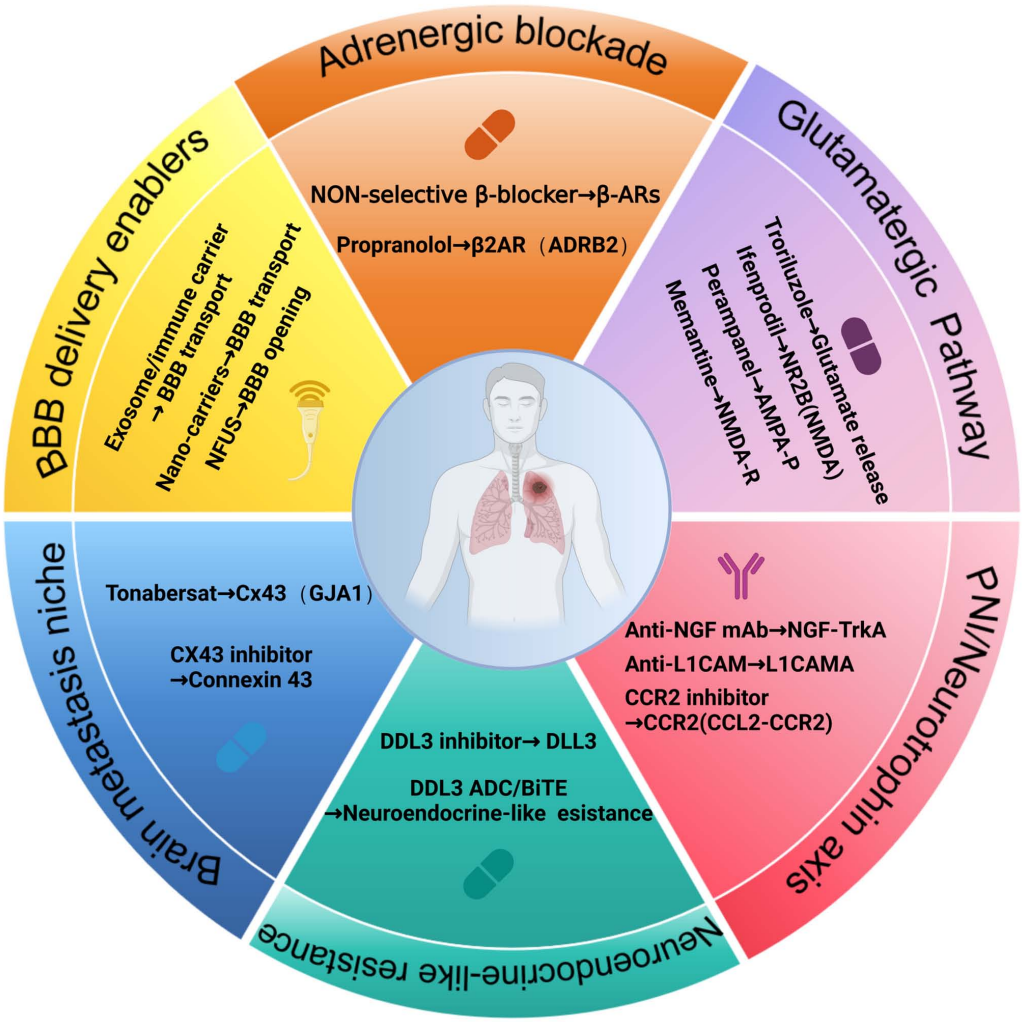

Figure 3. Schematic illustration of the multidimensional regulatory network and targeted intervention strategies in NSCLC brain metastases. Strategies include enhancement of BBB permeability (e.g., inhibition of efflux transporters to improve intracranial drug penetration), blockade of adrenergic signaling (e.g., propranolol targeting β2-adrenergic receptors), modulation of glutamatergic signaling (e.g., tianeptine inhibiting glutamate release; memantine blocking NMDA receptors), and suppression of neurokinin/chemokine pathways (e.g., targeting the NGF-TrkA, ICAM-1 and CCR2 axes), all of which represent important therapeutic avenues in NSCLC. NSCLC, non-small cell lung cancer; BBB, blood-brain barrier.

responses and delaying the emergence of resistance by alleviating stress-induced immunosuppression (136).

Interventions targeting glutamatergic signaling in NSCLC are currently achieved mainly through the use of pathway inhibitors. At the preclinical level, NMDA receptor antagonists, such as memantine and ifenprodil, have been shown in preclinical models to suppress downstream signaling and reduce NSCLC cell proliferation and migration (137). AMPA receptor antagonists, including perampanel, are considered to disrupt excitatory transmission between neurons and tumor cells, an effect that appears particularly pronounced in the context of brain metastases (138).

In terms of clinical translation, glutamate-release inhibitors such as troriluzole can reduce glutamate levels within the TME. The early clinical exploration of troriluzole in combination with nivolumab has demonstrated preliminary feasibility, providing a foundation for further optimization in immunotherapy combinations and patient selection (139). Overall, the translational focus of glutamatergic pathway-targeted strategies lies in defining receptor expression profiles and identifying suitable patient populations, particularly those with brain metastases or tumors enriched in neural components, who are most likely to benefit from interrupting excitatory neural inputs.

Therapeutic strategies targeting perineural invasion. Evidence for these strategies currently stems largely from preclinical and other tumor-type models. NGF and other neurotrophic factors also represent key interventional entry points. It has been demonstrated that the use of NGF-neutralizing antibodies for analgesia can concomitantly attenuate tumor dependence on neurotrophic support and growth signals, thereby limiting PNI (140,141). In addition, interventions targeting tumor migration along nerves may focus on disrupting cell adhesion and recruitment networks. For example, interference with L1CAM or the CCL2-CCR2 axis can weaken the cooperative interactions between tumor cells, SCs and immune cells (142,143). The clinical value of such strategies is more likely to manifest as a reduction in local recurrence and nerve-related complications, while complementing post-operative adjuvant therapy, radiotherapy, or other localized treatments.

Neural-associated signaling can also contribute to the evolution of therapeutic resistance through phenotypic reprogramming, with neuroendocrine differentiation and small cell-like transformation being the most representative examples. Such transitions can be viewed as adaptive responses in which tumors activate neural-related transcriptional programs under therapeutic pressure to acquire increased invasiveness and treatment resistance (144). As DLL3 is highly expressed in small-cell lung cancer and neuroendocrine phenotypes, but exhibits a relatively low expression in normal tissues, it has emerged as an attractive immunotherapeutic target (145). Related strategies recognize and eliminate resistant clones based on neural-like surface antigens: Clinically, the DLL3-targeting bispecific T-cell engager (BiTE), tarlatamab, has entered phase I evaluation in previously treated patients (146), whereas DLL3-targeting antibody-drug conjugates currently remain at the preclinical stage (147). A critical challenge in this direction lies in early identification and dynamic monitoring: Integrating histological and transcriptional features with liquid biopsy to establish early warning and stratification systems before and after phenotypic transformation, thereby enabling the deployment of targeted strategies within the most appropriate therapeutic window.

8. Current therapeutic strategies for NSCLC brain metastases

Brain metastasis is a major cause of mortality in NSCLC. Its therapeutic intractability is attributable not only to the blood-brain barrier (BBB), which restricts the penetration of numerous pharmacologic agents, but also to the adaptive support provided by immune networks formed by neural and glial cells within the brain (148). At the mechanistic level, preclinical studies have shown that brain metastases can engage in metabolic exchange and signaling crosstalk with astrocytes through Cx43-mediated gap junctions, thereby establishing a tumor-favoring protective microenvironment and enhancing resistance to chemotherapy (149). Consequently, Cx43 channel blockers, such as tonabersat, represent a potential strategy to disrupt astrocyte-mediated support (150,151).

In parallel, translational efforts are addressing BBB-related delivery constraints, with encouraging progress in receptor-mediated BBB nanocarriers, immune cell- or exosome-based 'Trojan horse' delivery and focused ultrasound (FUS)-mediated BBB opening (152-155). Notably, these technologies are not independent of neuro-oncological biology. If drugs targeting neural-dependent pathways, such as inhibitors of the glutamatergic signaling or glial interaction axes, can achieve effective concentrations brain metastatic lesions (156-158), their efficacy signals may emerge more clearly in brain metastases than in primary tumors, thereby in turn accelerating drug development and biomarker maturation in this field.

9. Spatial and single-cell omics enable precision treatment of NSCLC

Single-cell sequencing and spatial omics technologies are driving the field from mechanistic narratives toward testable and stratifiable frameworks (159). At the single-cell level, these approaches enable the identification of tumor cell subpopulations with neural-like or stemness-associated features, as well as key cellular states such as repair-like SCs, thereby illuminating potential drug targets and trajectories of resistance evolution (160). In parallel, spatial transcriptomics preserves tissue architecture, while elucidating spatial associations among nerve fibers, immune cells and tumor cells, rendering phenomena such as the co-localization of increased neural density and immune exclusion quantitatively assessable (161,162). Based on these spatial and single-cell insights, neural signal blockade may not only suppress tumor growth, but may also enhance immunotherapeutic responses by alleviating local immunosuppression, providing a more robust rational for combining local neural modulation with systemic therapies.

In summary, translational pathways targeting the NSCs-NSCLC axis are becoming increasingly defined, from rapid clinical entry via β-blockers and glutamatergic pathway inhibitors (163), to structural interventions targeting neurotrophic signaling and perineural invasion with added analgesic benefits (140), to the precision immunotherapeutic targeting of neuroendocrine differentiation-associated resistance branches (164), and further breakthroughs achieved by integrating glial interaction targets and advanced delivery technologies in the brain metastatic niche (80). Future research priorities may focus on three major areas: First, precision stratification: Not all NSCLCs are neural-dependent, underscoring the urgent need for scalable biomarkers based on neural density, neurotransmitter levels and receptor expression profiles to identify responsive populations. Second, brain metastasis intervention: Dissection of the 'neuron-astrocyte-tumor' triadic interaction network to develop combination therapies capable of penetrating the BBB and disrupting key interaction nodes. Third, multidisciplinary integration: Advancing oncology-neuroscience convergence under the framework of cancer neuroscience to open new therapeutic avenues for refractory lung cancer.

10. Challenges and future directions

The 'NSCs-NSCLC axis' framework proposed in the present review provides an integrated analytical perspective for understanding the interplay between neural stem cells and NSCLC. At present, studies on the interaction between NSCs and NSCLC remain limited, particularly as regards the regulatory mechanisms of the NSC-NSCLC axis within the TME. Translating discoveries in this field into clinical therapies presents both challenges and opportunities. One major obstacle is the BBB, which severely restricts the delivery of agents targeting key receptors, thereby rendering the highly active NSC-tumor interactions within brain metastatic lesions difficult to modulate effectively. Accordingly, the development of novel drug-delivery systems capable of traversing both the BBB and the blood-tumor barrier is of critical importance. Moreover, the same molecular signal may exert opposing effects depending on microenvironmental context or concentration, rendering single-target interventions prone to compensatory resistance or off-target toxicity. A more in-depth mechanistic analysis may facilitate the design of more precise multi-target combination strategies. Emerging

technologies, including single-cell sequencing and spatial omics, provide powerful tools to overcome these limitations. These approaches enable the characterization of NSC heterogeneity within the TME and the delineation of their spatial distribution at the tumor-immune interface, thereby identifying the specific NSC subpopulations that truly drive therapeutic resistance and metastasis and furnishing a solid basis for precision targeting. Looking ahead, the integration of spatial multi-omics with artificial intelligence-based analysis may enable the identification of patient-specific 'neural-immune-stem cell' molecular landscapes, allowing for individualized stratification and precise modulation of the neural microenvironment. Combined with the dynamic monitoring of peripheral blood biomarkers, such approaches could support the real-time adjustment of therapeutic regimens. Collectively, this paradigm may shift lung cancer treatment from direct tumor eradication toward reprogramming of the tumor microecosystem, transforming neural stem cells from 'drivers' of tumor progression into controllable therapeutic targets.

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Authors' contributions

YX, HD and FL contributed to the conception and design of the study. YX, HD and PL were responsible for the writing of the manuscript. PL and FL performed the analysis and interpretation of the data from the literature presented in the table. YX, HD and FL participated in manuscript revision. All authors have reviewed and approved the final version of the manuscript. FL served as the corresponding author, overseeing correspondence and final manuscript approval. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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