

Original Article



The Neuro-stromal-immune Axis in Triple-negative Breast Cancer: Sensory Nerves Drive Immune Exclusion and Therapeutic Resistance

Changyuan Guo¹

¹ Department of Pathology, National Clinical Research Center for Cancer/Cancer Hospital, National Cancer Center, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

***Correspondence to:** Guo C., Department of Pathology, National Clinical Research Center for Cancer/Cancer Hospital, National Cancer Center, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China. ORCID: <https://orcid.org/0009-0006-2749-0435>, E-mail: audreygcy@163.com

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Abstract

Triple-negative breast cancer (TNBC) exhibits substantial primary resistance to immune checkpoint blockade (ICB), a challenge driven largely by a desmoplastic and immunosuppressive tumor microenvironment (TME). Emerging multi-omics and spatial profiling technologies have unveiled the peripheral nervous system—specifically nociceptive sensory innervation—as an important regulator of this pathogenic remodeling. This review systematically dissects the “neuro-stromal-immune axis” in TNBC. We delineate how stressed tumor cells secrete nerve growth factor (NGF) to actively recruit TRPV1+ sensory fibers (axonogenesis) and hijack them for metastasis via PlexinB3-mediated perineural tracking. Critically, these infiltrating sensory nerves release the neuropeptide calcitonin gene-related peptide (CGRP), which binds to RAMP1 receptors on myofibroblastic cancer-associated fibroblasts (myCAFs). This neuro-stromal interaction triggers a cAMP-PKA-CREB1 signaling cascade that drives substantial collagen deposition, constructing a dense physical barrier that culminates in the spatial exclusion of cytotoxic CD8+ T cells. Concurrently, direct CGRP signaling induces functional exhaustion in infiltrating T cells. Finally, we explore emerging translational strategies, highlighting the repurposing of clinical CGRP receptor antagonists (migraine therapeutics) and localized denervation as potential combinatorial approaches to disrupt the neuro-fibrotic barrier and resensitize TNBC to ICB therapy.

Keywords:

Triple-negative breast cancer (TNBC); Tumor microenvironment (TME); Neuro-stromal-immune axis; CGRP-RAMP1 signaling; Immune exclusion; Perineural invasion (PNI); Cancer-associated fibroblasts (CAFs); Immunotherapy resistance.

1. Introduction

Triple-negative breast cancer (TNBC) is among the most aggressive and heterogeneous molecular subtypes of breast cancer, characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression.^{1–3} Because actionable targets are limited for conventional endocrine or HER2-targeted therapies, systemic management of TNBC has historically relied on cytotoxic chemotherapy.⁴

In recent years, advances in cancer immunology have reshaped the therapeutic landscape through immune checkpoint blockade (ICB). Landmark phase III clinical trials, such as KEYNOTE-522 and KEYNOTE-355,^{5,6} have established

combination treatment of PD-1 inhibitors (e.g., pembrolizumab) and chemotherapy as the standard-of-care frontline treatment for both high-risk early-stage and advanced metastatic TNBC.⁷ Despite these advancements, clinical evidence indicates that only a subset of patients achieves durable survival benefits from ICB, while a substantial proportion exhibits either primary or acquired immune resistance.⁸ This therapeutic impasse necessitates a more profound interrogation of the underlying mechanisms driving immune evasion in TNBC.^{9–12}

Historically, cancer biology was dominated by a “tumor-centric” paradigm. However, with the rapid evolution of spatial multi-omics and single-cell sequencing technologies, modern oncology has increasingly focused on the “tumor ecosystem”.

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Within this complex tumor microenvironment (TME), malignant epithelial cells coexist with infiltrating immune cells, cancer-associated fibroblasts (CAFs), and aberrant vascular networks, forming a dynamic and interdependent functional unit.^{13,14} Importantly, the peripheral nervous system (PNS)—a physiological component long overlooked in oncology—has recently emerged as a central regulatory hub within the TME.^{15,16} Rather than merely exerting passive mechanical pressure on adjacent nerves, tumors actively secrete neurotrophic factors to orchestrate axonogenesis and neurogenesis. This phenomenon has been profoundly conceptualized as “neural addiction”, reflecting the tumor’s active recruitment of and reliance on neural inputs to drive progression.^{17–19} Within the highly heterogeneous microenvironment of TNBC, peripheral sensory neurons—particularly nociceptors—occupy a dominant topological niche. Rather than acting as passive bystanders, these sensory nerve fibers infiltrating the tumor bed function as “relay amplifiers” that hijack and remodel stromal fibroblasts via the secretion of specific neuropeptides, such as calcitonin gene-related peptide (CGRP). This interaction constructs a dual physical and biological barrier that effectively excludes cytotoxic T cells from executing antitumor immunosurveillance.^{20–23} This review uses the “neuro-stromal-immune axis” as its core conceptual framework to analyze how tumors actively recruit neural innervation. We further describe how sensory nerves leverage the CGRP-receptor activity-modifying protein 1 (RAMP1) signaling pathway to drive collagen deposition and immune exclusion. Finally, we explore emerging translational strategies aimed at targeting this ecosystem to reverse immunotherapy resistance in TNBC.¹⁷

2. Genomic and spatial multidimensional heterogeneity of the TNBC microenvironment

Before examining the regulatory role of the nervous system in microenvironmental remodeling, it is important to establish a baseline understanding of the macro-omics landscape and spatial heterogeneity inherent to the TNBC microenvironment. TNBC is not a monolithic clinical entity; rather, its intrinsic genomic instability and metabolic reprogramming serve as the fundamental endogenous drivers of microenvironmental diversity and subsequent immune evasion.

2.1 Large-scale multi-omics cohorts and molecular subtype reconstruction

The decoding of TNBC heterogeneity has advanced substantially by large-scale clinical multi-omics profiling. A landmark study of 465 Chinese TNBC patients from the Fudan University Shanghai Cancer Center (FUSCC) cohort provided an unprecedented map of the disease’s unique genetic landscape.²⁴ This analysis revealed that TNBC harbors an exceptionally high somatic mutation burden, with TP53 (74%) and PIK3CA (18%) identified as the predominant driver mutations.

Furthermore, the landscape is defined by pervasive copy number alterations (CNAs), including MYC amplification (81%) and PTEN deletion (58%). Notably, compared to Western cohorts (such as the TCGA database), Chinese patients exhibit a significantly higher frequency of PIK3CA mutations and copy number gains in the 22q11 chromosomal region, suggesting distinct ethnic genetic architectures and potential population-specific therapeutic targets.^{24,25}

Based on comprehensive transcriptomic signatures, TNBC has been categorized into four molecular subtypes with substantial clinical implications (Table 1). Each subtype represents a distinct biological state with a unique microenvironmental state and therapeutic sensitivity profile²⁴:

Among the subtypes, the BLIS and MES variants illustrate the dual challenge of “stromal hyperactivity” and “immune suppression” in TNBC. Within these tumor nests—characterized by a lack of effective immune-cell infiltration and encased in dense connective tissue—that the invasive and regulatory influence of the nervous system becomes particularly critical and pronounced.

2.2 Intratumor heterogeneity (ITH) and epigenetic immune evasion

Intratumor heterogeneity (ITH) represents another key driver of immune resistance.¹¹ Owing to its marked genomic instability, TNBC can generate a wide range of subclones throughout its spatiotemporal evolution. Recent mechanistic studies have revealed that epigenetic regulators act as key catalysts in this process.²⁶

For instance, the loss of the zinc finger protein ZNF689 has been identified as a key pathogenic factor driving ITH in TNBC. Under physiological conditions, the ZNF689–TRIM28 complex directly binds and epigenetically silences Long Interspersed Nuclear Element-1 (LINE-1), a highly active retrotransposon. However, the frequent loss of ZNF689 in TNBC leads to the pathological reactivation of LINE-1. The resulting retrotransposition exacerbates genomic fragmentation and recombination, directly triggering an explosive increase in ITH.²⁷

This marked heterogeneity effectively dilutes the concentration of clonal neoantigens and impairs the efficiency of antigen presentation via the major histocompatibility complex (MHC). Consequently, T cells fail to achieve effective tumor recognition, culminating in profound resistance to immunotherapy.²⁸

2.3 Microenvironmental metabolic deprivation within spatial topological networks

Beyond the interplay of genomic and epigenetic factors, single-cell morphological topological profiling (sc-MTOP) and spatial transcriptomics have further revealed a challenging landscape of “metabolic competition” within the TNBC microenvironment.^{17,29–32} Malignant cells do not only physically displace immune cells; they systematically deprive them of es-

sential nutrients. Research has demonstrated that TNBC cells leverage a highly expressed HEBP2/GSTP1 metabolic axis to secure a dominant advantage in amino acid uptake. Through this mechanism, malignant clones engage in a competition for glutamine against antitumor macrophages within localized microecological modules. The excessive consumption of glutamine by tumor cells drives the microenvironment toward a state of extreme scarcity. This metabolic deprivation directly triggers severe lipid peroxidation within macrophages, ultimately inducing widespread ferroptosis of these immune effectors.^{17,33}

In summary, before the immune system attempts to cross physical barriers and attack the tumor, it is already impaired at the levels of genomic antigen recognition and basic metabolic maintenance. This immunosuppressive network, woven from multidimensional heterogeneity, provides highly fertile ground for sensory nerve endings to further remodel the physical stroma and enforce a state of physical sequestration. Furthermore, emerging evidence indicates that infiltrating sensory nerve fibers may directly contribute to this metabolic competition. Beyond building physical barriers, neuromodulators released by sensory terminals can alter the metabolic behavior of both tumor cells and CAFs. For instance, nerve-derived signaling can upregulate lipid uptake and promote amino acid scavenging pathways in malignant clones. This neural-metabolic crosstalk not only sustains tumor cell survival under hypoxic stress but also intensifies the localized depletion of critical nutrients, further accelerating the metabolic collapse of tumor-infiltrating immune cells.^{34,35}

3. Sensory nerve topological dominance and active recruitment in TNBC

With the complex microenvironmental landscape of TNBC established, research has increasingly focused on a phenomenon previously undervalued in pathology: perineural invasion (PNI).³⁶ Conventional perspectives traditionally framed PNI as the passive diffusion of tumor cells along “paths of least resistance” provided by the nerve sheath. However, in-depth anatomical and molecular studies have fundamentally overturned this hypothesis. The nerve sheath—composed of the epineurium, perineurium, and endoneurium—is enriched with dense collagen and a resilient basement membrane, making it anything but a low-resistance pathway.^{37–39} Instead, the infiltration of tumor cells into nerves, coupled with the exuberant sprouting of nerve fibers into the tumor core, represents a highly active, bidirectional, and reciprocal chemotactic process.

3.1 The absolute anatomical dominance of nociceptive sensory terminals

Neural infiltration in solid tumors exhibits high tissue specificity. To precisely delineate the neural-distribution landscape in human TNBC, researchers conducted high-resolution multi-

plexed immunohistochemistry (mIHC) on tissue microarrays from extensive cohorts of invasive ductal carcinoma patients. By employing the pan-neuronal marker beta-tubulin in conjunction with transient receptor potential vanilloid 1 (TRPV1)—a marker highly specific for nociceptive sensory neurons responsible for transmitting noxious pain signals—studies have revealed a striking remodeling of the microenvironment.^{17,40,41}

In the physiological architecture of healthy mammary tissue, nerve fibers are strictly sequestered within well-defined nerve bundles. These healthy bundles are typically negative for the sympathetic marker tyrosine hydroxylase (TH), indicating that the normal mammary parenchyma is primarily innervated by highly organized sensory branches with minimal sympathetic input. However, upon oncogenesis, this orderly architectural structure is systematically disrupted. In TNBC tissue, sensory nerves escape the confines of the nerve bundles, dissociating into myriad delicate, highly branched individual terminals that infiltrate the entire tumor parenchyma like a extensive network.^{17,41,42}

3.2 The clinical prognostic paradox of sensory nerve infiltration

Neural infiltration in TNBC is a phenomenon with substantial clinical consequences. Through analysis of public TNBC transcriptomic datasets, researchers have observed a prognostic paradox that has important clinical implications. While high mRNA expression of TRPV1 (sensory nerves) and TH (sympathetic nerves) shows no statistically significant correlation with survival in the general breast cancer population, the landscape shifts dramatically when the analysis is strictly restricted to the highly aggressive TNBC subtype. Within this cohort, elevated expression of TRPV1 or TH is strongly and significantly correlated with accelerated disease progression, higher rates of lymph node metastasis, and dismal overall survival (OS).^{17,43}

Notably, the prognostic relevance of TRPV1 expression exhibits cancer-type specificity. In melanoma, sensory nerve activation has been shown to facilitate the recruitment of cytotoxic T cells, thereby correlating with improved survival. Conversely, in prostate cancer, pancreatic cancer, and specifically TNBC, high TRPV1 expression heralds an exceptionally poor clinical trajectory.^{20,44–47} This stark divergence strongly suggests that within the densified stromal microenvironment of TNBC, sensory nerves execute a distinct, potent pro-tumorigenic biological program.

Conversely, in prostate cancer and particularly in desmoplastic malignancies such as pancreatic ductal adenocarcinoma (PDAC), gastric cancer, and TNBC, high TRPV1 expression is associated with an exceptionally poor clinical trajectory. Notably, a brief comparison with PDAC and gastric cancers highlights the broad relevance of this axis. Similar to TNBC, pancreatic and gastric tumors are notoriously rich in

stroma and exhibit aggressive perineural invasion (PNI). In these malignancies, sensory nerves also utilize neuropeptide signaling to drive CAF activation and subsequent immune exclusion. This stark divergence across cancer types strongly suggests that within heavily densified stromal microenvironments, the neuro-stromal axis acts as a conserved, broad-spectrum driver of therapeutic resistance.^{48,49}

3.3 Extending the “seed and soil”: Tumor-derived NGF and the active recruitment network

Why does a tumor invest metabolic resources to recruit sensory innervation? This process originates from a “distress signal” emitted by malignant cells under microenvironmental stress. Under conditions of nutrient deprivation, hypoxia, or exposure to chemotherapeutic agents, TNBC cells generate an marked increase of reactive oxygen species (ROS).^{50–52} As an upstream signaling stimulus, ROS strongly activate the intracellular c-Jun signal transduction pathway. The activation of this pathway directly drives malignant epithelial cells to upregulate and secrete high concentrations of potent neurotrophins into the microenvironment, most notably nerve growth factor (NGF) and, to a lesser extent, brain-derived neurotrophic factor (BDNF).¹⁷

During embryonic development, NGF is responsible for guiding the survival and directed axonal outgrowth of neural crest-derived sensory and sympathetic neurons. In the pathological context of TNBC, the tumor appears to co-opt this developmental program.^{20,53} High-resolution spatial transcriptomics (stRNA-seq) at the single-cell level has precisely delineated the spatial landscape of NGF expression. Spatial proximity analysis reveals that NGF-high malignant cells are anatomically organized in dense circular clusters, primarily enriched at the invasive margins associated with perineural invasion (PNI).⁵⁴

Additional spatial trajectory inference (stRNA trajectory analysis) confirms a steep gradient of NGF expression, rising along a vector from the non-innervated tumor core toward the peripheral zones of neural invasion. This chemotactic gradient of NGF precisely engages high-affinity tropomyosin receptor kinase A (TrkA) receptors distributed on the terminals of nociceptive sensory neurons originating from the host’s dorsal root ganglia (DRG). The robust activation of the NGF–TrkA axis drives DRG sensory neurons to extend axons, which penetrate the interstitial spaces and aggressively grow into the tumor depths—a process termed axonogenesis. Both in vitro and in vivo experiments have irrefutably demonstrated that specific knockdown of the *Ngf* gene via shRNA in TNBC cells completely abolishes this neural chemotaxis, identifying tumor-derived NGF as the key “on-switch” for neural recruitment.^{54–58}

3.4 PlexinB3-mediated physical hijacking and accelerated metastasis

Once sensory nerve fibers infiltrate the tumor core, malignant

cells immediately initiate a second strategy of “physical hijacking”. To evaluate the direct contribution of sensory innervation to tumor progression in vivo, researchers performed orthotopic co-injection experiments in the mammary fat pads of NOD-SCID-gamma (NSG) immunodeficient mice, utilizing human TNBC cell lines (MDA-MB-231) and purified TRPV1+ primary sensory neurons isolated from mouse dorsal root ganglia (DRG).²⁰ Monitoring of orthotopic growth curves revealed no statistically significant difference in the volume or velocity of primary tumor growth between the co-injection group and the MDA-MB-231 monotherapy control. However, comprehensive necropsy at the experimental endpoint revealed a marked increase in the number of distal pulmonary metastatic nodules in the sensory nerve co-injection group.^{59,60}

To decipher this phenotype—where metastasis is promoted while primary proliferation remains unaffected—researchers established a two-dimensional in vitro co-culture model of TNBC cells and sensory nerve fibers. Long-term time-lapse live-cell imaging showed that TNBC cells are capable of acutely sensing and tightly adhering to ultra-fine sensory fibers. Subsequently, the cells utilize these fibers as natural, high-speed physical scaffolds, undergoing rapid, directional sliding and migration—a process termed perineural tracking. The velocity of this nerve-tethered migration far exceeds that of stochastic crawling on a standard culture surface, and even surpasses the migration rates of cells treated solely with neuronal-conditioned media. These findings clearly indicate that the pro-metastatic core of innervation lies in physical contact rather than mere paracrine signaling.^{21,41}

Species-specific RNA sequencing further defined the molecular signature governing this neuro-adhesion. Following co-culture with sensory nerves, TNBC cells exhibited marked upregulation of gene clusters associated with cytoskeletal rearrangement, adhesion, and directional migration. Among these activated genes, researchers precisely identified a critical transmembrane receptor: PlexinB.³ A member of the Semaphorin receptor family, PlexinB3 physiologically functions as an axon guidance molecule, regulating the construction of neural networks during the embryonic development of the central nervous system.^{61,62}

In TNBC, malignant cells overexpress PlexinB3, using it as a “molecular anchor” to firmly anchor onto ligands expressed on the surface of sensory nerve fibers. Functional validation showed that genomic knockout or silencing of *PLXNB3* in TNBC cells leads to a precipitous decline in neuro-adhesion and a complete loss of the ability to migrate directionally along nerve fibers.^{63,64} Thus, PlexinB3 has been established as the central mediator of nerve-dependent metastasis in TNBC. In this context, the nervous system is ingeniously co-opted by the tumor, reduced to a high-speed transit network for the systemic dissemination of malignant cells.^{20,65}

4. Evolution of stromal heterogeneity and construction of the dense ECM physical barrier

In triple-negative breast cancer (TNBC), sensory nerves serve not only as “highways” for metastasis; but also orchestrate a comprehensive remodeling of the extracellular matrix (ECM), forming a physical barrier against immune cell infiltration. The central effectors of this process are cancer-associated fibroblasts (CAFs).

4.1 Population diversity and pathological subtype differentiation of CAFs

CAFs represent the most abundant stromal cell population within the TNBC microenvironment, yet they are far from a homogeneous group. Single-cell RNA sequencing (scRNA-seq) has resolved this complex assembly into several functionally distinct subpopulations, primarily categorized as follows.¹⁷

The first group comprises the myofibroblastic CAFs (myCAFs), which are spatially localized in close proximity to the periphery of tumor nests. Characterized by high expression of alpha-smooth muscle actin (alpha-SMA) and an highly active biosynthetic state, myCAFs are the primary producers of various collagens (e.g., Type I Collagen) and fibronectin. They are directly responsible for the induction of desmoplasia within the microenvironment.^{66,67}

The second group comprises the inflammatory CAFs (iCAFs), typically situated in the deeper stroma at a distance from the tumor parenchyma. Rather than primarily synthesizing matrix, their primary role is to serve as the “secretory hub” of the microenvironment, secreting a suite of pro-inflammatory cytokines (such as interleukin-6) and chemokines that facilitate the recruitment and polarization of immunosuppressive cell populations.

The third group comprises the antigen-presenting CAFs (apCAFs), a recently identified rare subpopulation. Expressing MHC class II molecules (MHC-II) on their surface, apCAFs can present antigens to T cells and may participate in the induction of immune tolerance.^{68–71}

In highly aggressive TNBC, specific fibroblast activation protein (FAP)-positive subpopulations—such as CAF-S1, ecm-myCAF, and TGF-beta-myCAF—exhibit marked enrichment.⁷² Neurons and perineural Schwann cells play an important role in modulating the transitions between these CAF subsets.^{73,74} Emerging evidence suggests that sympathetic and vagal nerve branches, through the secretion of specific neurotransmitters, or Schwann cells via paracrine signaling, can force a phenotypic shift of CAFs toward a highly inflammatory iCAF state. This neuro-stromal axis coordinately drives the plastic transformation of tumor cells toward a more invasive basal-like phenotype, thereby accelerating systemic disease progression.⁷⁵

Importantly, sensory innervation does not act in isolation. The tumor ecosystem is shaped by a complex interplay of sensory,

sympathetic, and parasympathetic (vagal) inputs. While sensory nerves primarily drive matrix stiffening and immune exclusion via the CGRP axis, sympathetic nerves—releasing norepinephrine—can activate beta-adrenergic signaling to further promote iCAF polarization and angiogenesis. Conversely, parasympathetic inputs via acetylcholine often exert complex immunomodulatory effects, sometimes restraining inflammation but also contributing to tumor cell dissemination.^{76,77} Thus, the combined action of these distinct neural branches creates a synergistic, multidimensional network that accelerates TNBC progression and microenvironmental remodeling.

4.2 Collagen deposition and the mechanical barrier of spatial “immune exclusion”

These highly activated myCAFs do not only accumulate matrix components at random; instead, they construct of a rigorous mechanical barrier. High-resolution imaging via Masson’s trichrome and Picrosirius Red staining under polarized light microscopy reveals that in TNBC regions characterized by high-density perineural invasion (PNI) and intensive sensory nerve infiltration, stromal scores reach their zenith, representing the most severe pathological grades of desmoplasia.^{10,78,79}

Central to this process is the substantial synthesis of type I collagen by myCAFs.⁸⁰ However, the mere accumulation of collagen is insufficient to establish a functional barrier; its true pathological impact lies in the remodeling of the microarchitecture. myCAFs secrete high levels of the lysyl oxidase (LOX) family enzymes, which catalyze the biochemical cross-linking of collagen fibers. Furthermore, the high expression of Discoidin Domain Receptor 1 (DDR1) on the surface of tumor cells acts as a molecular “comb”, aligning disordered collagen fibers into highly parallel, densely packed “collagen bundles”.^{81,82}

This aberrantly dense and highly ordered cross-linked collagen network results in a marked increase in macro-scale matrix stiffness. At the microscopic scale, this structure functions as a physical barricade. As the primary effectors of anti-tumor immunity—cytotoxic CD8+ T cells, helper CD4+ T cells, and natural killer (NK) cells—extravasate from the vasculature and attempt to infiltrate the tumor core, they are physically intercepted, ensnared, and sequestered by this resilient collagenous web.⁸³

Histopathological evidence indicates that in these sensory nerve-rich, high-stiffness regions, the number of stromal tumor-infiltrating lymphocytes (sTILs) undergoes a “cliff-like” decline. Not only are scattered effector immune cells unable to penetrate the stroma, but tertiary lymphoid structures (TLSs) or lymphoid aggregates (LAs)—the microanatomical hallmarks of robust adaptive humoral immunity and localized immune maturation—are virtually absent in areas of neural invasion. This characteristic spatial phenotype, termed “im-

immune exclusion”, provides the fundamental physical basis for the primary resistance to PD-1 inhibitors observed in TNBC.^{10,84,85}

5. Mechanistic dissection: The neuropeptide CGRP-RAMP1 axis as a driver of the neuro-fibrotic network

How can thin sensory nerve endings, which occupy a negligible fraction of the total tissue volume, exert such substantial influence to mobilize fibroblasts to produce a massive collagenous matrix? Through high-throughput spatial transcriptomics (Visium HD stRNA-seq) and sophisticated 3D co-culture models, a precision molecular network has been identified. This “tripartite crosstalk” consists of tumor cells initiating “distress signals”, sensory nerves acting as “relay amplifiers”, and CAFs serving as the “ultimate effectors”. At the epicenter of this mechanism lies a neuropeptide known as calcitonin gene-related peptide (CGRP).¹⁷

5.1 Physiological origins of CGRP and its receptor complex

CGRP is a potent 37-amino acid vasodilatory neuropeptide. Under physiological conditions, it is primarily synthesized and released by TRPV1-positive nociceptors in response to noxious stimuli, such as tissue injury, extreme thermal fluctuations, or chemical insults.⁸⁶ CGRP plays an important role in maintaining homeostatic balance and regulating the hemodynamics associated with severe migraines. Furthermore, recent advances in neuro-immunology have revealed that sensory nerve fibers can even infiltrate the white pulp of the spleen; upon antigenic stimulation, they release CGRP to act directly on B cells within germinal centers, thereby enhancing humoral immune responses.⁸⁷

CGRP cannot directly penetrate the plasma membrane to exert biological effects; it must bind to a highly specific transmembrane receptor complex. This heteromeric complex comprises two principal subunits: the calcitonin receptor-like receptor (CALCRL) and its essential chaperone, receptor activity-modifying protein 1 (RAMP1), the latter of which dictates ligand affinity and specificity.⁸⁸

5.2 Molecular cascade of the nerve-CGRP-myCAF axis in collagen matrix remodeling

Within the TNBC microenvironment, DRG sensory nerve endings—recruited by tumor-derived NGF—may remain persistently depolarized and hyperexcitable, driven by the chronic stimulation of hypoxia and extracellular acidosis. These sustained electrophysiological impulses trigger the massive exocytosis of synaptic vesicles from nerve terminals, leading to the continuous effusion of supra-physiological concentrations of CGRP into the narrow interstitial fluid of the tumor.⁵⁰

In-depth analysis of spatial transcriptomic data has shown: throughout the heterogeneous and complex TNBC landscape,

RAMP1—the indispensable receptor component that dictates CGRP responsiveness—is not expressed ubiquitously. Instead, it exhibits exquisite cell-type specificity, with high-abundance expression localized almost exclusively to the plasma membrane of myofibroblastic CAFs (myCAFs), while remaining negligible in tumor epithelial cells or other stromal constituents.^{15,89}

This spatial ligand-receptor coupling activates a pathological neuro-fibrotic axis. Upon diffusion and binding of nerve-derived CGRP to the CALCRL-RAMP1 receptor complex on myCAFs, an intracellular signaling cascade is triggered. This involves G protein-coupled activation that leads to an exponential surge in the cytosolic second messenger, cyclic adenosine monophosphate (cAMP). These elevated cAMP levels promptly alleviate the inhibition of protein kinase A (PKA), allowing activated PKA to translocate into the nucleus. Here, it specifically catalyzes the hyperphosphorylation of the transcription factor cAMP-responsive element-binding protein 1 (CREB1) at key serine residues. Once activated, phosphorylated CREB1 (p-CREB1) directly recognizes and binds with high affinity to the promoter regions of core profibrotic genes, such as Col1a1, thereby robustly driving their transcription.^{40,90}

Driven by this CGRP-RAMP1-cAMP-PKA-CREB1 molecular cascade, fibroblasts—originally quiescent or metabolically stable—are effectively “reprogrammed” and maintained in an highly activated myCAF phenotype. These cells continuously secrete large quantities of collagen into the extracellular space, culminating in the macro-scale assembly of a dense collagenous barrier that physically sequesters CD8⁺ T cells from the tumor parenchyma. Furthermore, CGRP-activated myCAFs upregulate the secretion of pro-tumorigenic paracrine factors, including WNT5A and interleukin-6, establishing a feedback loop that sustains tumor cell survival, proliferation, and aggressive invasion.¹⁵

Beyond driving fibrotic encapsulation, the CGRP axis also contributes to microenvironmental remodeling by promoting neoangiogenesis through non-canonical, VEGF-independent pathways. As a potent vasodilator, CGRP can directly bind to RAMP1 receptors expressed on the surface of tumor-associated endothelial cells. This interaction rapidly stimulates endothelial cell proliferation, migration, and tube formation. Consequently, sensory nerves not only construct a physical barrier via CAFs but also secure structural and metabolic support for the tumor by establishing aberrant vascular networks, further complicating the therapeutic landscape.^{91,92}

5.3 Multidimensional neural suppression: CGRP-driven direct immune cell exhaustion

Sensory nerves do not only rely on CAFs to establish physical segregation; CGRP also can to bypass stromal barriers and exert direct inhibitory effects directly against immune cells. While RAMP1 is predominantly expressed by myCAFs

in the TNBC landscape, seminal parallel findings in other solid tumor models, such as melanoma and head and neck squamous cell carcinoma (HNSCC), demonstrate that a subset of tumor-infiltrating cytotoxic CD8⁺ T cells also upregulate the RAMP1 receptor on their surface.^{40,93}

The direct binding of high concentrations of neurogenic CGRP to RAMP1 on these T cells generates potent immunosuppressive signals that impair their cytotoxic degranulation capacity and significantly reduce the synthesis and release of interferon-gamma (IFN-gamma). More critically, chronic CGRP exposure accelerates deep epigenetic remodeling of the T cell transcriptome, irrevocably driving them toward a state of terminal functional exhaustion. This is further corroborated by clinical single-cell sequencing data: within tumor biopsies, CD8⁺ T cells expressing RAMP1 exhibit significantly more profound transcriptomic signatures of exhaustion compared to their RAMP1-negative counterparts. Consequently, the overexpression of RAMP1 on immune cells is tightly correlated with inferior clinical prognosis.^{94–96}

6. Frontiers in translational medicine: Multidimensional targeting of the neuro-ecosystem to reverse immune resistance

The importance of the nervous system within the tumor microenvironment also reveals a critical vulnerability in the oncogenic ecosystem. By pharmacologically intercepting this neuro-stromal network, it is possible to not only disrupt the dense physical collagen barriers at their source but also directly unleash the biological activity of T cells, thereby robustly sensitizing tumors to immune checkpoint blockade (ICB) therapy.

6.1 Drug repurposing: The translational potential of CGRP receptor antagonists

Among potential intervention strategies, one promising route for rapid clinical translation is “drug repurposing”, specifically targeting CGRP receptor antagonists—a class of drugs already clinically approved and safety-characterized in neurology for the treatment of migraine.⁹⁷

Given the central role of CGRP in migraine pathogenesis, decades of pharmaceutical research have culminated in the regulatory approval of several highly specific, small-molecule CGRP receptor (RAMP1/CALCRL complex) antagonists, collectively known as “gepants” (e.g., rimegepant, BIBN4096).^{87,98}

Recent studies have demonstrated the potential oncological value of these agents. In TNBC murine models, systemic administration of rimegepant allows the small-molecule antagonist to penetrate the tumor microenvironment and competitively occupy RAMP1 receptor sites on both myCAFs and exhausted CD8⁺ T cells with high affinity. This “receptor occupancy” effectively blocks the binding of neurogenic CGRP,

thereby interrupting the pathological cAMP-PKA-CREB1-mediated intracellular cascade.⁸⁷

Therapeutic evaluations in animal models have demonstrated monotherapy and combination efficacy. CGRP antagonism alone significantly downregulates the collagen-synthetic capacity of myCAFs, leading to a marked softening of the tumor tissue, which previously functioned as a mechanical barrier. Importantly, combining CGRP antagonists with anti-PD-1 monoclonal antibodies (ICB therapy) may yield a synergistic effect. By promoting the dissolution of physical barriers and restoring the vigor of effector cells, CGRP antagonists successfully convert “cold tumors”—previously refractory to PD-1 blockade—into highly sensitive “hot tumors”, resulting in substantial tumor regression. These findings provide the theoretical foundation and evidence-based support for upcoming early-phase clinical trials investigating the combination of “migraine medications and immune checkpoint inhibitors” for the treatment of resistant, high-stroma TNBC.^{40,87,98}

From a clinical translation perspective, optimizing the dosing schedule is important. Specifically, sequential dosing regimens—characterized by a ‘stromal priming’ lead-in phase using CGRP antagonists prior to ICB administration—may outperform simultaneous co-administration. Because the reversal of the dense neuro-fibrotic barrier requires adequate time for collagen degradation and extracellular matrix remodeling, a pretreatment window with agents like rimegepant would physiologically ‘soften’ the tumor. This sequential approach ensures that by the time anti-PD-1 antibodies are introduced and peripheral T cells are activated, the mechanical barricades have been disrupted, allowing for maximum intra-tumoral penetrance of cytotoxic effectors.⁴⁹

6.2 Diverse approaches to direct nerve ablation and chemical neuromodulation

Beyond the pharmacological blockade of downstream receptors, the clinical community is actively investigating upstream strategies to “disrupt” the neural communication networks within the tumor. By integrating local anesthesia or chemical neurolysis into interventional oncology, “denervation” may be achieved physically while limiting systemic adverse effects.

One prominent approach involves local chemical nerve ablation. Resiniferatoxin (RTX), a potent capsaicin analog, poses safety risks due to its neurotoxicity; however, it has demonstrated significant potential as a localized interventional agent.⁹⁹ Guided by ultrasound or CT, low doses of RTX can be precisely injected into the tumor core or adjacent to major peritumoral nerve trunks. This approach triggers acute calcium overload and irreversible apoptosis of local TRPV1⁺ nerve endings, effectively disrupting the intratumoral communication network. Similarly, Botulinum toxin (Botox)—famed for its ability to completely inhibit synaptic vesicle fusion and

the subsequent release of neurotransmitters (such as acetylcholine and CGRP)—has shown promise. Multipoint array injections of Botox around the tumor bed have been demonstrated to significantly delay disease progression in various malignancies, including TNBC and prostate cancer, while effectively increasing the density of regional T cell infiltration.^{54,100,101}

Another potential strategy uses electrophysiological blockade via long-acting local anesthetics. The application of long-acting amide-type local anesthetics, such as bupivacaine, can provide sustained blockade of voltage-gated sodium channels in peripheral nerves. By intercepting the conduction of neural action potentials, this method suppresses sensory nerve excitatory impulses and reduces CGRP effusion. These “oncological surgical nerve block” concepts offer a low-toxicity palliative or sensitizing therapeutic modality, particularly for advanced TNBC patients who may not tolerate intensive systemic chemotherapy.¹⁰²

6.3 Combinatorial strategies targeting the multidimensional heterogeneity of the microenvironment

The inherent complexity of the TNBC microenvironment suggests that single-target interventions may be susceptible to secondary resistance. Consequently, the future therapeutic strategies may need to be an ecosystem-based, multidimensional combinatorial approach that integrates neural targeting with stromal and metabolic modulation.

First, collagen alignment can be disrupted (Stromal Targeting). While CGRP antagonists are employed to inhibit de novo collagen synthesis, the simultaneous application of monoclonal antibodies against DDR1 (Discoidin Domain Receptor 1) may be used. Since DDR1 is responsible for the parallel alignment and “combing” of collagen fibers, neutralizing this receptor transforms the tumor stroma from a “rigid, organized brick wall” into a “loose, disordered sediment”, thereby creating mechanical openings in the topological defense line for CD8⁺ T-cell infiltration.

Second, metabolic deprivation can be reversed (Metabolic Targeting). To counteract the aggressive metabolic competition in which TNBC cells overexpress HEBP2/GSTP1 to sequester glutamine—thereby inducing ferroptosis in immune cells—small-molecule inhibitors of GSTP1 may be applied. By disrupting these metabolic pathways, glutamine levels within the microenvironment can be restored, preserving the basal survival and metabolic fitness of antigen-presenting macrophages and effector T cells within the hostile niche.

In summary, using the “neurogenic CGRP-RAMP1 axis” as a primary point of intervention, supplemented by “DDR1-mediated stromal deconstruction” and “GSTP1-driven metabolic remodeling”, and further integrated with “PD-1 immune checkpoint blockade”, may constitute a synergistic, multi-pronged therapeutic regimen. This multidimensional approach may represent a future direction in disrupting the for-

midable barriers of immune resistance in triple-negative breast cancer.

7. Limitations of this review

Although this review systematically outlines the neuro-stromal-immune axis, several limitations must be acknowledged. First, most mechanistic insights—particularly concerning the CGRP-RAMP1 interaction—are derived from murine models and in vitro co-culture systems, which may not fully recapitulate the complexity of the human TNBC ecosystem. Second, the current lack of non-invasive, dynamic in vivo spatial tracking technologies limits our understanding of the exact spatiotemporal sequence of nerve infiltration versus matrix stiffening. Finally, while repurposing CGRP antagonists shows immense preclinical promise, their systemic effects on normal neuro-immune physiology during long-term oncological treatment require further robust clinical validation.

8. Perspectives: Toward an Era of ecosystem-based precision medicine

These mechanistic findings support the nervous system as a central regulatory hub of the tumor microenvironment. Neuro-dependent “denervation” strategies—particularly the repurposing of CGRP receptor antagonists—show substantial potential to reverse resistance through “mechanical deconstruction” and “immunosenitization”. Future research should focus on translating these insights into practice. By implementing integrated therapeutic strategies encompassing neural blockade, stromal deconstruction, metabolic remodeling, and immune activation, researchers may be able to target the TNBC ecosystem. Such approaches may help overcome current therapeutic bottlenecks and offer renewed hope for patients with this highly aggressive subtype.

9. Conclusions

In conclusion, this review highlights the “neuro-stromal-immune axis” as a key driver of immunosuppression in TNBC. Stressed tumor cells secrete NGF to actively recruit sensory nerves, which subsequently release the neuropeptide CGRP. This neural signaling strongly activates RAMP1 on myCAFs, triggering a cAMP-PKA-CREB1 cascade that promotes dense collagen deposition and forms a physical barrier against immune infiltration. Simultaneously, direct CGRP signaling drives functional exhaustion in infiltrating T cells. Targeting this neuro-fibrotic network via CGRP receptor antagonists may provide a potential therapeutic strategy. Targeting this vulnerability offers an important opportunity to remodel the desmoplastic microenvironment, potentially reversing primary resistance to immune checkpoint blockade and improving outcomes in TNBC.

Declarations

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Conflict of interest

The author declares no conflicts of interest related to this work.

Author contributions

CG is the sole author of the manuscript.

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Figures and Tables

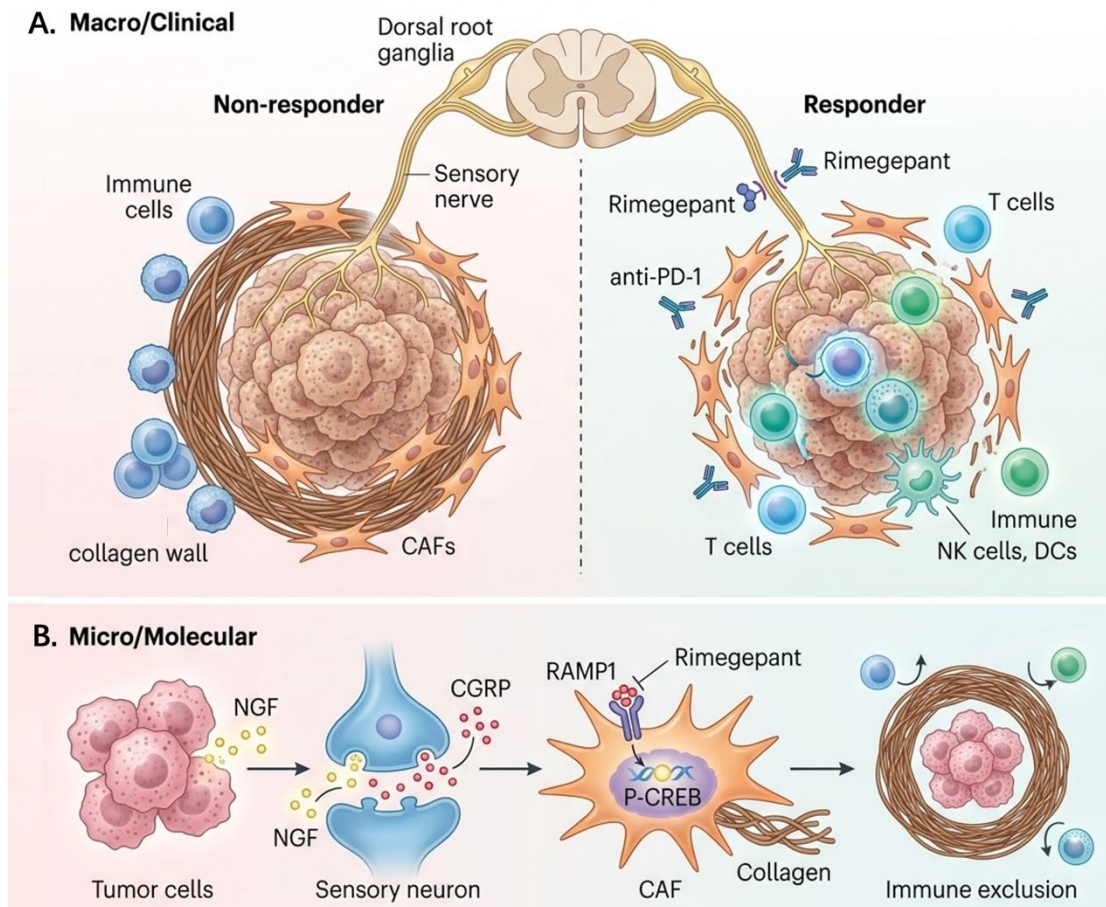


Fig. 1. The neuro-stromal-immune axis drives spatial immune exclusion and can be pharmacologically reversed via CGRP antagonism. (a) Macro/clinical landscape: In the immunotherapy-resistant state (Non-responder, left), sensory nerves from the dorsal root ganglia (DRG) innervate the tumor microenvironment. These neural networks activate cancer-associated fibroblasts (CAFs) to construct a dense collagen wall, creating a physical barrier that prevents immune cell infiltration (immune exclusion). In contrast, targeted intervention (Responder, right) with the CGRP receptor antagonist (Rimegepant) combined with anti-PD-1 blockade effectively dismantles this fibrotic shield, restoring robust intratumoral infiltration of effector immune cells, including T cells, natural killer (NK) cells, and dendritic cells (DCs). (b) Micro/molecular mechanisms: The intercellular signaling cascade underlying the neuro-fibrotic network. Malignant tumor cells secrete nerve growth factor (NGF) to actively recruit sensory neurons. Upon activation, these sensory nerve endings release the neuropeptide calcitonin gene-related peptide (CGRP), which binds to the RAMP1 receptor expressed on CAFs. This ligand-receptor interaction triggers downstream intracellular signaling, leading to the phosphorylation of CREB (P-CREB). Activated P-CREB robustly drives collagen synthesis and extracellular matrix deposition, culminating in physical immune exclusion. Systemic administration of Rimegepant competitively blocks the CGRP-RAMP1 interaction, severing the pathogenic communication between nerves and the stroma to overcome immunotherapy resistance. CREB, cAMP-responsive element-binding protein; P-CREB, phosphorylated cAMP-responsive element-binding protein; PD-1, programmed death-1; RAMP1, receptor activity-modifying protein 1.

Table 1. Molecular classification of TNBC and its microenvironmental and therapeutic heterogeneity

Molecular subtype	Core multi-omics and pathological features	Microenvironmental state and potential therapeutic strategy
Immunomodulatory (IM)	Pronounced enrichment of immune-related gene sets; robust antigen presentation activity.	Characterized by high levels of tumor-infiltrating lymphocytes (TILs) and active immunosurveillance. This subtype represents the optimal candidate group for immune checkpoint blockade (e.g., anti-PD-L1).
Basal-like (BLIS)	High homologous recombination deficiency (HRD) scores; profound cell cycle dysregulation	Exhibits a classic “immune-excluded” or “immune-desert” phenotype, lacking effective effector cell infiltration. Highly aggressive biological behavior; sensitive to platinum-based agents and PARP inhibitors.
Luminal androgen receptor (LAR)	Enriched for <i>PIK3CA</i> and <i>ERBB2</i> mutations, often accompanied by <i>CDKN2A</i> loss	Marked by androgen receptor (AR) expression and aberrant lipid metabolism. Generally resistant to immunotherapy but may derive clinical benefit from AR antagonists or CDK4/6 inhibitors
Mesenchymal-like (MES)	Aberrant activation of the JAK/STAT3 signaling pathway; high expression of epithelial-mesenchymal transition (EMT) markers	Enriched for cancer stem cell (CSC) properties with a high proportion of stromal cells (e.g., fibroblasts). Characterized by active proangiogenic signaling and high metastatic potential; STAT3 inhibitors represent a potential exploratory strategy

CSC, cancer stem cell; EMT, epithelial-mesenchymal transition; HRD, homologous recombination deficiency; JAK/STAT3, Janus kinase/signal transducer and activator of transcription 3; PARP, poly(ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; TILs, tumor-infiltrating lymphocytes; TNBC, triple-negative breast cancer.