Novera

Commentary

Rewiring the tumor microenvironment: sensory neurons as architects of immune exclusion in triple negative breast cancer

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The landscape of immunotherapy in triple negative breast cancer has evolved rapidly, yet a persistent clinical paradox remains. While immune checkpoint blockade has demonstrated meaningful benefit in selected patients, a substantial proportion fail to respond or develop early resistance [1]. This discrepancy cannot be fully explained by tumor intrinsic genomic features or checkpoint molecule expression alone. Increasingly, attention has shifted toward the tumor microenvironment as a determinant of therapeutic success or failure. In this context, the recent study by Zhang and colleagues provides a compelling conceptual advance by placing sensory neurons at the center of immune exclusion in triple negative breast cancer [2].

Traditionally, neural components in cancer have been viewed either as passive structures invaded by tumor cells or as contributors to metastatic dissemination [3]. The idea that neurons might actively orchestrate stromal and immune architecture has received far less attention, particularly in breast cancer. Zhang et al. challenge this perspective by demonstrating that sensory innervation is not only prevalent but dominant within the triple negative breast cancer microenvironment. More importantly, the presence of perineural invasion correlates with worse clinical outcomes, increased fibrosis, and diminished immune infiltration. These observations are strengthened by multi cohort validation and by mechanistic interrogation in several in vivo models. Sensory neuron activation enhances tumor growth, expands cancer associated fibroblast populations, and reduces infiltration of multiple immune cell subsets, whereas genetic or pharmacologic ablation of these neurons reverses these features.

What distinguishes this work is not merely the identification of a correlation between nerves and poor prognosis, but the delineation of a functional axis that links tumor cells, neurons, fibroblasts, and immune exclusion. The authors show that tumor derived nerve growth factor acts as a key upstream signal that activates sensory neurons. These neurons in turn release calcitonin gene related peptide, a neuropeptide with well characterized roles in nociception but less explored functions in tumor biology. The downstream effects of this signal are not exerted directly on tumor cells but are instead mediated through cancer associated fibroblasts, which emerge as the primary recipients of neuronal input.

This shift in focus toward fibroblasts is particularly important. In many solid tumors, including triple negative breast cancer, fibroblasts are increasingly recognized as major regulators of extracellular matrix composition and immune accessibility. Zhang et al. demonstrate that sensory neuron derived signals preferentially drive fibroblasts toward a myofibroblastic phenotype characterized by elevated alpha smooth muscle actin expression and enhanced collagen production. The resulting dense extracellular matrix, especially enriched in type I collagen, forms a physical and biochemical barrier that limits immune cell infiltration. Rather than suppressing immune function directly, the neural stromal axis effectively prevents immune cells from reaching their targets.

This spatial dimension of immune evasion is an important conceptual advance. Many current frameworks for understanding immunotherapy resistance focus on molecular signaling pathways within tumor or immune cells. However, the ability of cytotoxic lymphocytes to access tumor nests is a prerequisite for any downstream effector function. By demonstrating that sensory neurons indirectly restrict this access through fibroblast mediated matrix remodeling, the study highlights a mechanism of immune exclusion that operates upstream of canonical immune checkpoints.

At the mechanistic level, the identification of the CGRP RAMP1 signaling axis in fibroblasts provides a clear molecular entry point [4]. The receptor component RAMP1 is shown to be selectively enriched in cancer associated fibroblasts, particularly in the myofibroblastic subset. Activation of this receptor triggers a cAMP dependent signaling cascade involving protein kinase A and CREB1, ultimately leading to transcriptional upregulation of extracellular matrix related genes such as COL1A1 and FN1. This pathway neatly connects neuronal signaling to structural remodeling of the tumor microenvironment.

One of the most attractive aspects of this work is its immediate translational relevance. CGRP inhibitors such as rimegepant are already approved for the treatment of migraine and have well characterized safety profiles. Zhang et al. demonstrate that pharmacologic inhibition of the CGRP RAMP1 axis reduces collagen deposition, decreases fibroblast activation, and enhances immune cell infiltration in murine models. When combined with anti PD 1 therapy, this approach produces a synergistic antitumor effect. This finding suggests that targeting the neural stromal interface could convert immunologically cold tumors into more responsive ones.

From a precision medicine perspective, the implications are significant. Current patient stratification strategies for immunotherapy in triple negative breast cancer rely heavily on PD-L1 expression, tumor infiltrating lymphocyte levels, and, to a lesser extent, genomic features. These markers provide an incomplete picture, particularly in tumors where immune exclusion is driven by structural barriers rather than intrinsic immune dysfunction. The observation that CGRP expression correlates with poor prognosis and reduced immune infiltration raises the possibility that neural signatures could serve as complementary biomarkers. Although the clinical data presented are preliminary, they point toward a future in which patients are stratified not only by immune activation status but also by the presence of neuro stromal programs that shape tissue architecture.

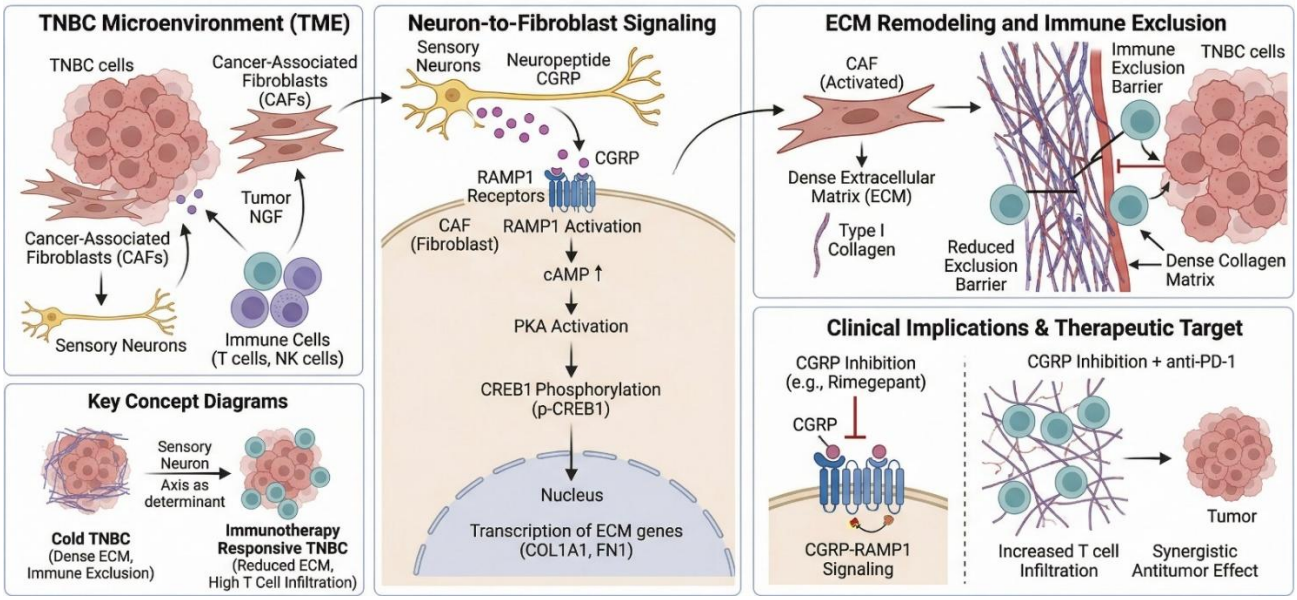

Figure 1. This graphical abstract summarizes a sensory neuron–fibroblast–immune axis that drives immune exclusion in triple-negative breast cancer (TNBC). In the TNBC tumor microenvironment, tumor-derived NGF activates sensory neurons, which release CGRP. CGRP signals through RAMP1 receptors on cancer-associated fibroblasts (CAFs), triggering a cAMP–PKA–CREB pathway that induces transcription of extracellular matrix genes (e.g., COL1A1, FN1). This drives fibroblasts toward a myofibroblastic, collagen-producing state, leading to dense ECM remodeling. The resulting collagen-rich matrix forms a physical and biochemical barrier, limiting T cell infiltration and promoting an immune-excluded ("cold") tumor phenotype associated with poor immunotherapy response. Therapeutically, CGRP inhibition (e.g., rimegepant) disrupts this axis, reduces fibrosis, enhances immune infiltration, and synergizes with anti–PD-1 therapy, suggesting a strategy to convert immune-excluded TNBC into immunotherapy-responsive tumors.

The study also prompts a broader reconsideration of how different components of the tumor ecosystem interact. The tumor microenvironment is often conceptualized as a collection of discrete cell types, each contributing independently to disease progression. In contrast, the neural fibroblast axis described here illustrates a coordinated network in which signals from one compartment reshape the behavior of another, with downstream consequences for immune surveillance. This systems level view aligns well with emerging approaches in spatial biology, which emphasize the importance of cellular proximity and physical organization.

Despite its strengths, several questions remain. The spatial transcriptomic analysis, while informative, is derived from a limited number of samples, and it remains unclear how universally this neural stromal axis operates across the heterogeneous landscape of triple negative breast cancer. The degree to which different molecular subtypes of TNBC exhibit similar patterns of innervation and fibroblast activation warrants further investigation. Additionally, while CGRP inhibition appears promising, the broader physiological roles of this pathway raise potential concerns. CGRP is involved in vascular regulation, mucosal homeostasis, and hematopoietic processes, suggesting that systemic inhibition could have unintended effects, particularly in combination with immunotherapy.

Another consideration is the temporal dimension of this axis. The current study focuses largely on primary tumor models, leaving open the question of whether similar mechanisms operate in metastatic sites. Given that extracellular matrix remodeling and immune exclusion are also hallmarks of metastatic progression, it is plausible that neural inputs continue to play a role, but this remains to be demonstrated. Furthermore, the interaction between sensory neurons and other neural subtypes, such as sympathetic or parasympathetic fibers, may add additional layers of complexity that are not fully captured in the present work.

The clinical translation of these findings will require careful validation in prospective studies. The use of an already approved drug such as rimegepant lowers the barrier to clinical testing, but identifying the patient population most likely to benefit will be critical. Biomarker driven trial designs incorporating CGRP or RAMP1 expression, along with spatial metrics of collagen density and immune infiltration, may provide a rational path forward.

In summary, the work by Zhang and colleagues represents an important step toward integrating neural biology into the framework of cancer immunology. By demonstrating that sensory neurons can actively shape the tumor microenvironment through fibroblast activation and extracellular matrix remodeling, the study provides a mechanistic explanation for immune exclusion in a subset of triple negative breast cancers. It also highlights a therapeutically actionable pathway that could enhance the efficacy of existing immunotherapies. For the field of precision oncology, the key insight is that effective treatment strategies must account not only for tumor cell intrinsic features but also for the structural and signaling networks that govern immune access. In this regard, the neural stromal axis described here offers both a new lens through which to view tumor biology and a promising target for intervention.

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Author Contributions

Z.G. and J.C. conceived the initial concept for this manuscript. Z.G., H.C. and J.C. wrote the first draft of the manuscript, which was revised by all authors. All authors contributed to and approved the manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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