



Astrocytes and Microglia Regulate Opioid Receptor-Driven Cancer Brain Metastasis and Neural Injury: Remodeling the Brain Microenvironment

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Abstract: Brain metastasis is a common complication in the progression of multiple solid tumors and is associated with poor prognosis. Its occurrence is not determined solely by the intrinsic invasiveness of tumor cells. After tumor cells enter the central nervous system (CNS), their survival and expansion largely depend on the brain microenvironment. Circulating tumor cells (CTCs) must first cross the blood-brain barrier (BBB). They then encounter a defensive microenvironment centered on reactive astrocytes and disease-associated microglia. This “colonization bottleneck” prevents most disseminated cells from surviving. Under tumor-derived stimulation, neuroglial cells undergo functional reprogramming. They shift from a predominantly restrictive state to a tumor-supportive adaptive state. This shift involves amplified inflammation, enhanced immunosuppression, and altered metabolic coupling, which together reshape the metastatic niche in the brain. At the same time, disruption of microenvironmental homeostasis affects neuronal survival. This links brain metastasis with neuronal injury. Opioid receptors (ORs) are functionally expressed in astrocytes and microglia. Their activation regulates inflammatory responses, metabolic states, and immune signaling networks. They may serve as key signaling nodes that control functional shifts in neuroglial cells. Opioid receptor signaling does not directly drive tumorigenesis. Instead, it likely resets how neuroglial cells respond to external perturbations. This process amplifies brain microenvironmental dysregulation. As a result, it indirectly promotes brain metastatic colonization and aggravates neuronal injury. In summary, brain metastasis results from long-term interactions between tumor cells and the brain microenvironment. Elucidating glia-mediated selection mechanisms and their regulatory nodes will deepen the understanding of the biological nature of brain metastasis.

Keywords: brain metastasis, astrocytes and microglia, microenvironmental dysregulation, opioid receptor signaling, neural injury

Introduction

Brain metastasis from cancer typically occurs at late stages of malignant tumor progression and is one of the most destructive complications in current clinical practice, with extremely high difficulty of intervention.¹ Its occurrence is often accompanied by progressive neurological dysfunction, a marked decline in quality of life, and poor long-term prognosis.^{2–5} Unlike common metastatic target organs such as the lung, liver, or bone, the formation of brain metastasis cannot be simply attributed to increased intrinsic invasiveness or enhanced circulatory dissemination of tumor cells. Instead, it largely depends on the selective constraints and remodeling capacity of the highly specialized microenvironment of the CNS.⁶ The structural integrity of the BBB, a glucose-centered metabolic pattern, and unique immune regulatory features together impose strong constraints on incoming tumor cells. These factors make the brain one of the most selective target organs in the metastatic cascade.^{7–9}

For a long time, brain metastasis was considered the result of abnormal proliferation of tumor cells after crossing the BBB. However, accumulating basic and translational studies indicate that this process is not a single “tumor cell-driven event,” but

rather a multicellular, coordinated process centered on dynamic remodeling of the brain microenvironment.⁹ In this context, glial cells, especially astrocytes and microglia, have been increasingly recognized as critical regulatory units during metastatic colonization.¹⁰ As key regulators of neural homeostasis, these cells initially restrict disseminated tumor cells through inflammation, phagocytosis, and barrier functions.¹¹ Accumulating evidence indicates that this process is not solely tumor cell-driven. Instead, it is a coordinated multicellular process involving dynamic remodeling of the brain microenvironment.

Notably, this imbalance in the brain microenvironment does not only support tumor colonization. It also serves as an important pathological basis for neuronal injury and neurological dysfunction.¹² Sustained amplification of neuroinflammation, disruption of metabolic homeostasis, and weakening of BBB function act in combination. They are considered key mechanisms underlying the progressive worsening of neurological symptoms in patients with brain metastasis.¹³ However, based on current research, the regulatory hub linking “brain metastasis-microenvironmental dysregulation-neuronal injury” has not been systematically integrated. The causal chain and key nodes remain insufficiently defined.

ORs are a class of G protein-coupled receptors that are widely expressed in the CNS. They have long been regarded as key regulators of pain perception.^{14,15} However, accumulating evidence indicates that ORs also participate in the regulation of inflammatory responses and the shaping of neuroglial cell functions. They exert multi-level roles in maintaining neural microenvironmental homeostasis.¹⁶ According to receptor subtypes, ORs are classified into μ (MOR), δ (DOR), and κ (KOR). MOR is most abundantly expressed in the CNS. DOR and KOR are functionally expressed in astrocytes and microglia and participate in processes such as inflammatory responses.^{17–19} Under physiological conditions, transient activation mediated by endogenous opioid peptides helps limit excessive inflammation and maintain neural homeostasis. However, under chronic stimulation or sustained exposure to exogenous opioid agonists, OR signaling becomes biased. This shift leads to amplified neuroglial inflammation, metabolic alterations, and immune imbalance.^{20,21} This subtype-dependent signaling is not simply “pro-inflammatory” or “anti-inflammatory.” Instead, it may reshape the functional spectrum of glial cells and alter brain microenvironmental homeostasis. In tumor research, OR signaling can influence the tumor microenvironment and indirectly regulate tumor progression and metastasis. Some studies suggest that MOR activation affects tumor-associated inflammation and immune cell function.²² However, in the context of brain metastasis, it remains unclear whether ORs regulate neuroglial cell states, amplify brain microenvironmental dysregulation, and promote metastatic colonization. Systematic integration is lacking. Based on this gap, an overlooked question emerges: in the specific context of brain metastasis, could ORs act through modulation of neuroglial functional states as intermediate factors, thereby amplifying brain microenvironmental dysregulation, exacerbating neuronal injury, and promoting metastatic colonization and progression?

Based on existing evidence, we propose that ORs serve as key signaling nodes linking neural homeostasis regulation and tumor microenvironment remodeling. They may bias the functional states of neuroglial cells, thereby amplifying the vicious cycle of “microenvironmental dysregulation-pro-tumor growth-neuronal injury” during brain metastasis. Under certain conditions, this process may further accelerate the initiation and progression of brain metastasis from cancer. This review is based on a comprehensive survey of relevant literature in the PubMed and Web of Science databases, focusing on the keywords “brain metastasis,” “neuroglial cells,” “ORs,” and “tumor microenvironment,” and integrates and summarizes research progress over the past 20 years (2006–2026). On this basis, we propose that this vicious cycle may involve several key components, including: (1) mechanisms of brain microenvironment remodeling mediated by neuroglial cells during metastatic colonization; (2) the roles of ORs in regulating neuroglial inflammation, metabolism, and immune functions; and (3) how opioid receptor imbalance links microenvironmental dysregulation with neuronal injury in the context of brain metastasis, thereby providing a theoretical basis for intervention strategies targeting the neuro-tumor microenvironment axis.

Brain Metastatic Colonization: A Selective Process Centered on the Brain Microenvironment

From the overall framework of the metastatic cascade, brain metastasis is not the passive endpoint of tumor cell dissemination but a highly selective colonization event. Even if CTCs successfully traverse the BBB, the vast majority are still eliminated at early stages within the brain and fail to form stable metastatic lesions^{23,24} (Figure 1). Definitions of relevant terms are provided in the Brief Glossary (Table 2).

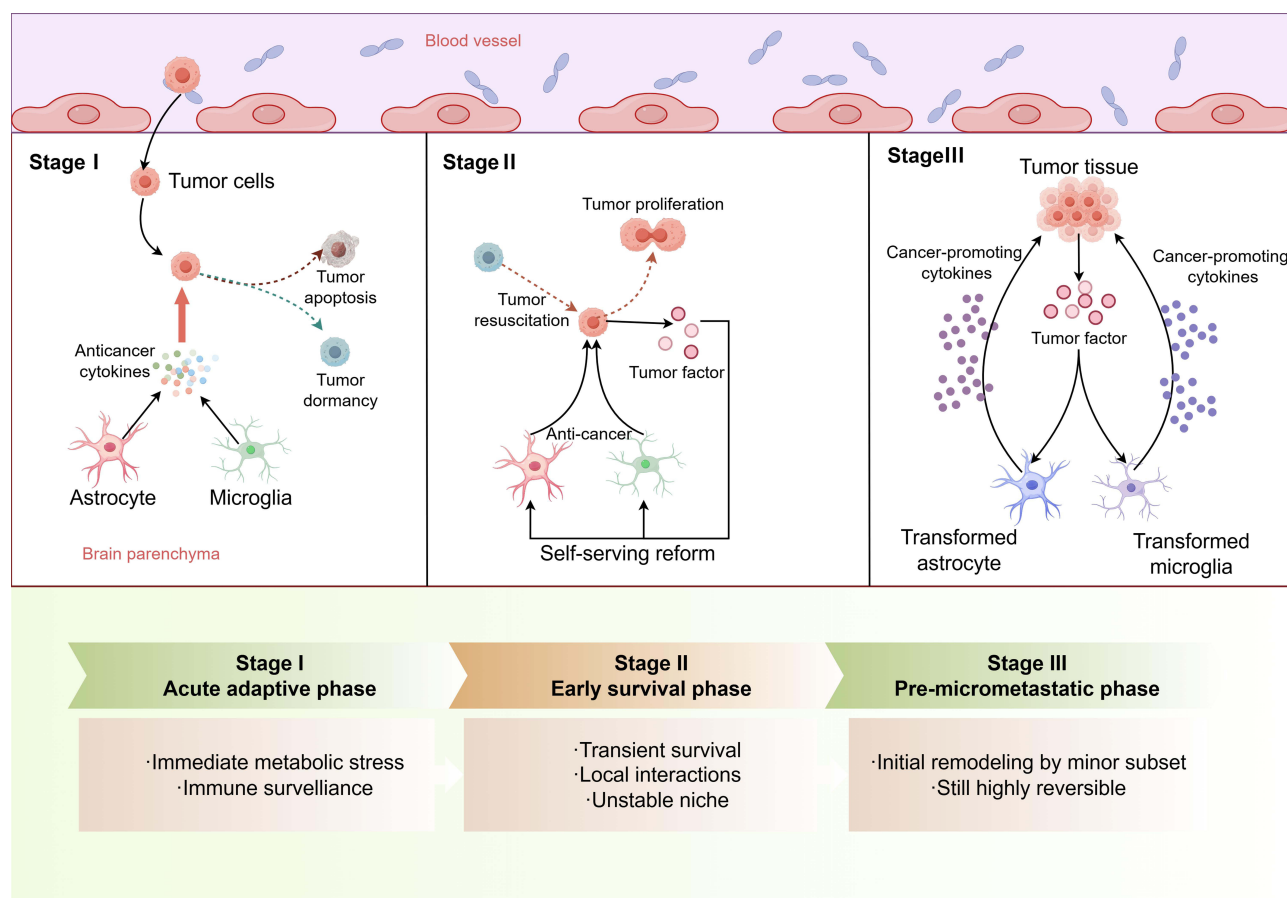


Figure 1 Brain Microenvironmental Dysregulation and the Formation of Tumor Metastasis (By Figdraw). Traversal of the BBB alone is insufficient to achieve brain metastasis, as disseminated tumor cells undergo multi-stage selection within the brain. In the initial stage (Stage I), metabolic and immune pressures create a colonization bottleneck. Subsequently (Stages II–III), surviving cells must acquire tolerance to the microenvironment or actively remodel it within an unstable niche. This process is inefficient and exhibits a degree of reversibility. Astrocytes and microglia continuously participate in regulating this selection process across different stages.

During the immune clearance phase, that is, the “earliest stage” after CTCs enter the brain parenchyma, neuroglial cells predominantly exhibit a restrictive program. Astrocytes and microglia can rapidly sense the invasion of tumor cells and form the first line of defense against disseminated tumor cells through the release of pro-inflammatory factors, phagocytic activity, and enhancement of local barrier functions.^{25,26} For CTCs, this abruptly altered microenvironment imposes substantial survival pressure. They must rapidly adapt to this entirely new environment; otherwise, they face elimination. As a result, a large proportion of CTCs are cleared at this stage or are forced into a dormant state.^{27–29} From this perspective, the key determinant of brain metastatic colonization is not whether tumor cells enter the brain tissue, but whether they possess the capacity to remodel and “educate” the neuroglia-dominated brain microenvironment. This constitutes the immediate stress response and the first round of selection following CTCs traversal of the BBB.

CTCs that survive the initial stage can persist only transiently and have not yet acquired stable and sufficient survival support. Tumor cells then enter the early phase of immune equilibrium. At this stage, they have not established robust immune evasion mechanisms and cannot effectively resist recognition and attack by the host immune system.³⁰ Accordingly, the surrounding microenvironment remains hostile and suppressive, with limited support for proliferation. The overall survival state is therefore highly unstable. During this phase, tumor cells begin to influence the local environment through progressive interactions and initiate adaptive remodeling. Some early anti-tumor signals may undergo functional transition. For example, sustained type I interferon signaling can induce CCL2 and recruit monocyte-derived myeloid cells. This process gradually weakens immune clearance and lays the foundation for the subsequent establishment of an immunosuppressive environment.²⁶

With continued remodeling of the local microenvironment, a small subset of tumor cells gradually acquires more favorable survival conditions and enters an active remodeling phase within immune equilibrium. For example, astrocytes in the brain can be induced to shift from a tumor-suppressive phenotype to a tumor-promoting phenotype, while the phagocytic and cytotoxic functions of microglia are concurrently suppressed. Tumor cells may also initiate metabolic reprogramming to acidify the brain microenvironment, thereby supporting their own survival, or promote the formation of neovascular networks to sustain colonization.^{9,31,32} At this stage, the microenvironment has undergone initial remodeling but remains reversible, thereby laying the foundation for subsequent tumor expansion.

This process also indicates that the brain microenvironment has features distinct from those of peripheral tissues, imposing additional selective pressure on tumor cells. Existing evidence suggests that brain tissue relies predominantly on glucose metabolism, and its tight metabolic coupling may limit the rapid adaptation of incoming cells, thereby constituting a form of metabolic “selection.” At the same time, immune surveillance in the brain is primarily mediated by microglia and astrocytes. Although these cells can exert clearance functions at early stages, some studies indicate that they may undergo functional transitions under sustained stimulation.^{33,34} In addition, the strict regulation of the BBB not only restricts the entry of most cells but also provides a relatively isolated growth environment for tumor cells that have already colonized, enabling further adaptation to the local niche.

Taken together, these factors indicate that brain metastasis is not a purely passive process, but a highly selective colonization event regulated by multiple microenvironmental factors. Although some evidence is derived from studies of central inflammation unrelated to brain metastasis or from peripheral tumor microenvironments, these models share common features in inflammatory states and patterns of glial activation, and thus provide informative references for understanding the functional consequences of inflammatory responses.

Remodeling of Neuroglial Functional States and Their Roles in Brain Metastasis-Related Processes

Under physiological conditions, glial cells maintain relatively stable functional states. They contribute to neural network homeostasis by coordinating inflammatory responses, energy metabolism, and support of synaptic structure and function.^{10,35–37} However, when the CNS is exposed to pathological stimuli, neuroglial responses are not simply “activation” or “suppression.” Their functional states exhibit marked heterogeneity and change dynamically with the nature and duration of the stimuli.³⁸ Transient acute stimuli typically induce defensive and protective states. In contrast, when inflammatory signals persist, metabolic burden continues to increase, or tumor-associated factors exert sustained effects, the functional balance among different glial cell subsets is gradually disrupted, and cellular states shift in a directional manner.³⁹ During this process, neuroglial cells transition from maintainers of homeostasis to key executors that drive pathological progression, thereby creating conditions that support intracranial tumor colonization and expansion.

Early Stage of Brain Metastasis: Reactive Gliosis and Neuroinflammation

During the micrometastatic stage of brain metastasis, neuroglial cells typically first exhibit a defensive activation state. Studies have shown that 2–4 weeks after resection of primary melanoma tumors, the characteristic marker of reactive astrocytes, GFAP, is upregulated.⁴⁰ This proliferative response occurs well before the formation of metastatic lesions, indicating that astrocytes are early responders in the metastatic cascade. At this stage, focal neuroinflammatory responses can be induced, and by enhancing BBB integrity and restricting nutrient diffusion, an unfavorable survival environment for tumor cells is established.⁴¹ Disease-associated microglia participate in the early clearance of tumor cells through phagocytosis and antigen presentation. The coordinated actions of these two cell types maintain a predominantly anti-tumor microenvironment characterized by inflammation and immune defense.⁴² The glial response at this stage essentially serves the maintenance of neural homeostasis.

Under Sustained Stimulation: Changes in Glial Cell States and Characteristics of the Immune Microenvironment

Under such sustained stimulation, the functional states of neuroglial cells gradually shift and drive the reconstruction of the central microenvironment. Existing studies indicate that, in the context of chronic inflammation, metabolic stress, and prolonged intercellular signaling, astrocytes and microglia can transition from defensive phenotypes to states that support tumor survival and expansion. This transition is typically characterized by biased amplification of inflammatory responses, enhanced immunosuppressive signaling, and adaptive support for tumor metabolic demands.

For example, astrocytes can be recruited to brain metastases by Reelin secreted from lung cancer cells and can secrete pro-survival factors such as SERPINE1 to support the growth of small cell lung cancer. They can also activate the EGFR pathway through secretion of IL-11 to increase PD-L1 expression, while IL-11 binding to its intrinsic receptor further facilitates tumor immune evasion.^{43,44} A more conservative interpretation is that this “pro-tumor” shift does not represent a complete loss of glial function, but rather a redirected mode of homeostatic regulation, ultimately leading to the formation of a relatively permissive ecological niche for tumor colonization in the brain.

Intrinsic Link Between State Transition and Neuronal Injury

Functional reprogramming of neuroglial cells promotes tumor colonization and may also be accompanied by changes in the microenvironment surrounding neurons. Sustained activation of pro-inflammatory signaling, disruption of metabolic homeostasis, and weakening of BBB function are all associated with neuronal injury and synaptic dysfunction, although their causal relationships remain to be further validated. These observations suggest that brain metastasis-associated neuronal injury may involve multi-level links to alterations in glial cell function, rather than being solely attributable to direct tumor invasion of neurons (Figure 2).

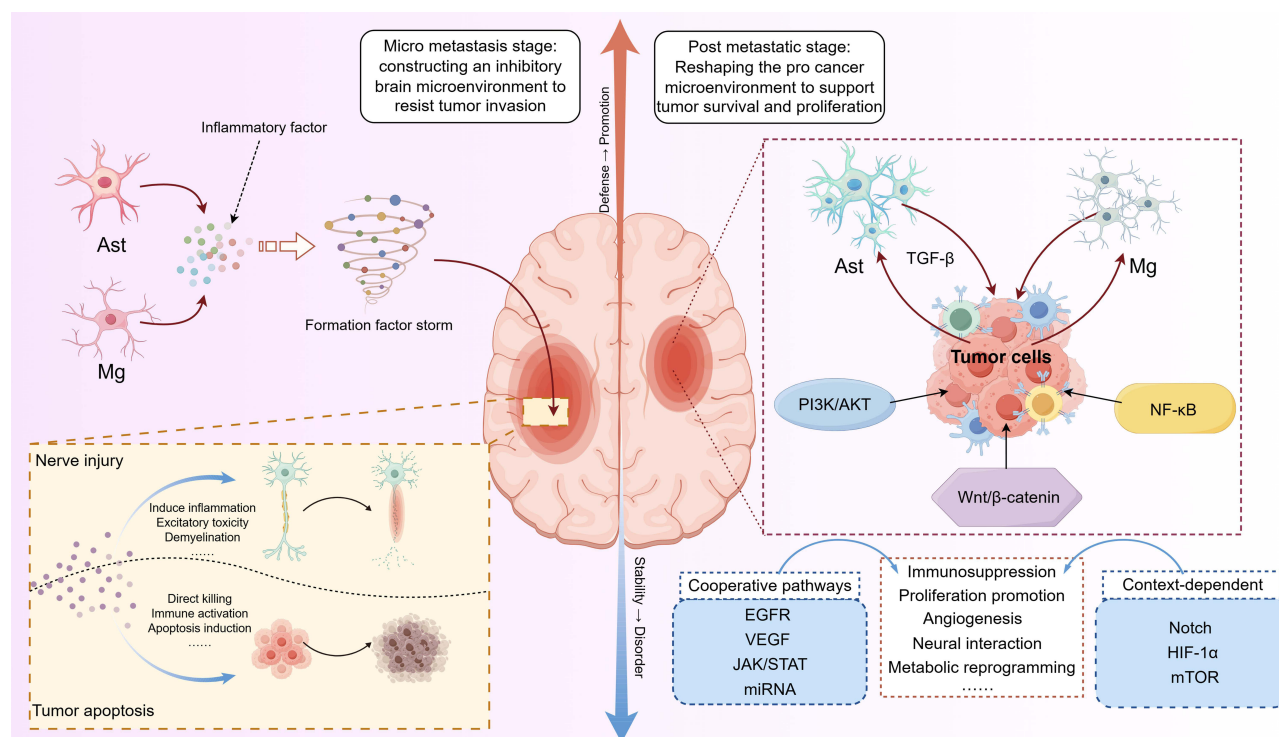


Figure 2 Schematic illustration of brain microenvironment remodeling centered on neuroglial cells (By Figdraw). During brain metastasis, astrocytes and microglia coordinately regulate inflammatory responses and immune surveillance through their interactions. Intercellular crosstalk engages multiple signaling pathways to remodel the brain microenvironment, thereby influencing tumor cell survival and adaptation.⁴⁴⁻⁵⁴

Amplified Inflammation and Neurotoxic Microenvironment

During the tumor-promoting stage, astrocytes and microglia are often in a persistently activated state. For example, in the context of melanoma and non-small cell lung cancer, the release of pro-inflammatory cytokines such as IL-6 and IL-8, together with the sustained involvement of signaling axes including NF- κ B, STAT3, and CXCL10-CXCR3, establishes a relatively stable inflammatory background^{55–62} (Table 1). This response pattern may provide a relatively favorable microenvironment for tumor cell survival and is accompanied by reduced efficiency of immune clearance. From the perspective of the nervous system, this “persistently active” inflammatory state may be associated with certain long-term alterations in neuronal function. Some studies suggest that chronic inflammation may impair neuronal homeostasis over time. This effect may involve oxidative stress, excitotoxicity, and altered synaptic pruning.^{63–65} However, direct evidence for this sequence of events in the context of brain metastasis remains insufficient. Notably, such inflammatory responses often lack clear termination signals. Their effects may extend beyond the initial lesion site. Some studies indicate that these inflammatory signals can propagate along neural networks and, if sustained, may create a microenvironment with potentially adverse effects on overall neural circuitry. If confirmed, this process likely reflects gradual accumulation rather than abrupt change.

Disruption of Metabolic Coupling and Synaptic Dysfunction

Under physiological conditions, astrocytes maintain neuronal metabolic homeostasis and synaptic activity through multiple mechanisms, including the supply of energy substrates and the precise coordination of neurotransmitter cycling.⁶⁶ However, under tumor-associated reprogramming states, this supportive role may shift, accompanied by changes in the allocation of metabolic resources and response priorities. This change does not necessarily manifest as overt “metabolic failure,” but may be associated with reduced efficiency of metabolic coupling, thereby affecting the buffering capacity of neurons in maintaining energy and neurotransmitter homeostasis.⁶⁷ In this context, some studies have observed that synaptic plasticity shows decreased tolerance to minor metabolic disturbances, and the stability of neural networks may be correspondingly weakened. In other words, metabolic imbalance may be better understood as a persistently existing vulnerability rather than an acute injury triggered by a single event.

BBB Imbalance and Neural Network Vulnerability

Alongside inflammatory and metabolic alterations, shifts in neuroglial function may also affect the regulation of the perivascular microenvironment in the brain. Glial cells normally exert fine control over components such as vascular endothelial cells, pericytes, and the basement membrane. If this regulatory capacity is partially weakened, it may lead to dysregulation of the perivascular microenvironment, which is not necessarily equivalent to a simple structural disruption of the BBB. Such dysregulation may, on the one hand, facilitate the diffusion of tumor-associated factors within the

Table 1 Key Steps of the Inflammatory Cascade and Their Functional Consequences in Brain Metastasis

Stage	Key Event	Participating Cells	Pathway/Molecules	Research Background/Model Context	Functional Outcome
Inflammation initiation	Initial inflammatory signal release	Tumor cells/microglia	IL-1 β , TNF- α	Breast cancer/lung cancer brain metastasis models; tumor cell-microglia interactions (in vitro + mouse models) ⁶⁰	Activation of local responses
Glial response	Microglial activation	Microglia	NF- κ B, STAT3	Breast cancer/lung cancer brain metastasis models; microglial inflammatory activation (in vitro stimulation and in vivo validation) ^{59,60}	Amplification of inflammation
Cellular interaction	Astrocyte involvement	Astrocytes	CXCL10-CXCR3	Melanoma brain metastasis model; inflammation-activated astrocytes (in vitro + mouse models) ⁵⁶	Signal propagation
Positive feedback formation	Sustained release of inflammatory factors	Glial cell populations	IL-6, etc.	Multiple brain metastasis models (breast cancer/lung cancer); glia-mediated chronic inflammation ^{57,60}	Maintenance of inflammation
Microenvironmental alteration (For key terms and definitions, see Table 2)	Enhanced neurotoxicity	Neurons + glial cells	ROS/glutamate	Neuroinflammation/neurotoxicity models; neuron-glia interactions (in vitro and animal experiments) ^{58,62}	Neuronal injury

Table 2 Brief Glossary

Colonization bottleneck	Refers to the critical stage during brain metastasis that limits the successful colonization of disseminated tumor cells. At this stage, tumor cells must overcome constraints imposed by the brain microenvironment. The outcome can be characterized by colonization success rates or sustained growth capacity.
Microenvironmental alteration	Refers to a state in which the homeostatic maintenance mechanisms of the brain microenvironment deviate from normal conditions. It is characterized by abnormalities in glial cell activation patterns, immune regulation, vascular function, and intercellular signaling, and can be assessed by relevant molecular or functional indicators.

brain, and on the other hand increase the exposure of neurons to abnormal inflammatory signals and metabolic stress.^{45,68} Its potential effects may extend beyond structural changes and could also involve alterations in the overall stability of neural networks. Therefore, neurological dysfunction associated with brain metastasis may not be fully attributable to neuronal death alone, but is more likely the result of the combined effects of multiple processes, including glial functional shifts, perivascular microenvironmental imbalance, and inflammatory and metabolic changes. The precise causal relationships among these factors remain to be further clarified.

ORs Influence Cancer Metastasis and Progression by Modulating the Tumor Microenvironment

Early clinical observations suggest that perioperative patterns of opioid use may be associated with postoperative recurrence risk in some cancer patients.⁶⁹ This correlation has drawn attention to the potential role of ORs in tumor progression and has prompted subsequent mechanistic investigations at the molecular and cellular levels.

Subsequent basic and translational studies indicate that, across multiple solid tumors, changes in opioid receptor expression levels are associated with invasive tumor phenotypes and metastasis-related processes.¹⁹ For example, activation of DOR can influence signaling pathways such as JAK1/2-STAT3. This, in turn, alters the mode of communication between tumor cells and the surrounding microenvironment and, in specific contexts, is associated with enhanced migration and invasiveness of breast cancer cells. In addition, DOR signaling has been reported to be linked to processes such as epithelial-mesenchymal transition (EMT), suggesting that it may participate in tumor progression by modulating cellular plasticity and microenvironmental adaptability.¹⁸

Similarly, in certain experimental models, μ -opioid receptor (MOR)-related signaling can regulate tumor cell responses to microenvironmental cues through pathways such as PI3K/AKT and mTOR. This regulation affects cell migration, adhesion, and the formation of vascular-related structures.^{22,70–72} These changes may create a microenvironment that favors CTC survival and colonization. Current evidence suggests that ORs are not independent oncogenic drivers. Instead, they bias metastasis-related phenotypes by modulating the interactions between tumor cells and their surrounding microenvironment.

On this basis, a further question arises: whether these regulatory effects also operate in brain metastasis, a process that is highly dependent on microenvironmental adaptation, and whether they may have even greater significance in this context. The CNS represents a specialized niche with immune and metabolic characteristics that differ markedly from those of peripheral tissues. Its metastatic colonization process largely depends on remodeling of the local microenvironment, in which glial cells are considered key regulators.

Existing studies indicate that ORs in the CNS not only participate in classical pain regulation, but also contribute to maintaining the functional balance of the neural microenvironment by modulating inflammatory signaling pathways, glial cell activation states, and the expression of multiple cytokines. Moreover, the dynamic transitions of glial cell subsets not only reflect changes in cellular functional states, but may also be accompanied by reprogramming of opioid receptor expression and signaling responses.

It should be noted that the expression profiles and strength of evidence for ORs differ among glial cell types. In microglia, MOR and KOR show relatively consistent evidence of expression, whereas in astrocytes, receptor expression appears more heterogeneous and, to some extent, depends on specific inflammatory or experimental conditions.^{73–77}

Based on these observations, it can be hypothesized that opioid receptor-related signaling may shape a brain microenvironment favorable for tumor cell survival and colonization by regulating glial cell activation states and their interactions with tumor cells, thereby exerting potential modulatory effects during the initiation and progression of brain metastasis. However, this inference is primarily based on the integration of cross-level evidence, and its precise mechanisms and applicability across different tumor types remain to be validated by further experimental studies.

Potential Regulatory Roles of ORs in Glial Cell-Cancer Cell Crosstalk Within the Brain Metastatic Microenvironment

Within the highly specialized microenvironment of brain metastasis, molecular systems that can alter glial response patterns may, in principle, also influence the formation of the metastatic niche. Based on this premise, we propose a “neuroglial sensitivity model,” in which the core role of ORs in the brain metastatic microenvironment may not lie in directly inducing inflammation or driving tumor-associated responses, but in resetting the effective sensing range and response slope of neuroglial cells to external perturbations.

This shift in the effective sensing range can be defined as a systematic change in the stimulus intensity required to trigger specific functional outputs in glial cells under the same external conditions. Such changes can be quantified by the following metrics: (i) the dose-response curves of inflammatory factor release; (ii) ratios associated with immune activation phenotypes in astrocytes and microglia (eg., the proportion of pro-inflammatory versus reparative features in microglia, and the relative proportions of reactive astrocyte subtypes); and (iii) metabolic shifts in astrocytes and microglia (eg., increases or decreases in the glycolysis/oxidative phosphorylation ratio). In terms of temporal scale, this process can be divided into short-term (minutes to hours, primarily reflecting receptor-mediated signaling transduction changes) and long-term (hours to days, involving transcriptional and epigenetic regulation) components. Different opioid receptor subtypes may play distinct roles in this process, thereby altering the response curves of glial cells to stimuli.

Based on the above definition, a falsifiable hypothesis can be further proposed: opioid receptor signaling, by modulating the effective sensing range of glial cells, may alter the distribution of their functional states under different stimulus intensities, thereby amplifying or suppressing inflammation-related cascade responses within a certain range. Specifically, ORs may be better understood as microenvironmental modulators. By regulating the functional states of neuroglial cells and their intrinsic signaling networks, they may indirectly shape the functional crosstalk between glial cells and tumor cells. In this way, inflammatory, stress, or chemotactic signals of a given intensity may be transformed into more propagative collective responses, thereby amplifying or attenuating their microenvironmental effects at the network level (Figure 3). However, whether they trigger a transition from homeostatic to pro-inflammatory or pro-tumor states within specific stimulus ranges, or instead suppress such transitions, remains to be determined by further experimental validation.

Neuroglial Cells as the Critical Interface for Opioid Signaling Entry into the Brain Metastatic Niche

Within the framework of “opioid receptor-mediated resetting of the effective sensing range of glial cells,” neuroglial cells can be regarded as a key interface through which opioid signaling engages the brain metastatic microenvironment. As principal regulatory units of the brain microenvironment, astrocytes and microglia not only participate in the maintenance of inflammatory responses, but also largely determine the dynamic balance of local immune and metabolic states. Existing studies have shown that ORs are detectably expressed in these cell types and possess functional signaling capacity.^{78,79}

In this context, ORs are more likely to influence the overall response trajectory of brain tissue to tumor-associated stimuli by modulating the response properties of glial cells, rather than by directly triggering inflammatory responses. For example, under specific stimulus conditions, MOR-related signaling can affect the release of inflammatory mediators from astrocytes and indirectly regulate the activation state of microglia through paracrine pathways. This process typically exhibits time-dependent characteristics, with more pronounced effects under conditions of sustained stimulation.^{19,80}

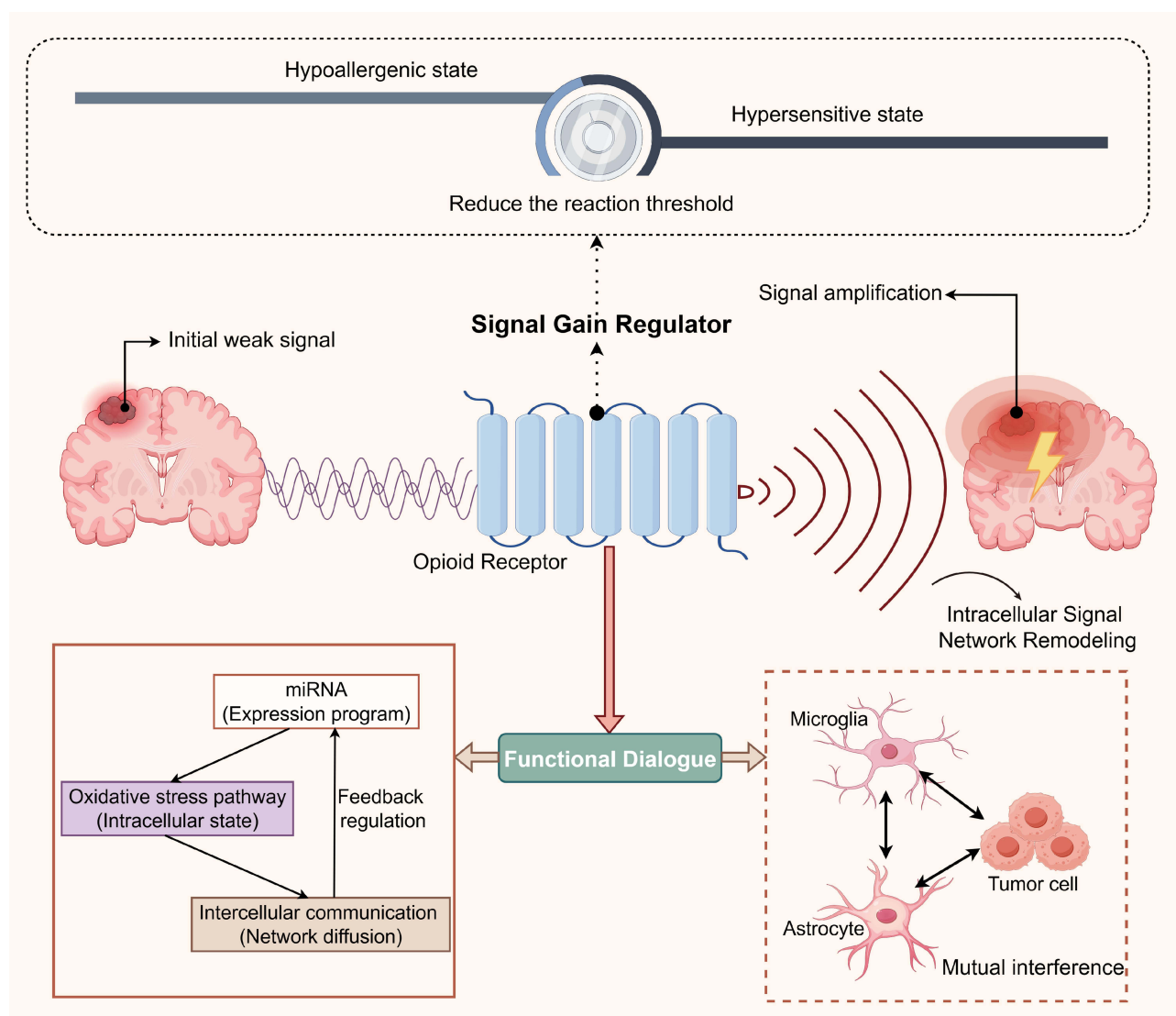


Figure 3 Schematic illustration of opioid receptor-mediated regulation of neuroglial sensitivity states (By Figdraw). Opioid receptor signaling may act as a “Signal Gain Modulator” by regulating the functional states of astrocytes and microglia and their intracellular signaling networks. In this process, local inflammatory, stress, or chemotactic signals are amplified and propagated, thereby influencing, in a context-dependent manner, glial cell-tumor cell interactions, metastatic colonization, and neuronal injury.

Multilevel Signaling Networks Reset the Functional Phenotypes of Glial Cells

Further mechanistic studies suggest that the regulation of glial cells by opioid receptor signaling is not confined to single intracellular processes, but is achieved through amplification and integration within multi-level intercellular communication networks. This network includes classical signaling pathways (such as MAPK and JAK/STAT), microRNA-mediated post-transcriptional regulation, and extracellular vesicle (EV)-dependent long-range information transfer.^{14,81–84} In astrocytes, activation of KOR can engage stress-related pathways such as p38 MAPK, upregulate specific miRNA expression, and is accompanied by downregulation of homeostasis-related molecules such as xCT. These changes may, to some extent, disrupt glutamate metabolic balance and drive a shift toward a reactive state. At the same time, activation of μ -opioid receptor (MOR) can induce astrocytes to release extracellular vesicles enriched in miR-138. After uptake by microglia, these vesicles can influence their transcriptional programs and functional states through the TLR7 pathway.^{46,85} Overall, these mechanisms collectively form a non-linear regulatory network centered on microRNAs as key nodes, enabling opioid receptor signaling to coordinate the functional outputs of glial cell populations at both intracellular and intercellular levels.

Evidence Limitations and Context-Dependent Modes of Action in the Setting of Brain Metastasis

It should be noted that direct evidence is still lacking to demonstrate that opioid receptor signaling causally mediates specific interactions between glial cells and tumor cells during the development of brain metastasis. A more plausible interpretation is that ORs integrate signals related to inflammation, stress, and intercellular communication, and modulate the overall response pattern of the existing microenvironment, thereby influencing, to some extent, the conditions for tumor cell survival and colonization.

Within this framework, opioid receptor signaling is highly context-dependent, shaped by receptor subtype, ligand source, and exposure duration. Acute, physiological activation—typically driven by endogenous opioids—tends to restrain excessive inflammation, whereas sustained or chronic stimulation (for example, by exogenous agonists) may bias glial cells toward pro-inflammatory or dysregulated states. Distinct receptor subtypes are likely to contribute differentially. Thus, opioid receptors primarily modulate the threshold and gain of glial responses, enabling dynamic bidirectional regulation rather than fixed pro- or anti-inflammatory effects. This framework may reconcile divergent findings and underscores the need to consider stimulus intensity, duration, and microenvironmental context.

Future Perspectives

Although recent studies have increasingly highlighted the critical roles of neuroglial cells in brain metastasis and the potential involvement of ORs in mediating brain microenvironmental imbalance, several key scientific questions remain unresolved. Future research should systematically elucidate, at the mechanistic level, how ORs regulate the functional states of neuroglial cells in the context of brain metastasis, and further define their boundaries of action across different pathological conditions. Particular attention should be given to the molecular mechanisms by which ORs distinguish between endogenous endorphin signaling and exogenous opioid drug signaling, and whether this distinction determines the directional shift of neuroglial cells toward homeostatic support or inflammatory activation. At the same time, it remains to be determined whether inflammation-related signals, under sustained biased regulation by ORs, can act synergistically with tumor-derived signals to amplify responses and drive brain metastatic colonization and progression. These questions require validation using time-resolved and cell type-specific models.

Beyond the CNS, alterations in the peripheral immune system (such as T lymphocytes and B lymphocytes) can exacerbate inflammatory states within the CNS. At the same time, inflammatory factors released by activated astrocytes and microglia in the brain can enter the peripheral circulation via cerebrospinal fluid, further promoting activation of the peripheral immune system and amplifying inflammatory responses.^{86–88} Within this bidirectional interaction, it remains to be clarified whether the peripheral immune system participates in the expression of ORs and the regulation of their associated signaling pathways.

Overall, opioid receptor signaling pathways are more likely to represent a class of regulatable microenvironmental control nodes. Precise modulation of OR signaling may preserve analgesia and neuroprotection while limiting pro-inflammatory and pro-metastatic effects, thereby providing a new theoretical basis for achieving coordinated benefits of “analgesia-neuroprotection-metastasis control” in patients with brain metastasis from cancer.

Limitations

Some mechanistic inferences currently lack sufficient direct evidence, and the related conclusions rely, to some extent, on indirect or secondary evidence, requiring further experimental validation. In particular, in the context of brain metastasis, direct evidence for interactions between ORs and glial cells remains limited. Current understanding is largely derived from studies across different disease settings, and its applicability needs to be systematically confirmed in brain metastasis-specific models.

Abbreviations

CNS, Central nervous system; ORs, Opioid receptors; MOR, Mu opioid receptor; DOR, Delta opioid receptor; KOR, Kappa opioid receptor; CTCs, Circulating tumor cells; BBB, Blood-brain barrier; CCL2, C-C motif chemokine ligand 2; GFAP, Glial fibrillary acidic protein; SERPINE1, Serpin family E member 1; IL-11, Interleukin-11; EGFR, Epidermal growth factor receptor; PD-L1, Programmed death-ligand 1; IL-6, Interleukin-6; IL-8, Interleukin-8; NF- κ B, Nuclear

factor kappa B; STAT3, Signal transducer and activator of transcription 3; CXCL10, C-X-C motif chemokine ligand 10; CXCR3, C-X-C motif chemokine receptor 3; JAK1, Janus kinase 1; JAK2, Janus kinase 2; EMT, Epithelial-mesenchymal transition; PI3K, Phosphoinositide 3-kinase; AKT, Protein kinase B; mTOR, Mechanistic target of rapamycin; MAPK, Mitogen-Activated Protein Kinase; EV, extracellular vesicle; miRNA, MicroRNA; xCT, Cystine/glutamate antiporter; miR-138, MicroRNA-138; TLR7, Toll-like receptor 7.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

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Author Contributions

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. D.C. was mainly responsible for the conceptualization, investigation, writing - original draft and writing - review and editing of the manuscript. X.W. and X.L.S. contributed primarily to the conceptualization, supervision, and funding acquisition of the manuscript.

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Disclosure

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