Review

How Schwann Cells Are Involved in Brain Metastasis

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Abstract: The current lack of a comprehensive understanding of brain metastasis mechanisms presents a significant gap in cancer research. This review outlines the role that Schwann cells (SCs) have in this process. SCs are already known for their role in myelination and nerve repair within the peripheral nervous system (PNS), but there is less information on their function in facilitating the transport and activation of neoplastic cells to aid in the invasion of the blood–brain barrier and brain. Detailed insights into SCs’ interactions with various cancers, including lung, breast, melanoma, colon, kidney, and pancreatic cancers, reveal how these cells are coerced into repair-like phenotypes to accelerate cancer spread and modulate immune responses. By outlining SCs’ involvement in perineural invasion and BBB modification, this review highlights their functions in facilitating brain metastasis.

Keywords: brain metastasis; cancer; Schwann cells; perineural invasion

1. Introduction

Autopsies have revealed that metastatic brain tumors occur in 10–26% of patients, making it one of the most common complications of cancer [1]. Brain metastases most often originate from primary cancers such as those in the lung, breast, kidney, and pancreas, as well as melanoma [2]. The 2-year survival rate after the diagnosis of brain metastases is strikingly low, approximately 8%, indicating the necessity to research the mechanism behind this process [3].

Metastasis occurs through the “metastatic cascade”, encompassing the cancer cell’s pathway for successful metastasis to new tissue [4]. During the metastatic cascade, neoplastic cancer cells detach from the main tumor body and travel through the blood or lymph to reach niche tissues with the proper growth factors and environment for the formation of micrometastases [4]. In the brain specifically, neoplastic cells must penetrate the blood–brain barrier (BBB), which is difficult without previous weakening of the BBB or assistance from other cells. Once neoplastic cells have adhered to and breached the BBB, they can hijack activated microglia and astrocytes to stimulate the release of inherent neural growth factors from the glia [4]. Neoplastic cancer cells are capable of hijacking and utilizing many cell types or mechanisms to infiltrate the BBB. For example, case reports have indicated an under-researched metastatic pathway that propagates through the peripheral nervous system (PNS) [5]. Tumor innervation from the PNS is strongly correlated with poor prognosis because it is associated with aggressive tumor phenotypes and has been implicated in tumor metastasis by way of locally delivered neurotransmitters [6,7]. Recently, however, it has been found that extracellular vesicles (EVs) can also induce tumor innervation by way of the release of axon guidance and neurotrophic factors [8]. The connection between tumor innervation and Schwann cells (SCs) is less well understood, but EVs have also been found to activate SCs to induce metastases through mechanisms discussed later in this review. Several cell types (SCs, macrophages, etc.) and potential activation and cell
hijacking mechanisms (EVs, perineural invasion, etc.) are being studied to try to elucidate this phenomenon [9–11].

Among the cell types identified as key contributors to metastasis are Schwann cells (SCs), the main glial cells in the PNS, which are responsible for myelination and repair of peripheral nerve injuries [12]. These repair capabilities can be hijacked by cancer cells, with new evidence suggesting that tumor-activated SCs can heavily contribute to the tumor microenvironment (TME) and transport of neoplastic cells [10,13–15]. This narrative review focuses on the relatively new field of SC metastasis research. Case reports of brain metastasis from primary cancers have been pooled along with animal and in vitro models of brain metastasis and SC interference. Some examples of search criteria included “brain metastasis and SCs”, “SCs metastasis”, “SC perineural invasion”, and “SCs and (a specific type of primary cancer)”.

2. Schwann Cells and Metastasis

SCs are capable of extensive plasticity and transdifferentiation, implicating them in different pathologic-like demyelinating disorders and neoplastic processes [16]. The mutual attraction of cancer cells and SCs can lead to a dangerous hijacking of these cellular programs in the absence of nerve damage, resulting in the promotion of perineural invasion and metastatic progression [17]. Many theories have been proposed to account for the attraction and activation of SCs by cancer cells, but without a well-defined mechanism to explain how everything fits together, there is still much that is unknown. It is known that SCs can be attracted by or attract cancer cells through paracrine signaling, direct contact, or through extracellular vesicles (EVs) (Figure 1) [14,18]. Several receptors expressed by SCs are necessary for the interaction with and activation caused by cancer cells. For example, CXCR4 is expressed by SCs and is necessary for their recruitment and activation by CXCL12 [19]. SCs also express p75NTR, which is a low-affinity receptor for nerve growth factor that also activates the migration of both SCs and cancer cells [11]. Tumor-activated SCs are also known to highly express GFAP and other premacular genes such as NCAM and L1-CAM, which are necessary for nerve repair functions and metastatic functions [16,17]. These attraction and activation mechanisms vary across pathologies, suggesting that the specific SC phenotype, interaction with neoplastic cells, and the microenvironment play foundational roles in how SCs are involved in metastatic transformation.

Figure 1. Mechanisms of Schwann cell activation and contributions to metastasis. Myelinating SCs are activated to a nonmyelinating state by cancer cells. Tumor-activated SCs can then aid in metastasis by inducing cancer cell migration, immunomodulation, or perineural invasion.
SCs can assume multiple phenotypes, readily undergoing dedifferentiation and redifferentiation, and all phenotypes have proposed metastatic mechanisms [14]. For example, in their repair state, SCs can enter a dedifferentiated state, also known as a tumor-activated state, to promote metastatic processes and release immunomodulatory, migratory, and growth-promoting factors (Figure 1) [13]. In addition to repair states, SCs can also take on two other phenotypic variants. The nonmyelinating phenotype has shown a correlation with multiple pathways relating to cancer progression and invasion, including epithelial-to-mesenchymal transition (EMT), when enriched with tumor cells [20], whereas the myelinating phenotype shows integrin-dependent invasiveness in prostate and pancreatic cancers [21,22]. These findings suggest that multiple pathways may be involved in promoting metastatic changes or that different cancers utilize different mechanisms to promote invasive properties.

The perineural area is frequently the site of SC/cancer cell interactions, supporting the proposed mechanism of neoangiogenesis [17,20]. This process involves neoplastic cells secreting growth factors that stimulate blood vessel growth into tumors, subsequently transforming SCs into a tumor-activated phenotype [17,20]. These altered SCs generate tumor-activated Schwann cell tracks (TASTs), facilitating the migration of cancer cells through neural tissue, an interaction that is crucial in promoting perineural invasion, which is the process of cancer cell infiltration and migration in the PNS (Figure 1) [17,20]. The identification of TASTs supports the concept that SCs can induce neoplastic migration directly and indirectly through modification of the microenvironment, immunoenvironment, and SC reprogramming [23,24].

Perineural invasion allows cancer cells to directly migrate up TASTs, most commonly in autonomic nerves (Figure 1) [25]. In vitro studies show that cancer cells co-cultured with dorsal root ganglion (DRG) extracts and SCs demonstrate that SCs guide cancer cells toward the nerve, thereby enhancing invasion through contact-dependent mechanisms [26]. c-Jun-expressing SCs guide cancer cells along TASTs by promoting protrusion formation in the cancer cells through the expression of neural cell adhesion molecule 1 (NCAM1) [17,27]. In mice lacking NCAM1, there has been a noticeable reduction in perineural invasion by cancer cells [17].

SCs can also influence the TME, resulting in significant implications for the role of SCs in tumor formation and resistance. For instance, increased dietary intake of palmitic acid induces a pro-metastatic state in oral and melanoma cancer cells, which has been linked to increased activation of SCs and greater tumoral innervation [28]. Activated SCs from these experiments were able to secrete proregenerative extracellular matrix (ECM) [28]. When this ECM is ablated, the initiation of metastasis by cancer cells is inhibited [28]. These changes are induced by the transcription factor EGR2 in cancer cells and the peptide galanin [28].

Finally, evidence suggests that SCs can play an active role in neoplastic cell invasion and the modulation of immune responses [23,29]. The most often identified mechanism in which this occurs is through the SC activation of M2 macrophages. EMT through SC-derived factors, like CXCL5 and BDNF, has been identified to initiate the transition process with interaction from GDNF, IL-6, and CCL2 stimulating migration through modification of the extracellular matrix via interaction from matrix metalloproteinases (MMPs) [30]. SCs can also induce the activation of M2 macrophages, through IL-10, and reduce T cell activation, allowing cancer cells to evade immune responses [15,31].

The involvement of SCs is becoming more evident as emerging evidence suggests an intimate involvement of the PNS with different types of cancers. However, there appear to be nuances to how SCs are directly involved with different types of tumors and their relation to brain metastases, as we describe below.

2.1. Lung Cancer

Over 90% of patients with lung cancer have metastases to the lymph nodes, brain, bone, liver, and adrenal glands [32]. Up to 50% of patients with advanced lung cancer
develop brain metastases at some point during their disease [32,33]. Interaction between lung cancer cells and SCs can accelerate and induce metastatic changes [34]. For instance, SCs induce metastatic changes in lung cancer cells by releasing CXCL5, which subsequently activates the PI3K signaling pathway to promote EMT, migration, and invasiveness in lung cancer cells [34]. SCs that release CXCL5 are activated by lung cancer cells through an unknown mechanism, highlighting not only the important interaction between these cells but also how much knowledge is still lacking about these processes [34].

One way SCs can be activated by lung cancer cells is through direct contact [35]. Through direct contact with cancer cells, SCs dedifferentiate from a myelinating state and begin to express proteins that were expressed before differentiation, like glial fibrillary acidic protein (GFAP) and NCAM1 [35]. The association of SCs with lung cancer cells then causes the migration of cancer cells from neighboring tissues and the promotion of invasive properties [35]. These patterns have been especially seen in small-cell lung cancer, where phenotypic analysis of SCs indicated that SCs secrete cytokines into the tumor microenvironment to influence a larger group of cells [36].

The secretion of paracrine signals or EVs can also accelerate the progression of certain lung cancers, such as lung adenocarcinoma and lung squamous cell carcinoma [29,35]. Paracrine signaling with glial cell line-derived neurotrophic factor (GDNF) from SCs, for example, can increase the invasion of tumor cells along the nerves of the lungs, which are highly innervated [11,37]. With further help from SCs, which are able to degrade the ECM and form tunnels coated with laminin, tumor cells can infiltrate the epi- neurium or perineurium to migrate along the PNS toward the brain and spinal cord [35]. SCs can further facilitate the migration along nerves by expressing NCAM1 to strongly adhere and pull cancer cells [13,38–40]. In addition to paracrine signaling, EVs derived from SCs can also accelerate the progression of lung cancers such as lung adenocarcinoma. This occurs through the activation of multiple signaling pathways like MAPK, PI3K, and TNF and exosomal secretions of miRNA-21-5p, which are associated with a poor prognosis and lung cancer spread [29].

Additional evidence also suggests that SCs may have a more disseminated involvement with the microenvironment than previously thought. SCs have the ability to induce an M2-like phenotype in macrophages, which causes them to lose their antitumor ability and promotes the aggression of tumor cells, contributing to metastatic risk [30].

### 2.2. Breast Cancer

The Centers for Disease Control and Prevention indicates that breast cancer is the most common cancer in women in the United States [41]. Metastasis is one of the most common causes of death in women with breast cancer and is recognized as the most common malignancy while being the second leading cause of cancer-related deaths among women worldwide [41]. Nearly half of all localized breast cancers were found to have metastatic properties for those diagnosed [42].

The established mechanistic model for breast cancer metastasis involves manipulation and degradation of the extracellular matrix with the use of matrix metalloproteinases [29,43]. Classically, breast cancer metastasis is thought to occur through EMT, the spread through lymphatics and vasculature, mesenchymal-to-epithelial transition (MET), and the deposition of neoplastic cells at distant sites [43]. Perineural invasion in breast cancer is a new method of metastasis that does not rely on lymphatics of vasculature to transport neoplastic cells [35]. SCs have the ability to enable metastasis through perineural invasion via regulation of cancer cell expression of MMP9 by releasing L1 cellular adhesion molecule (L1CAM) [23]. The well-established involvement of SCs in the degradation of the ECM through MMP9 provides a mechanism for how a neoplastic pathology may metastasize to the brain and erode the BBB to seed in the neural parenchyma [44].

Aside from being activated by cancer cells, SCs have a remarkable ability to manipulate neoplastic cells as well. When SCs come into contact with cancer cells, they have the ability to induce protrusions from cancer cells utilizing molecules like NCAM1 [17]. SCs can
then insert between cancer cells, leading to the dispersal of cancer cells away from neighboring cells [17,23]. Previous work has demonstrated that breast cancer cells contact the microenvironment through cadherins, which help facilitate this invasion [45].

Evidence also points to other mechanisms, in the absence of direct contact, that can be used to activate SCs to induce perineural invasions and cancer cell mobility. For example, SCs have the ability to recognize antigens through the expression of Toll-like receptors (TLRs), which are able to recognize endogenous ligands called alarmins [23]. Alarmins are known to be expressed upon tissue injury or cell death and are seen in several different types of cancers, including breast cancer [46,47]. In 2011, Antonyak et al. found that EVs released from breast cancer cells can transform fibroblasts and epithelial cells to display the characteristics of cancer cells, a known mechanism of activation in other cell types that requires more research to determine how necessary direct contact by breast cancer cells is for the transformation of SCs into tumor-activated SCs [48].

SCs activated by breast cancer cells can use chemokine signaling to attract neoplastic cells from distance sites through the expression of CXCL12, which is predominately expressed in lymph nodes [23,43]. There is a positive correlation with invasion when the breast cancer cells are involved in physical interaction with macrophages, which are known to be polarized to M2 subtypes by cytokine and chemokine signaling from tumor-activated SCs [49,50]. Further work to establish concrete evidence of the direct involvement of not only SC interaction in breast cancer metastasis but also the specific mechanisms of these interactions is necessary to develop therapies and stave off potential pathways of metastasis.

2.3. Melanoma

In a population of patients with stage IV melanoma, over 70% had metastasis to the brain, making it a common and serious complication of a cancer affecting millions of people [51]. Melanoma seems to be uniquely influenced by innervation from the PNS compared to other solid primary tumors, which could be a contributing factor in the high incidence of brain metastasis. Research into innervation in melanoma and other primary tumors has revealed that interference with the autonomic innervation of these tumors yields positive effects [25]. However, when sensory nerves are damaged in melanoma, tumor progression occurs more readily [25].

Innervation patterns are not the only area of melanoma research generating interesting results. In a 2019 study by Shurin et al., it was discovered that melanoma cells can activate the repair pathways of SCs to support tumor growth by enhancing motility, recruitment of M2 macrophages, and the breakdown of collagen [50]. Activation of SCs could occur via the release of EVs, which have been found to induce progenitor bone marrow cells toward a metastatic phenotype in previous studies [52]. Further studies looking at the breakdown of tumor innervation found that in the acute response to denervation, when the SCs were naturally in their repair state, melanomas grew faster, and transdifferentiated SCs attracted more melanoma cells [50].

Another unique finding is the high expression of p75NTR in spindled melanoma cells compared to epithelioid melanoma cells [53]. Desmoplastic subsets of spindled melanomas have a higher incidence of perineural invasion, which could be due to the overexpression of p75NTR, a neurotrophin factor that is expressed heavily in SCs [53]. Melanoma cells have also been observed to adopt characteristics of SCs, enabling them to exhibit a neurotropic growth pattern [54]. In other studies, melanoma-treated SCs attract myeloid-derived suppressor cells and enhance their ability to suppress T cell proliferation, which is believed to be due to the increased expression of myelin-associated glycoprotein [15]. Overall, there are multiple ways in which SCs can be activated and aid in brain metastasis in melanoma, but more research is needed to connect these ideas into a cohesive mechanism.
2.4. Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) exhibits extensive SC distribution within the TME, and the interaction between the two could potentially serve as a prognostic indicator of poor survival in patients [21]. The interaction between the tumor and the neuroglia plays a significant role in inducing the SCs to acquire a tumor-facilitating phenotype [21]. The presence of intratumoral SC markers may be able to predict the likelihood of distant metastasis and a poor five-year survival rate for patients with PDAC [21]. A supportive mechanism is thought to be the stimulation of an immature phenotype of SCs, which leads to the upregulation of cytokines that accelerate the transformation of cancer cells [21].

EVs derived from pancreatic tumor cells (PANC-1s) are known to induce SCs to transition into a repair state by dedifferentiating from their mature form, a process thought to involve IL-8 [55]. Experiments found that exposure to IL-8-containing EVs resulted in heightened SC activation, which is mitigated when IL-8 is inhibited [55]. This observation indicates that IL-8 signaling may orchestrate accelerated perineural invasion by SCs [55]. Furthermore, the PANC-1-derived EVs promoted the nuclear translocation of the NF-κB subunit and p65, potentially initiating cytokine secretion that could further expedite perineural invasion [55]. NF-kB in SCs can also be activated in the absence of EVs by the secretion of IL-1β from cancer cells [21].

Pancreatic cancer cells can induce tumor-activated SCs to activate intracellular machinery in the tumor cells and induce MET [18]. As seen in other cancers, SCs play a role in both EMT and MET, allowing them to accelerate the metastatic transformation of neoplastic cells [18,24,29]. Further molecular signaling pathways in PDAC provide evidence for multiple mechanistic pathways to accomplish metastatic transformation [21]. When SCs are co-cultured with pancreatic cancer cells harvested from PDAC patients, the SCs secrete IL-6, augmenting cell migration and invasion through activation of the STAT3 signaling cascade, which was diminished upon neutralization of IL-1β from cancer cells [21].

2.5. Kidney Cancer

The incidence of metastatic brain tumors in patients with renal carcinoma is likely higher than reported, due to historically inadequate monitoring of the central nervous system—a situation that is now showing signs of improvement [56,57]. Additionally, individuals diagnosed with brain or spinal cord metastases are frequently excluded from clinical trials [56,58]. The incidence of perineural invasion is believed to be underreported; most malignancies facilitating this process are only identified posthumously and remain poorly researched [59,60]. Despite growing evidence of potential links, research on the role of SCs in these metastases remains notably sparse.

Only one paper from 2016 discussed the unmet need for research into perineural invasion in renal cancer examining cases with intradural extramedullary metastases from renal cell carcinoma [59]. After chart review, the authors traced cases of spinal metastases from the kidneys and hypothesized the route of cancer cell migration to be originating in autonomic nerves supplying the kidney, continuing to the renal plexus, through the autonomic ganglia and along the splanchnic nerves to the spinal nerves and spinal column [59]. This pathway is heavily influenced by SCs, a vital aspect in the dispersion and invasion of cancer cells via perineural invasion [13].

As in other cancer types, CC and CXC chemokines play a pivotal role in renal metastasis due to the immune system and inflammatory pathway’s impact on the brain [60]. Chemokines have already been heavily implicated in lung cancer metastases, which is expected given that a substantial proportion of renal cell carcinoma patients concurrently exhibit metastases to both the lung and the brain [60]. Autopsies revealed that 15% of renal cell carcinoma patients had brain metastases, and all but one patient had lung metastases [60]. This connection is notable, particularly as SCs have been more extensively studied in lung cancer patients, and it is established that chemokine regulation can be executed by activated SCs [34].
2.6. Colon Cancer

Compared to other primary tumors, metastatic brain tumors originating from colon cancer are relatively rare, with an average incidence of 2.1% [61]. Brain metastases in colorectal cancer patients are often asymptomatic at initial diagnosis and are only identified later by the presentation of severe neurologic symptoms and multiple other sites of metastasis [62]. Despite their rarity, colorectal cancer cells warrant attention due to their interactions with SCs and the enteric nervous system (ENS). Historically, colorectal cancer cells exhibit a reliance on neural structures for growth, and there is a high incidence of perineural invasion, significantly elevating metastatic risk [63]. The reliance on neural structures could be connected to the necessity for ENS and sympathetic and parasympathetic nervous system innervation in the digestive system. The ENS is considered the intrinsic controller of the digestive organs and does not contain SCs [64,65]. Instead, it consists of enteric glia that play a supportive role to the enteric neurons but are unique from SCs [64]. The extrinsic control of the digestive system is under the control of the sympathetic and parasympathetic nervous system, which contains SCs [65]. This distinction indicates the complexity of metastases from colon cancer, as the unique metastatic capabilities arise from cancer cell interactions with the ENS or PNS, respectively, or in combination.

The ENS and PNS have largely been researched separately for their roles in the metastatic risk of colon cancers. A 2018 study by Duchalais et al. found that tumor epithelial cells derived from human primary colon adenocarcinomas adhered strongly to ENS explants [66]. Evidence suggests that N-cadherin and L1CAM on colon cancer cells were able to maintain trajectory and migrate along enteric nerves, identifying potential mechanisms of cancer cell migration to other tissues [66]. Other research into enteric glial cells specifically has found that once activated by colorectal cancer cells, these glial cells take on a pro-tumorigenic phenotype [67]. By activating the prostaglandin E22/EP4/epithelial growth factor receptor-dependent pathway, they are able to stimulate tumorigenesis and provide the necessary factors to induce micrometastatic growths [67]. This points to the general ability of most cancer cells to hijack glial cells in both the central and peripheral nervous systems.

SCs of the sympathetic and parasympathetic nervous system can also be recruited and activated by colon cancer cells. In 2022, Chen and Chen found that the TME of colorectal cancer tumors was heavily influenced by SCs [63]. Similar to that seen in pancreatic cancer models, the NF-kB signaling pathway was activated in cultured SCs through contact with colorectal cancer cells [63]. This signaling promoted the secretion of IL-8, which induced migration of colorectal cells and subsequent invasion of new tissues, leading to malignancy [63]. These are all indications that the glia in all systems are important modulators of metastasis that require more research.

3. Conclusions

Metastatic brain tumors are a common complication of cancer, often originating from other primary cancers. The survival rate after the diagnosis of brain metastases is strikingly low, emphasizing the need to understand the mechanisms behind this process such as the hijacking of glial cells to increase metastatic success. This process is being increasingly researched in the main glial cells of the PNS, SCs, which play a part in routes of metastasis such as perineural invasion and immune modulation.

SCs influence metastasis from many primary tumors in similar ways, but there are some unique mechanisms based on the tumor type that often present with varied cytokine or chemokine secretion or recruitment of different glial cells inherent in the originating organ system. In lung cancer, neoplastic cells can differentiate SCs to repair-like phenotypes through EVs or direct contact, allowing SCs to modulate the immune cells such as M2 macrophages—patterns that are heavily represented in other cancer types [21,29,30]. In breast cancer, SCs mainly act through perineural invasion via regulation of cancer cell expression of MMP9 by releasing L1CAM [23]. Hijacking of the SCs in the autonomic nervous system to cause perineural invasion is also common in colon cancer, melanoma,
and kidney cancer [25,59,66]. In pancreatic cancer, SCs play a significant role in both EMT and MET and are activated by EVs increasing SC exposure to IL-8 [18]. The significant effect of SCs in metastatic change in the PNS but also their influence on the BBB and immune system indicate the importance of continued research in this field.

The information in this review shows the lack of clinical diagnosis of SC identification in brain metastasis and discusses research specific to primary cancers that could shed light on the mechanisms for metastasis from each of these cancer types. With this information, future research can focus on these mechanisms to potentially target treatments for patients at high risk for SC-involved brain metastasis. Specifically, future research in this area should focus on how cancer cells affect repair SCs that have already been activated from nerve injury and delve deeper into how SCs can be activated by EVs. Additionally, looking into metastasis in demyelinating diseases that are comorbid with primary cancers could be a novel way to examine how damaged SCs might impact or slow metastasis.

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