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Schwann Cells in Peripheral Cancers: Bystanders or Promoters?

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The tumor microenvironment is subject to intense investigation in terms of its influence on tumorigenesis. Despite the fact that Schwann cells are cancer cells' early interaction partners, investigations on tumor progression and the molecular drivers of carcinogenesis do not place enough emphasis on them. Recent studies have shown that malignant cells and nerves interact on several levels during early carcinogenesis. For instance, the emergence of nerves in cancer, known as cancer neo-neurogenesis, is one important mechanism that contributes to cancer progression. Recent studies on Schwann cells brought the investigation of tumor–nerve interactions to a whole new level. Schwann cells make up the majority of glial cells in the peripheral nervous system, are outstandingly plastic cells, and serve a variety of roles in most organs. All these properties make Schwann cells excellent potential targets for tumor cells to exploit and turn them into promoters of carcinogenesis. In the present review, the distinctive features of Schwann cell–tumor cell interactions and the implications of this interaction on the tumor microenvironment are outlined. Further, this study points out the neglected aspects of Schwann cells in the tumor microenvironment and provides a potential new avenue for future research.

1. Introduction

The tumor microenvironment is built up of a wide variety of elements like the extracellular matrix (ECM) components and various cell types, including immunosuppressive immune cells, macrophages, regulatory T cells, cancer-associated fibroblasts, endothelial cells, also nerves[1] (**Figure 1**). All these cell types have been shown to contribute to tumor evolution in multiple ways. Yet among these, glial cells have received only very little attention. In fact, recent studies have shown that glial cells, particularly Schwann cells, may play an essential role during cancer progression.[2,3] Based on these findings, Schwann cells are now believed to possess the potential to drive tumorigenesis, to produce signals to promote cancer invasion, and to reshape the ECM.[2,3] However, Schwann cells in cancer are still underinvestigated, and especially mechanistic studies are largely lacking to date. In this review, we illustrate and discuss the role of Schwann cells in the tumor microenvironment and also outline their modulatory effects on non-cancerous cells in tumors. Moreover, we draw attention to uninvestigated aspects of Schwann cells in cancer and thus propose potentials new avenue for future research.

2. Schwann Cells: Beyond Repair and Regeneration

Schwann cells are the prevailing glia cells in the peripheral nervous system.[8] They have immunomodulatory, inflammatory, and regenerative capabilities.[9] As a cardinal component of peripheral nerves, they maintain homeostasis in the peripheral nervous system and modulate neuronal function and repair.[8] Unlike oligodendrocytes in the central nervous system, Schwann cells can be regenerated if their neurolemma is damaged.[8] Moreover, Schwann cells are able to change their phenotype and undergo cellular reprogramming in response to nerve damage, enabling peripheral nerve regeneration, possibly both directly and indirectly.[10,11] As part of the indirect regeneration, Schwann cells may recruit immune cells, such as macrophages, to support the regeneration of injured peripheral nerves.[12,13] On the other hand, as part of the direct regeneration, the injured nerves' Schwann cells undergo an epithelial–mesenchymal transition (EMT)-like process.[14] Within this process, the Myc stemness and core pluripotency modules are activated, and the polycomb-related factors are inhibited.[15] This is in accordance with the well-established relationship between

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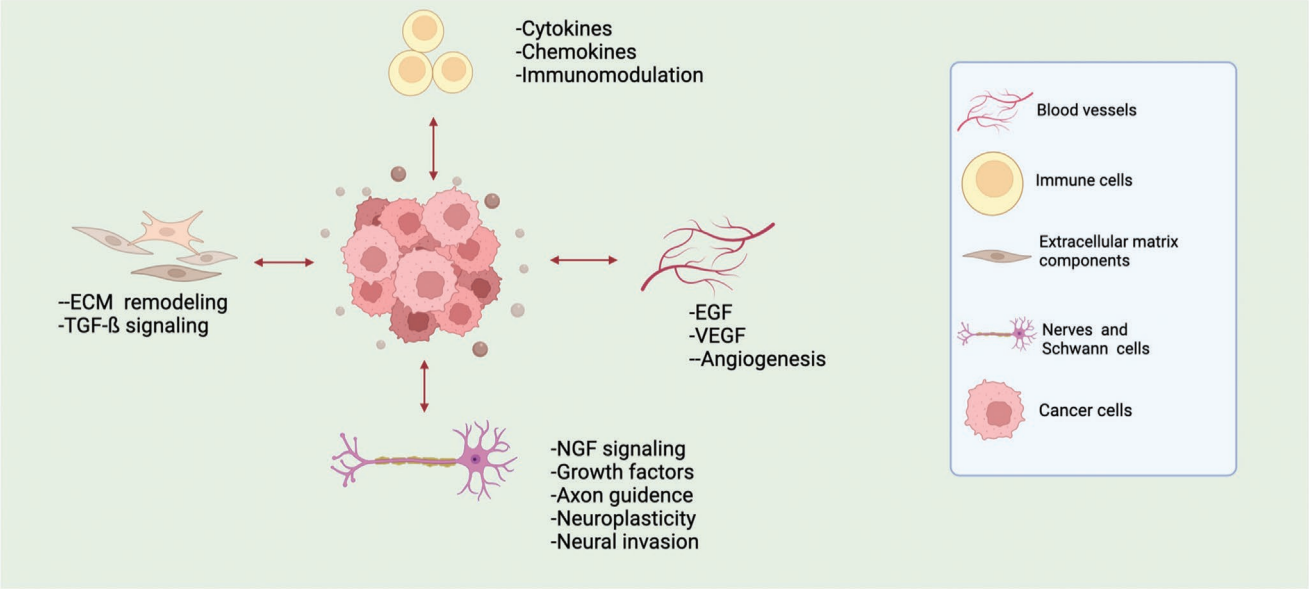

Figure 1. A schematic representation of the tumor microenvironment. The growth and evolution of solid tumors are influenced by a variety of cell types and signaling molecules.[1] Immune cells secrete cytokines and chemokines in response to the immune–cancer cell interaction, resulting in immunomodulation.[4] Stromal-extracellular matrix components, such as collagen and fibronectin, are also found in the tumor microenvironment. They enable ECM remodeling and shape the stroma of the tumor microenvironment.[5] When blood vessels interact with cancer cells, they proceed to secrete epidermal growth factor and vascular endothelial growth factor, which promote angiogenesis.[6] Neurons and Schwann cells secrete growth factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF), which promote axon guidance and neural invasion.[7] Created with BioRender.com.

EMT and cell survival, as EMT allows cells to evade cell death mechanisms such as apoptosis, anoikis and senescence.[16] Furthermore, tissue regeneration in the distal stump comprises the conversion of myelin and non-myelin Schwann cells into repair cells in Bungner bands, whereas the studies on the tissue modification in the bridge indicated a migration of Schwann cells, fibroblasts, and immune cells to generate new tissue.[17,18] Clements et al. stated that EMT/stemness shift of Schwann cells in the bridge, connected with transforming growth factor (TGF) signaling, is a prominent inducer of EMT and stem cell features.[15] Therefore, in direct regeneration, Schwann cells acquire trophic features and exhibit enhanced growth, thereby supporting nerve regeneration.

Interestingly, another study found convincing evidence that solid tumors can damage and even kill neurons as they grow, causing glial cells around the tumor to activate neurodegenerative and nerve repair processes.[19] In the same study, it was reported that the tumor cells can use the neuroregenerative properties of Schwann cells for their own favor. In fact, the observation of damage to intratumoral nerves in cancer is quite an old one, and was, for example, reported in 1994 by Dale Bockman in electron microscopic studies in pancreatic cancer.[20] He stated that the cancer cells penetrate the perineurium and becomes intimately associated with Schwann cells and axons in the endoneurium, and that nerves are damaged in their integrity.

These findings can be considered as one of the indicators for the critical role of Schwann cells in the tumor microenvironment in terms of regeneration and repair. Furthermore, due to their extensive distribution throughout the body, these cells are an attractive target for malignant cells, especially during the early stages of cancer development and the formation of the tumor microenvironment.[21,22]

3. Cross-Talk between Schwann Cells and Cancer Cells during Tumor Progression in Peripheral Cancers

Several in vitro and in vivo studies revealed a mutual attraction between cancer cells and Schwann cells.[2,3,23] Accordingly, Schwann cells have been shown to actively migrate toward cancer cells and their precursors.[2,23] Schwann cells have been detected around pancreatic intraepithelial neoplasms and intestinal adenomas before perineural invasion (PNI) and severe malignancy.[23] This emergence of Schwann cells around premalignant lesions of pancreatic and colon cancer is thought to be an early indicator and driving factor of tumor formation.[2,3,23] Following the migration, Schwann cells can also obtain anti-nociceptive features in the example of pancreatic cancer, possibly delaying the diagnosis.[21] Importantly, the early emergence of Schwann cells around precursor lesions of cancer is assumed to be the initiator of PNI.[2,23] This "carcinotropism" of Schwann cells seems to be mediated by four different classes of molecular mediators, i.e., neurotrophins (nerve growth factor/NGF, brain-derived neurotrophic factor/BDNF, neurotrophin-3, neurotrophin-4), glial-cell-line-derived neurotrophic factor (GDNF) family (GDNF, neurturin, artemin, persephin), guidance molecules (semaphorins, Slit, plexin family), and other molecules such as matrix metalloproteases and neurotransmitters such as acetylcholine.[3] In pancreatic cancer, the chemoattraction of Schwann cells to cancer precursors was markedly attenuated upon genetic or pharmacological targeting of the low-affinity NGF receptor p75NTR.[23]

Solid tumor innervation has been proposed as a way to restore the natural nerve degeneration and regeneration processes that occur during tissue repair.[24] Schwann cells may potentially

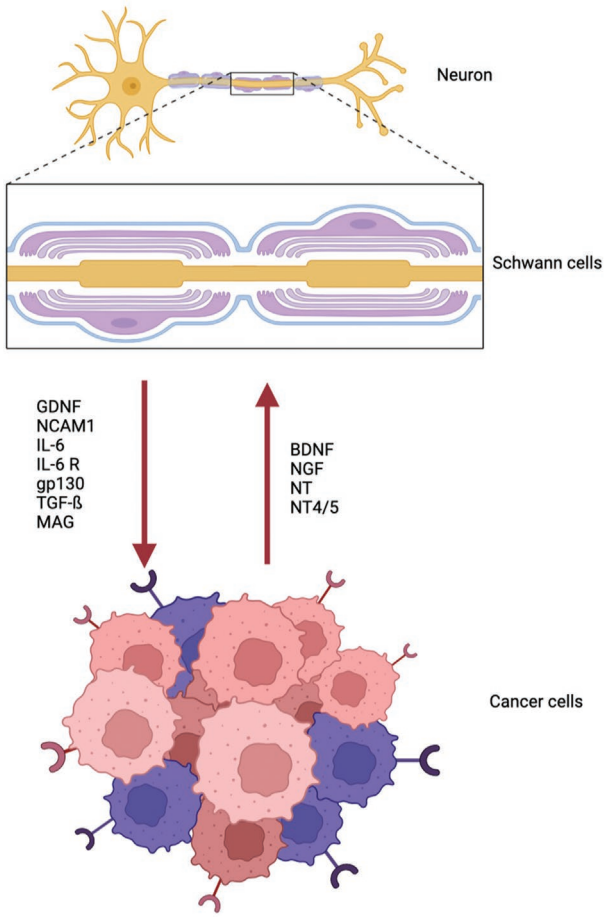

Figure 2. The bidirectional interaction of Schwann cells and malignant cells. The compensating interaction between cancer cells and Schwann cells is provided by various signaling molecules, thereby transforming the cell structure and functioning to support the malignant spread of cancer. NGF, BDNF, NT3, NT4/5, and other neurotrophic factors secreted by tumor cells enhance the tumor cell migration towards nerves through binding to the TrkA receptor and the p75NTR.[3] Schwann cells produce GDNF, which interacts with the GDNF Receptor Alpha (GRF) to initiate migratory signaling pathways.[3] Schwann cells also release cytokines such IL-6, soluble IL-6R, and sgp130, which stimulate the STAT3 / AKT pathway, which constitutes a significant mechanism in tumor inflammation.[38,39] Schwann cells also express NCAM1,[2] a cell surface adhesion protein that promotes tumor migration, and myelin-associated glycoprotein/MAG, which enhances their adhesive properties.[40] Created with BioRender.com.

have a role in tumor innervation as well as contribute to the environment that promotes and supports tumor development. Even though Schwann cells' primary function is to maintain axonal integrity and nourish axons, they also promote pancreatic cancer and guide malignant cells to migrate toward nerves, contributing to the perineural invasion[23,21] (**Figure 2**). In addition Ferdoushi et al. showed with their in vitro experiments that Schwann cells might secrete proteins, such as matrix metalloproteinase 2, cathepsin D, plasminogen activator inhibitor-1, or galectin-1, that promote pancreatic cancer cell proliferation and invasion.[25] The oncogenic potential of pancreatic cancer cells is also supported by Schwann cell-derived TGFß.[26] In the example of cervical cancer, Huang et al. demonstrated that Schwann cells triggered by cancer cells have an increased expression of metalloproteinases, such as MMP2, MMP9, and MMP12, which dissolve the extracellular matrix and create a perineural invasion-facilitating tumor microenvironment.[27] Moreover, the same study also revealed that Schwann cells promote the proliferative and invasive properties of cancer cells via the secretion of CCL-2.[27]

Just like in tissue healing, reprogramming of Schwann cells to a pre-repair progenitor-like state shows that Schwann cells' flexibility and their diverse regenerative strengths may contribute to the plasticity of the tumor microenvironment.[28] According to current discoveries, the microenvironment itself is also likely to have the ability to increase the flexibility of Schwann cells and to activate them.[29] In oral cancer, the Schwann cells are activated by TNFalpha overexpressed in human oral cancer tissues.[30] Activated Schwann cells not only promote oral cancer proliferation but also release pro-nociceptive mediators. In contrast, the activation of Schwann cells was linked to analgesia in the pre-invasive stage of pancreatic cancer.[21,31] Based on these findings, Schwann cells not only play a key role in cancer progression, but also in cancer-related pain. Recently, the transient receptor potential ankyrin 1 (TRPA1) channel, which is typically expressed by nociceptors, was detected on Schwann cells and to be a major mediator of neuropathic and cancer-induced pain through promotion of macrophage infiltration and oxidative stress around nociceptors.[32,33]

It has been revealed that neurons protect cancer cells from starvation and support tumor progression by secreting serine in a serine-deprived pancreas cancer microenvironment.[34] Given these findings, and the fact that Schwann cells are the primary contact partners of malignant cells, the impact of Schwann cells on amino acid pathways in the tumor microenvironment should be investigated. Moreover, in one of the recent studies, palmitic acid, a dietary metabolite, was shown to cause stable transcriptional and chromatin changes in the tumor that cause long-term stimulation of metastasis.[35] These changes were linked to a pro-regenerative state of Schwann cells, which become active by interacting with the tumor and produce increased amounts of a regenerative matrix.[35] Based on these findings, the interactions of Schwann cells with the protein and lipid metabolism and the impact of these interactions on cancer cell metastasis could constitute an exciting, new field of investigation in the future.

Although it is known that Schwann cells induce EMT, drive cell migration to the nerves in pancreatic cancer[36] and can stimulate metastasis,[35] the molecular mechanisms and elements that Schwann cells utilize to promote metastasis remain unclear. In the example of lung cancer, however, it has been shown that Schwann cells can expedite lung cancer cell metastasis by promoting the EMT of lung cancer cells by upregulating the Twist and Snail expression in cancer cells.[37]

4. Schwann Cells and Their Roles in Immunomodulation

The significance of the neuroimmune axis in the tumor microenvironment is not well understood, and less is known about how regulating neuroimmune crosstalk in cancer could impact tumor formation. There are genetic, phenotypic, and functional

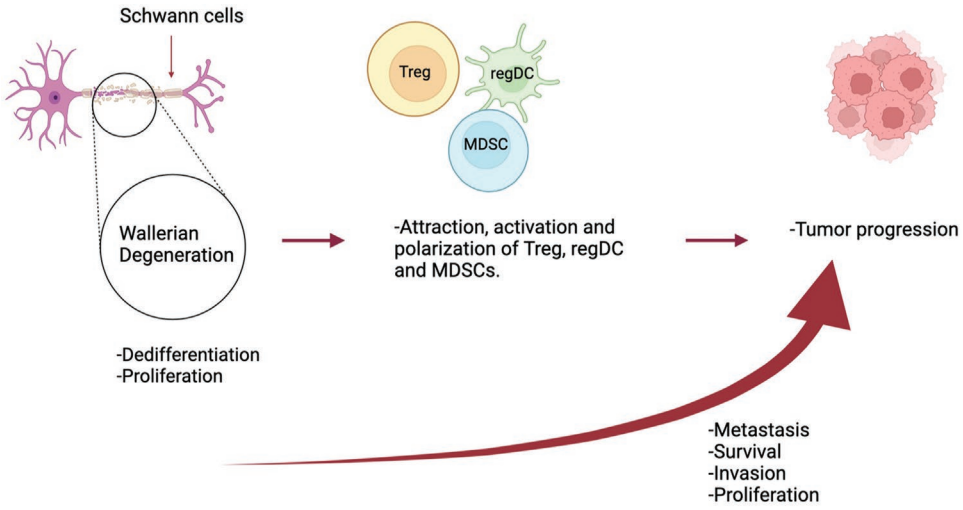

Figure 3. The neuro-immune axis of the tumor microenvironment. Different subsets of immune effector and regulatory cells, as well as neurofilaments and neuroglial cells, each play a role in the tumor's survival and spread by surviving the immune system filter and promoting tumor development in the tumor microenvironment. Schwann cells, which dedifferentiate and proliferate as part of the Wallerian degeneration, support the tumor progression by accelerating the perineural invasion, enhancing the migratory capacity of tumor cells and recruiting cancer cells to nerve fibers. Schwann cells also operate as immunomodulators, attracting immature myeloid, dendritic and T cells and polarizing them into immunosuppressive myeloid derived suppressor cells (MDSCs), regulatory dendritic cells (regDC) and regulatory T cells (Treg).[46] Created with BioRender.com.

similarities between tumor-reactive Schwann cells (repair-like Schwann cells) in the tumor microenvironment and nerve-damage repair Schwann cells.[19,41]

There may be a link between Schwann cells and the immune response of the microenvironment to the tumor (**Figure 3**). In vitro experiments have shown that Schwann cells can lead to the M2-phenotype in macrophages that support the repair of peripheral nerves.[42,13,43,44] Likewise, Schwann cells were shown to promote the M2 polarization of macrophages in lung cancer, which supports the proliferation of lung cancer cells.[44] In cancer, a similar profile of tumor-associated macrophages is linked to poor prognosis.[45] Schwann cells most likely alter the immune system and tumor microenvironment either directly after getting activated by tumor cells, or indirectly by the tissue damage induced by the tumor.[46] Schwann cells can also polarize dendritic cells in melanoma mice models by adopting an administrative phenotype.[47] These findings are crucial in understanding the possible reasons why melanoma cells in contact with Schwann cells have a more rapid tumor development compared to melanoma cells without any Schwann cell contact.[19] Although Schwann cells have been shown to have similar effects in other peripheral cancers, the clarification of the underlying mechanisms of these trophic and pro-tumorigenic effects remains as an objective for future studies.

In addition to their direct effects on malignant cells, Schwann cells impact the production of numerous chemokines and can modify the immune response in this context by recruiting myeloid derived suppressor cells (MDSCs) into the tumor environment.[41] The immunosuppressive capacities of MDSCs can be verified by measuring the suppression of pre-activated T cells. For instance, Martyn et al. was able to show that tumor-conditioned Schwann cells were not only able to attract MDSCs, but they also enhanced their immunosuppressive properties in vitro.[46] The mechanistic steps of this attribute of Schwann cells, however, are yet to be elucidated.

5. Directions of Future Studies and Conclusion

Schwann cells play an important role in the immunological control, nerve regeneration and maintenance, and non-neuronal tissue regeneration. The tumor microenvironment encompasses a wide variety of cells, i.e., blood vessels, lymphatic system, immune and stromal cells and elements. These benign cells contribute to the growth of the tumor through many pathways and molecular players. Cancer cells and other elements in the tumor microenvironment might be affected directly or indirectly by the cells of the nervous system. Although similar interactions have been observed in the cancerous microenvironment of the central nervous system, nerve fibers and glia in the periphery, particularly Schwann cells, have received less attention. Studies suggest that Schwann cells play an active and crucial part in the tumor microenvironment. In order to better understand tumor development and create suitable treatment strategies, it is critical to identify the activities and interactions that Schwann cells undertake in the tumor microenvironment, particularly considering their vast contribution to tissue plasticity.

Although previous studies have clearly shown the mutual tropism between Schwann cells and cancer cells, the underlying mechanisms and molecular players are still unclear. Furthermore, it is also now known whether these mechanisms and modes of activation of Schwann cells are comparable between different forms of cancer. When considering the tumor microenvironment and its heterogeneity, it seems possible that differences in the availability of various neurotrophic factors and inflammatory cytokines may lead to different types of tumor cell-Schwann cell interactions in various cancer types. As such, different cancer types may have divergent Schwann cell activator molecules, e.g., tumor necrosis factor alpha (TNFalpha), IL6, or CXCL12.[21] It is also conceivable that the induction of mechanisms proceeds in a cascade, with one mechanism

igniting the activation of another. A particular emphasis should be placed on the impact of Schwann cells on protein and lipid metabolism, as this interaction has recently been shown to impact cancer cell metastasis.[35] It is also imaginable that Schwann cell-derived metabolites are necessary for cancer growth, similar to what has recently been shown for neuron-derived serine in cancer.[34]

A comprehensive understanding of Schwann cell activation in various cancers, the modes and mechanism of activation, and the interplay between other stromal elements, are likely to guide future tumor-targeting treatment strategies that incorporate this exciting class of cells.

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Conflict of Interest

The authors declare no conflicts of interest.

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