Cancer Immunol Immunother (2017) 66:959–968
DOI 10.1007/s00262-016-1929-z

FOCUSSED RESEARCH REVIEW

Schwann cells: a new player in the tumor microenvironment

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Received: 3 September 2016 / Accepted: 14 November 2016 / Published online: 24 November 2016

Abstract Cancerous cells must cooperate with the surrounding stroma and non-malignant cells within the microenvironment to support the growth and invasion of the tumor. The nervous system is a component of every organ system of the body, and therefore, is invariably at the front line of the tumor invasion. Due to the complexity of the nervous system physiology, this review separately discusses the contributions of the central and peripheral nervous systems to the tumorigenesis and tumor progression. We further focus the discussion on the evidence that Schwann cells aid in tumor growth and invasion. Schwann cells, a largely unexplored element of the tumor microenvironment, may participate in the creation of tumor-favorable conditions through both bi-directional interaction with cancer cells and the facilitation of the immune-suppressive microenvironment through the mechanism of neural repair and immunomodulation.

Keywords Tumor microenvironment · Schwann cell · Nervous system · Neuroinflammation · Regulatory myeloid suppressor cells

Abbreviations

BDNF	Brain-derived neurotrophic factor
CCR1	C-C chemokine receptor type 1
CNS	Central nervous system
CXCR4	C-X-C chemokine receptor type 4
DRG	Dorsal root ganglia
ERK	Extracellular signal-regulated kinase
GDNF	Glial cell-derived neurotrophic factor
HER2	Human epidermal growth factor receptor 2
IFN-α	Interferon alpha
IL	Interleukin
IP-10	Interferon gamma-induced protein 10
JNK c-Jun	N-terminal kinase
MAG	Myelin-associated glycoprotein
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein 1
MDSC	Myeloid-derived suppressor cell
NCAM	Neural cell adhesion molecule
NF-κB	Nuclear factor of kappa light polypeptide gene enhancer in B-cells
NGF	Nerve growth factor
NRG1	Neuregulin 1
NTRK1	Neurotrophic receptor tyrosine kinase type 1
P75NTR	p75 neurotrophin receptor
PNS	Peripheral nervous system
SNS	Sympathetic nervous system
STAT1	Signal transducer and activator of transcription 1
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor alpha

This paper is a Focussed Research Review based on a presentation given at the conference *Regulatory Myeloid Suppressor Cells: From Basic Discovery to Therapeutic Application* which was hosted by the Wistar Institute in Philadelphia, PA, USA, 16th–19th June, 2016. It is part of a *Cancer Immunology, Immunotherapy* series of Focussed Research Reviews.

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Introduction

It is now well established that cancer cells rely on the recruitment and interaction with various non-malignant cells to support tumor growth, creating what is referred to as the tumor microenvironment [1, 2]. Endothelial cells, fibroblasts and other stromal cells, as well as various immune cells play an important role in enabling or enhancing tumor capabilities [2]. Similar to the vasculature, neurons are found in virtually every organ system of the body and therefore serve as an early witness of the emerging tumor. The nervous system is not a simple bystander, however, and has also been extensively implicated in promoting tumor growth and progression. For simplicity, the discussion in this article is divided into two parts: the central nervous system (CNS), which includes the brain and the spinal cord, and the peripheral nervous system (PNS). PNS can be further subdivided into afferent neurons which sense various ques and send signals from the periphery to the CNS, and efferent neurons which control the motor and autonomic functions via the signaling from the CNS to the peripheral organs. Sympathetic and parasympathetic neurons comprise the visceral efferent system, controlling the involuntary activity of the body such as heart rate, respiration and perspiration.

In the last two decades, preclinical and clinical studies have established examples of the interaction between CNS as well as peripheral neurons and some tumors. We will review here several of these examples which implicate nervous system in playing either a direct role or indirectly influencing the tumor microenvironment.

Neuroglial cells (glia or neuroglia) are non-neuronal cells that provide support and protection for neurons through myelin formation and maintenance of homeostasis. In the CNS, glial cells include astrocytes, oligodendrocytes, ependymal cells and microglia. Schwann cells and satellite cells comprise the glia of the PNS. The glia of the CNS is known to contribute to the establishment of the microenvironment niche for brain metastasis through the production of pro-inflammatory mediators. The role of the peripheral glia in tumorigenesis and tumor progression is less defined. Schwann cells, which are best known for myelinating peripheral nerves, play an important role in neural regeneration, in part though the modulation of the immune system. In doing so, Schwann cells may be inadvertently aiding in the maintenance of microenvironment favorable to the tumor progression. We will review what is known currently about the interactions of tumors with Schwann cells, and provide additional perspective on the possible role Schwann cells play in modulating the tumor microenvironment.

Central nervous system

The potential bidirectional link between the brain and the peripheral malignant tumor has been the subject of multiple studies [3, 4]. Clinical imaging studies detect altered brain metabolism in patients with malignant disease [5–7]. Epidemiological studies indicate that psychosocial factors such as stress, depression and social isolation likely play a role in cancer progression [8–11]. These results indicate that CNS may sense and affect tumor progression, but while psychosocial interventions that teach stress management often provide positive effects on the quality of life [12], it remains controversial whether such interventions ultimately affect cancer progression and survival [13–16]. Nevertheless, accumulating evidence from clinical, in vitro and in vivo studies highlights specific stress response pathways which may influence cancer progression [17]. These stress response pathways directly affect well known "hallmarks of cancer" [1], including tumor proliferation and invasion, angiogenesis and evasion of the immune surveillance. The main signal transduction during the activation of the stress response occurs through the hypothalamic–pituitary–adrenal axis or the autonomic nervous system. The hypothalamic–pituitary–adrenal stress response results in downstream release of glucocorticoid hormones such as cortisol from the adrenal cortex [18]. Stress also modulates the levels of other neuroendocrine factors such as substance P, nerve growth factor, dopamine, oxytocin and prolactin [17, 19]. Patients with cancer exhibit alterations in diurnal serum cortisol rhythms [20], and flattening of such rhythms in patients with breast and lung cancer predicts early mortality [21, 22]. Several cancer cell types downregulate the expression of glucocorticoid receptor to escape glucocorticoid-induced apoptosis [23, 24]. Additional direct protumorigenic effects of glucocorticoids may be through the compromise of DNA repair mechanism [25], or the suppression of cell-mediated immunity [26]. The stress response may, therefore, contribute to tumor progression, but it is still unknown whether the CNS receives signaling from the periphery about the presence of the tumor, and if so, how is that information processed and what responses are generated as a result?

Autonomic nervous system

The peripheral autonomic nervous system regulates gene expression of the cancer cells directly and elicits a wide influence on the tumor microenvironment [27]. The sympathetic nervous system (SNS) in particular plays a major role in tumorigenesis [27]. Practically, all organ systems

in humans are regulated by the SNS via the catecholamine neurotransmitters either through the release of norepinephrine by the tissue localized nerve terminals or through the vascular distribution of epinephrine secreted by the adrenal gland. The influence of the SNS on tumor progression likely occurs not via an acute "fight-or-flight" stress response, but through sustained changes in basal levels and circadian cycles of SNS activity leading to durable alteration of the gene expression profile of cancer and supporting stroma elements [28–31]. Catecholamines released by the SNS bind adrenergic receptors which are expressed by most tissues and organ systems, including tumor cells and tumor stroma [32, 33]. The density of autonomic nervous fibers in prostate cancer and surrounding tissue is associated with poor clinical outcomes [34], and the link between SNS signaling and cancer is further supported by pharmaco-epidemiologic studies which suggest that β-adrenergic antagonists may reduce the progression of certain tumors [33, 35–38]. Chronic and circadian variations in the SNS activity alter hematopoietic environment, leading to a shift toward a pro-inflammatory pool of circulating leukocytes [39]. In addition, β-adrenergic signaling within tumor microenvironment may lead to the release of pro-inflammatory cytokines, chemotactic and pro-angiogenic factors, and matrix metalloproteinases, further aiding in tumor survival and progression [40–46]. Catecholamines may also lead to chromosomal instability and tumor initiation via direct effects of β-adrenergic signaling on tumor cells such as activation of Src and HER2 oncogenes [47, 48], inhibition of DNA damage repair and apoptosis [49, 50].

It is evident through the multitude of the epidemiologic and experimental body of work that stress response induced through the CNS driven hypothalamus–pituitary–adrenal axis and the sympathetic nervous system plays a significant part in the early stages of tumor progression via direct effects on the malignant cells and indirectly via aiding in the creation of tumor-favorable microenvironment.

Afferent nervous system

Compared with the SNS, much less is known about the role of the afferent (sensory) division of the PNS in tumor progression. Ablation of the sensory neurons in the mouse models of basal cell carcinoma and pancreatic ductal adenocarcinoma attenuates the initiation and progression of tumors [51, 52]. Thus, while this area of research is still in the early phase, sensory neurons likely make an important contribution to the tumor microenvironment. Most organs are innervated by the sensory neuron fibers through either the nodose (via the vagal nerve) or the spinal ganglia (via splanchnic nerves). The bulk of the cell soma of primary afferent neurons is located in the dorsal root ganglia (DRG) of the vertebral column. Pain, temperature, pressure, proprioception and other sensory information is carried by afferent neurons to the CNS. In response to tissue damage, injury or infection, DRG neurons are able to modulate the inflammatory response through the production of chemokines, cytokines and their associated receptors, including IL-1, IL-6, TNF-α, MCP-1, IP-10, CCR1 and CXCR4 to name a few [53–56]. Sensory neurons also produce neurotrophic factors, Toll-like receptors [53, 56, 57], and secrete histamine and glutamate as well as neuropeptides such as substance P, vasoactive intestinal polypeptide and calcitonin [58, 59]. Neurogenic inflammation has been primarily studied in the context of neurodegeneration, neuropathic pain and chronic pain syndrome [53, 56].

Most of the work on the relationship between afferent neurons and cancer focused on cancer-related pain syndrome and perineural invasion [60–62], two processes which are directly related to the pro-inflammatory activity of the sensory neurons and the upregulation of neurotrophic factors. The link between neurogenic inflammation and the development of cancer is well illustrated by the studies of the mouse models of pancreatitis and pancreatic cancer. Chronic pancreatic inflammation is a significant risk factor for the development of adenocarcinoma in humans. DRG-driven neurogenic inflammation in the spinal cord occurs early in the development of pancreatic ductal adenocarcinoma, promotes cancer associated pain and perineural invasion and is significantly reduced upon ablation of sensory neurons, slowing tumorigenesis and leading to the increase in overall survival [52, 63]. Direct effects of tumor on the sensory neurons and specific mechanisms by which DRG neurons may support pro-tumorigenic microenvironment remain largely undetermined. We have recently demonstrated that mouse B16 melanoma directly stimulates the growth of DRG neurons in vitro, altering their chemokine expression and leading to chemoattraction of MDSCs [64]. The presence of DRG neurons in the melanoma in vivo was associated with the enrichment of intra-tumoral granulocytic subset of MDSCs and the acceleration of tumor growth [64]. Therefore, the creation of immunosuppressive pro-tumorigenic microenvironment through the chemoattraction of MDSCs may be one way DRG neurons are utilized by cancer cells to support tumor progression.

Co-culture experiments of tumor cells and neurons demonstrate that human prostate cancer, pancreatic cancer and colon adenocarcinoma cells are able to induce neurite extensions by the neurons [65–68]. Reciprocal effect of neurons on cancer cells increases their migratory potential in vitro [69–71]. Based on the in vitro data, it is, therefore, reasonable to expect an enhanced density of nerve fibers within the tumor. However, while some studies do provide evidence of neurogenesis within the tumor

[34, 66, 68, 72–74], others report normal or even reduced neuronal density within the tumor foci, and the presence of nerve fibers exclusively around the vasculature or in the peripheral stroma of the tumor [75–78]. The challenge in quantifying neuronal fibers by immunohistochemistry and the difficulty of differentiating between autonomic and sensory fibers in tissue may contribute to the discrepancy of reported tumor innervation. However, it is now clear that peripheral neurons, both afferent and efferent fibers, contribute to tumor progression through the modulation of the tumor microenvironment.

Neuroglia

Similar to the neuronal fibers, the glia of the CNS and the PNS are the source and target of chemokines, cytokines, neuropeptides and neurotrophic factors and participate in signaling with neurons, immune cells and other stromal components [53]. Glial cells such as astrocytes and Schwann cells express TLRs and Nod-like receptors which enables them to respond to neuronal injury, tissue damage or infection [79–81]. Neuroglia of the brain has been implicated in the pathogenesis of neurodegenerative diseases, traumatic brain injury and epilepsy [82–84], while peripheral glia has been extensively studied in the context of demyelinating diseases and peripheral neuropathy [85, 86]. Significantly, less is known about the role of glia in the tumor microenvironment.

The glia of the CNS has been largely investigated in the context of brain metastasis of breast or lung carcinoma. It is now well established that astrocytes are able to form gap junctions with the metastatic cancer cells, leading to the exchange of signaling molecules and the release of pro-inflammatory cytokines such as IFN-α and TNF-α [87]. The inflammatory microenvironment created by the astrocytes in this way further supports tumor growth and chemoresistance by activating NF-κB and STAT1 pathways and upregulating survival genes in breast and lung carcinoma cells [87–89]. The glia of the PNS has not been as rigorously studied. Specifically, how peripheral glia may contribute to tumorigenesis or tumor progression remains poorly understood.

Schwann cells

Schwann cells, the body's most widely distributed neural crest-derived cells, form the major component of the PNS glia, functioning in myelination, axonal maintenance and repair [90–92]. As is the case with afferent neurons, Schwann cells also participate in neuropathic pain and may promote cancer-related analgesia [93–95]. Perhaps the best example of the direct interaction between Schwann cells and the tumor is illustrated in neuroblastoma—malignancy which originates from primitive sympathetic nervous system, where the presence of Schwann cell-rich stroma correlates with differentiated tumor cells and a more favorable prognosis [96, 97]. Low vascularity in Schwann cell-abundant stroma is another favorable prognostic factor in neuroblastoma, and part of the explanation may be attributed to an observation that Schwann cells can inhibit angiogenesis in vitro [98]. Another study described direct cross talk between neuroblastoma cells and Schwann cells via NRG1-mediated stimulation of Schwann cells by NTRK1-expressing tumor, leading to the expression of NGF by the activated Schwann cells, which in turn promoted the maturation of neuroblastoma [99]. The expression of neurotrophic factors by Schwann cells such as NRG1 and NGF and their tyrosine-kinase receptors of ErbB, p75 and Trk families is essential for Schwann cell development, proliferation, migration, as well as myelination and neuronal regeneration [90–92, 100]. Tumor types which share neural crest origin with Schwann cells, such as neuroblastoma and melanoma, also strongly rely on these signaling pathways. It is, therefore, reasonable to expect bidirectional communication between Schwann cells and tumor cells through neurotrophic and, likely, other factors. However, it is yet unclear whether these signaling pathways promote or inhibit tumor progression. For example, elevated expression of ErbB2 and ErbB3 carries an unfavorable prognosis in melanoma, breast and lung carcinoma, while the opposite appears to be true for neuroblastoma [101, 102]. Interestingly, recent study demonstrated a significant reduction of sympathetic nerve fibers, Schwann cells and nestin^{+} mesenchymal stem cells in the bone marrow of patients with myeloproliferative neoplasms and mouse model of the disease [103]. Nestin^{+} mesenchymal stem cells also originate from the neural crest, and together with their sympathetic innervation and supporting Schwann cells form hematopoietic stem cell niche, abrogation of which leads to myeloproliferative neoplasms [103, 104].

The presence of Schwann cells in the tumor stroma is a subject of some debate. Data supporting the migration of Schwann cells to the tumor parenchyma are contradicted by several examples of possible dedifferentiation of tumor cells to glial phenotype [105–109]. However, numerous examples in vitro and in vivo demonstrate mutual affinity of cancer cells and Schwann cells, supporting the hypothesis that Schwann cell presence in tumor microenvironment results from their migration. Schwann cells were found to migrate to the pancreatic intraepithelial neoplasm and intestinal adenoma in humans and mice before the onset of perineural invasion and advanced malignancy [110]. The strongest evidence for tumor cell-glial tropism comes from the models of perineural invasion [111]. Schwann

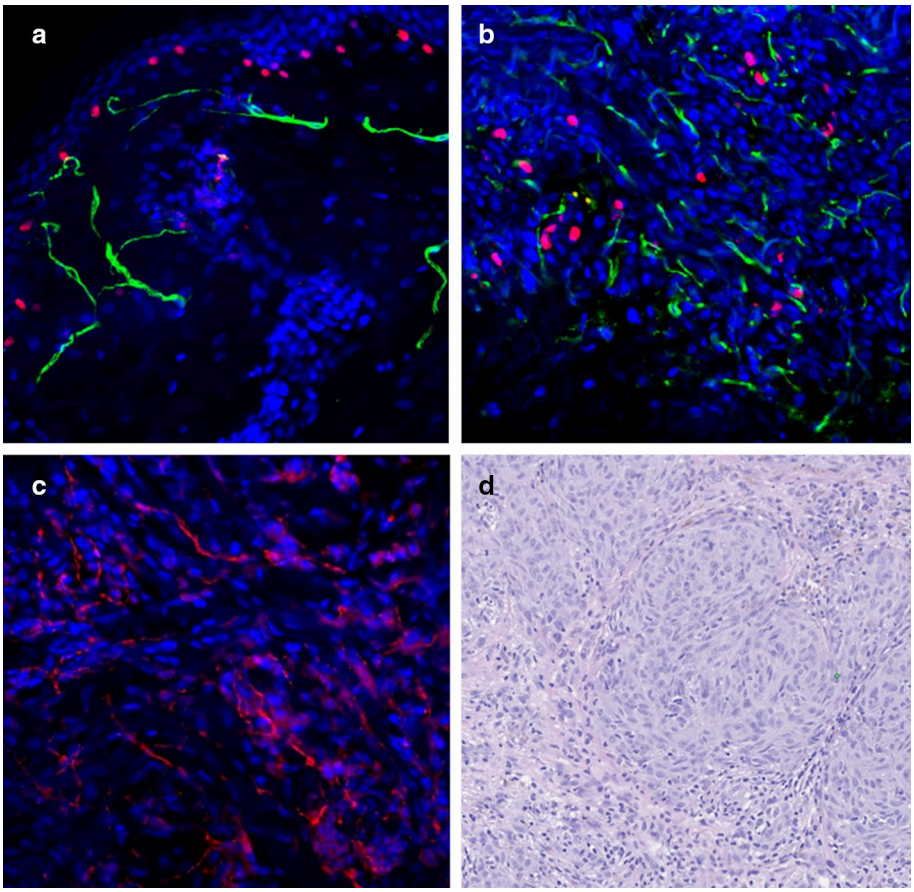

Fig. 1 Co-localization of neuronal fibers, Schwann cells and malignant melanoma cells in human skin. Schwann cells and neuronal fibers in normal human skin and human melanoma were determined by immunohistochemistry. Representative fluorescent images of normal human skin (**a**) and human primary melanoma (**b**, **c**) are shown. H&E staining of human primary melanoma is also shown (**d**). Staining: *red* MITF, for melanocytes; *green* p75NGFR, for Schwann cells (**a**, **b**). *Red* PGP9.5, for neuronal fibers (**c**). Magnification: ×20

cells may be able to promote perineural invasion of neurotropic tumor by direct contact with cancer cells in an integrin, NCAM-1, or MAG dependent manner [112–114]. We observe Schwann cells and neuronal fibers within the stroma of the invasive human melanoma (Fig. 1).

The abundance of Schwann cells in most organs and their virtually assured presence adjacent to early malignancy and within tumor microenvironment suggests that they may play a role in tumor progression or suppression. The question of how Schwann cells modulate tumor microenvironment remains largely unanswered. Schwann cells may interact with neuronal fibers and cancer cells directly, as well as with other stromal cells and immune cells. Furthermore, they are responsible for the remarkable robust regeneration response of the PNS after nerve injury [115, 116]. Axonal injury is followed by the loss of the neural fiber distal to the injured site (termed Wallerian degeneration), and the elimination of the contact between the axon and the supporting Schwann cells [117]. Those Schwann cells without contact with the axon undergo a series of signaling cascades leading to their dedifferentiation, proliferation and repair of the damaged nerve [116]. Within hours of nerve injury, supporting Schwann cells undergo an increase in the activity of multiple pathways, including Notch, JNK/c-Jun and ERK/MAPK [118, 119], and an increase in the expression of neurotrophic factors and their receptors, such as BDNF, GDNF, p75NTR and NRG1, as well as elevated secretion of cytokines and chemokines [116, 120]. Neuronal injury is followed by a local inflammatory response, and chemoattraction of macrophages in particular by the Schwann cells to the injured site aids in the clearance of myelin debris [117, 121, 122]. Interestingly, one study demonstrated that the process of Schwann cell dedifferentiation and immune cell recruitment in vivo may be triggered by the activation of only RAF/MEK/ERK pathway within the Schwann cells, even in the absence of nerve damage [123]. While the dedifferentiation of Schwann cells is critical to nerve injury response, these results suggest a possibility that activation of similar process may occur in other pathological states such as tumor invasion, and lead to Schwann cell modulation of the tumor microenvironment. Dysregulated tissue regeneration and chronic inflammation are the hallmarks of cancer [1, 124] in which Schwann cells could play a central role.

Schwann cells may be a link between cancer cells and a tumor-favorable immune response of the microenvironment. In vitro data suggest that Schwann cells may induce M2-phenotype in macrophages, which supports efficient

repair of the peripheral nerves [125, 126]. The same phenotype of tumor-associated macrophages is correlated with worse clinical prognosis in malignancies [127]. Whether through a direct tumor activation or tumor-induced axonal and tissue injury, Schwann cells likely modulate the immune system and the tumor microenvironment.

Conclusions

Tumor microenvironment has attracted much attention, and numerous examples of non-malignant cell contribution to tumor progression are emerging. Nervous system may directly or indirectly influence the cancer cells and the tumor microenvironment. The best examples of such modulation are from the work on the sympathetic nervous system. Sensory fibers and neuroglia are less well studied, but the emerging evidence illustrates that their function in the tumor microenvironment is important. Schwann cells, in particular, add an exciting new dimensionality to the tumor–stroma interaction research. Schwann cells are extraordinarily plastic cells with rich profusion in most organs and a multitude of functions, and additional studies are warranted to further uncover their role in creating specific tumor microenvironment and supporting tumor progression.

Acknowledgements The research is supported by P50CA121973 NIH Career Development Award to Y.L. Bunimovich.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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