Neuronal signatures in cancer

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Abstract
Despite advances in the treatment of solid tumors, the prognosis of patients with many cancers remains poor, particularly of those with primary and metastatic brain tumors. In the last years, “Cancer Neuroscience” emerged as novel field of research at the crossroads of oncology and classical neuroscience. In primary brain tumors, including glioblastoma (GB), communicating networks that render tumor cells resistant against cytotoxic therapies were identified. To build these networks, GB cells extend neurite-like protrusions called tumor microtubes (TMs). Synapses on TMs allow tumor cells to retrieve neuronal input that fosters growth. Single cell sequencing further revealed that primary brain tumors recapitulate many steps of neurodevelopment. Interestingly, neuronal characteristics, including the ability to extend neurite-like protrusions, neuronal gene expression signatures and interactions with neurons, have now been found not only in brain and neuroendocrine tumors but also in some cancers of epithelial origin. In this review, we will provide an overview about neurite-like protrusions as well as neurodevelopmental origins, hierarchies and gene expression signatures in cancer. We will also discuss how “Cancer Neuroscience” might provide a framework for the development of novel therapies.

KEYWORDS
cancer neuroscience, glioma neuroscience, neurobiology, neurodevelopment, tumor microtubes

1 | INTRODUCTION

Neurons can be found throughout the body, where they constitute the peripheral and the central nervous system (PNS and CNS, respectively). In recent years, it became evident that interactions between the nervous system and cancers can foster cancer growth,1,2 but also that tumor cells exploit neuronal and neurodevelopmental pathways to thrive.3 This concept of “Cancer Neuroscience” explains many features related to the basic biology and therapy resistance of primary and metastatic brain tumors, but has also a relevant impact on tumors outside the brain.1,4

Malignant gliomas, including glioblastomas (GBs), represent only 1% to 2% of all cancers,5 but are particularly disabling and lethal diseases6 due to the high resistance against cytotoxic therapies as well as the early diffuse colonization of the whole brain, which impedes complete surgical resection. Nowadays malignant gliomas are further subdivided based on molecular, epigenetic and genetic features.7,8 In addition, increasing evidence suggests that neurodevelopmental...
mechanisms involved in proliferation, migration and network formation are exploited by tumor cells to thrive. Brain metastasis of solid tumors is tenfold more common than primary brain tumors. Although of nonnervous system origin, brain-metastatic cells adopt to the brain microenvironment and can acquire neuronal characteristics. Importantly, increasing evidence suggests that this exploitation does not seem to be limited to brain tumors.

In this review, we will discuss how brain and some other tumors use neurite-like protrusions for invasion and the formation of multicellular networks, which neurodevelopmental pathways are exploited for the extension of these protrusions, how distinct neurodevelopmental origins provide an explanation for the heterogeneous brain tumor entities and which neurodevelopmental subpopulations can be found in different tumor entities. Recent findings demonstrate that these protrusions, pathways and subpopulations are also relevant in some tumor entities outside the brain, hence providing the basis for the field of "Cancer Neuroscience." Together this provides a framework for a better understanding of the fundamental biology of these cancers, including crucial mechanisms of progression and resistance, and finally new ideas how to target them.

2 | NEURITE-LIKE PROTRUSIONS IN PRIMARY BRAIN TUMORS

A few years ago, our group described that tumor cells of adult incurable gliomas extend neurite-like cellular protrusions which are not just used as leading structures for the diffuse infiltration of the brain parenchyma but also interconnect tumor cells to dense multicellular networks (Figure 1). Functional brain tumor cell networks have now been confirmed by other groups, and also in pediatric gliomas, particularly in those entities which are incurable and particularly malignant. These cellular protrusions have growth cone-like tips and were named "tumor microtubes" (TMs), as they are distinct from other protrusions described to play a role in glioma cells such as filopodia or invadopodia. The formation of TMs and multicellular networks is widely absent in 1p/19q-codeleted oligodendroglioma, which are characterized by sensitivity to cytotoxic therapies and a more benign course of disease. Recently, the neurite-like nature of TMs has been underlined by the identification of bona fide glutamatergic synapses on TMs. Synaptic input partially drives intercellular calcium waves between connected tumor cells.

These networks are of potential clinical significance as it could be demonstrated that interconnected cells are highly resistant against cytotoxic therapies, hence disconnection could emerge as a novel therapeutic paradigm. In addition, TMs allow efficient invasion of the brain parenchyma and lead to a repair response after surgery, which contributes to treatment resistance and glioma recurrence. A recent work by the group of Peter Friedl suggests that effective brain colonization even depends on the network formation by allowing a novel mechanism of collective cell migration: network invasion. In line with the neurite-like characteristics of TMs, Gap43, Ttyh1 and p120 catenin have been identified as potent drivers of TM outgrowth (Figure 1). While Gap43 and Ttyh1 directly promote neurite extension during neurodevelopment, p120 catenin seems to be an upstream regulator of neuronal morphogenesis. Gap43 and p120 catenin downregulation reduced both network formation and tumor cell invasion, whereas Ttyh1 knockdown reduced TM-dependent tumor cell invasion but promoted interconnection. These differences suggest that different subtypes of TMs exist. In a drosophila model of GB, tumor cells use TMs to enwrap neurons and deplete them of WNT thereby leading to

**Figure 1** Neurite-like protrusions in cancer. Schematic overview about functions and known molecular drivers of neurite-like protrusions in cancer. Neurite-like protrusions are used by tumor cells for collective as well as single cell invasion. After cell division, nuclei are transported along neurite-like protrusions. In addition, tumor cells use these protrusions to form dense communicating networks. Direct synaptic connections with neurons enable these networks to receive neuronal input. While some molecular drivers seem to be involved in many known functions of neurite-like protrusions (such as Gap43), others (such as p120 catenin and Fez1) seem to play a role for neurite-like protrusions involved in invasion only. Cx43, connexin 43; Fez1, fasciculation and elongation protein zeta-1; Gap43, growth associated protein 43; p120, p120 catenin; Ttyh1, tweety homolog 1
neurodegeneration. In addition to impaired peritumoral neurotransmitter signaling, this mechanism provides novel insights into how even single invading glioma cells could lead to cognitive dysfunction and potentially also epileptic seizures which are frequent in glioma patients.

3 | NEURODEVELOPMENTAL FEATURES OF EXTRACRANIAL MALIGNANCIES AND BRAIN METASTASES

Neurite- and TM-like protrusions, which are also driven by neurodevelopmental pathways including Gap43, have recently been found in small cell lung cancer (SCLC), where they promoted invasion and metastasis. It needs to be seen whether those protrusions are also used for the formation of multicellular networks and for interaction with host cells, for example, those of the brain, an organ where these tumors frequently metastasize to. Even at their primary sites, SCLC cells are characterized by neuronal characteristics and are thought to arise from neuroendocrine cells, thereby providing one explanation for the activation of programs of neuronal morphogenesis. Neurite-like protrusions seem not to be limited to cells with neuronal characteristics though as they were also detected in breast cancer cells, which are of epithelial origin. Here the neurite-like protrusions are induced by the sodium channel β1 subunit and promoted metastasis and tumor cell growth.

Tunneling nanotube (TNT)-like protrusions, which are thinner, shorter and less stable then TMs and neurite-like protrusions, have been described in a variety of cell types, including colon, pancreatic and prostate cancer, and also GB in vitro. Although the in vitro relevance of these structures still remains to be elucidated, in vitro studies suggest that TNT-like structures promote resistance against cytotoxic therapies, much as described for TMs. In drosophila, specialized neurite-like protrusions called cytonemes have been described during tissue development and tumorigenesis. Similar to TMs and neurites, glutamatergic synapses on cytonemes induce intracellular calcium transients.

Finally, even in brain metastasis, only a minority of cells manages to colonize the brain, and these cells are genomically distinct from extracranial metastases, suggesting that certain preexisting expression profiles of cancers might promote brain colonization. Interestingly, gene expression analyses suggest that brain metastases of breast cancer gain neuronal and neurogenic features, including Gap43 and neurotransmitter receptor expression in comparison to the primary tumor or bone metastases. In nonsmall cell lung cancer, expression of Gap43 was associated with a higher risk for brain metastasis. The upregulation of neurodevelopmental pathways in the brain colonizing, pre-(macro)metastatic breast cancer cells suggests that these properties might enable cells to better integrate into the brain microenvironment, including the recently described formation of pseudo-tripartite synapses. In addition, breast and lung cancer cells are able to form gap junctions with brain astrocytes, thereby promoting metastasis growth and chemoresistance. The brain microenvironment seems to be responsible for the reversible induction of the expression of neuronal genes.

In summary, neurite-like protrusions and other neuronal features are increasingly recognized as being important for different aspects of cancer biology, and their therapeutic targeting emerges as novel paradigm in the treatment of various malignancies. It remains to be seen whether this applies to only some or many tumor entities and/or tumor cell subpopulations in a given tumor.

4 | NEURODEVELOPMENTAL ORIGINS OF GLIOMAS

In contrast to brain metastases, malignant gliomas directly arise from cells of the brain, which provides a straightforward explanation for the reactivation of neurodevelopmental pathways. GB is the most common and, with a median survival of under 2 years, the most malignant glioma type in adults. Based on bulk molecular and gene expression profiles, GBs can be divided into several subclasses, namely a proneural, classical, mesenchymal and neural type. The delineation of the latter has been recently contested, but controversies regarding this point remain as recent single cell analyses again supported the existence of neuronal tumor subpopulations. Likewise, epigenetic DNA methylation patterns which are very stable throughout tumor evolution and in tumor regions and thus appear to faithfully reflect the cell of origin also allow a biologically and clinically relevant brain tumor classification. Recent single tumor cell analyses revealed links between glioma cell types and normal CNS cell types found in development and adulthood, given that different tumor cell subpopulations were identified resembling stem, progenitor and differentiated glia cells in the healthy brain. Different progenitor cells seem specifically susceptible for distinct mutations. Interestingly, the degree of differentiation of the putative cell of origin as well as their preserved gene expression profile in the malignantly transformed cells seems to inversely correlate with malignancy and prognosis (Figure 2).

The intricate wiring of the mature CNS results from the temporally and spatially precisely orchestrated regulation of neurogenic and gliogenic processes during development. The generation of different new cells in the brain occurs in waves, is most pronounced after birth and declines with age. One subtype of high-grade glioma (HGG), diffuse midline glioma (DMG; this group includes classical diffuse intrinsic pontine gliomas) which accounts for nearly 50% of HGGs in children and young adults and which is virtually exclusive for these age-groups, arises mainly in the ventral brainstem and thalamus (Figure 2). Distinct from other pediatric HGGs, DMGs bear a characteristic histone H3 K27M mutation and exhibit a specific gene expression profile that includes the expression of developmentally regulated cellular pathways such as regulators of brainstem development. Pontine DMGs occur in the ventral pons in a narrow time window between the age of 5 and 9 years. Before this, that is, during the time period between birth and the age of 5, there has been marked growth of the pons.
A distinct progenitor cell population was identified that showed a decline in cell number after the age of 2, but exhibited again an increase in the ventral pons around the age of 6. This developmental pattern corresponds with the temporal and spatial incidence of pontine DMG.68,69,72 Interestingly, DMGs in other midline structures such as the thalamus show a later peak incidence in the young adulthood,70 possibly reflecting that different progenitor cells exhibit variable susceptibility for malignancy. The distinct origin and associated molecular biology of DMGs provides the basis for more targeted therapeutic approaches, such as Chimeric Antigen Receptor T-cell73 or histone deacetylase inhibitor therapy.16,74-76

In adults, the majority of diffuse (WHO II) and anaplastic (WHO III) gliomas but less than 10% of GBs (WHO IV) harbor a mutation in the isocitrate dehydrogenase (IDH) genes.7 The incidence of IDH mutant glioma increases abruptly in the third decade of life, and decreases in the fourth and fifth decade.77 These tumors are, in contrast to G34 mutant and IDH wild-type tumors, commonly located in the frontal lobes.63,77 Tumors harboring an IDH1 mutation show a distinct gene expression profile resembling that of lineage-committed progenitor cells found in the frontal lobe.77 These oligodendrocyte precursor cells (OPCs) in the frontal lobe, which are characterized by proliferative capacity and lineage plasticity,78,79 possibly reflecting that different progenitor cells exhibit variable susceptibility for malignancy. The distinct origin and associated molecular biology of DMGs provides the basis for more targeted therapeutic approaches, such as Chimeric Antigen Receptor T-cell73 or histone deacetylase inhibitor therapy.16,74-76

Finally, GBs that lack an IDH mutation represent the most common type of malignant primary brain tumors. Their incidence increases with age and is most often found in patients >55 years.7 In contrast to IDH mutant gliomas, IDH wild-type glioma often display a gene expression profile resembling that of neural stem cells (NSCs) (in particular the most aggressive "mesenchymal" and "proneural" molecular subtypes),50-52,82,83 NSCs, which accumulate alterations...
with age, they are thus likely the origin of IDH wild-type GBs. This is supported by the finding that the mutation burden in adult HGGs is approximately 3-fold higher than in childhood HGGs. Hence, apparently fewer alterations are required in children to reach the oncogenic threshold, possibly due to a more permissive microenvironment and the propensity to proliferate of the cell of origin. Recent molecular genetic evidence further underlines the distinct cell of origin of IDH mutant and IDH wild-type tumors. In this study, Lee et al found low level driver mutations of IDH wild-type GB in the macroscopically unaffected subventricular zone (SVZ), the largest neurogenic region in adults, which was not the case for IDH mutant GB. The data suggests that NSCs in the SVZ acquire mutations, such as Chromosome 7 gain, 9p or 10 loss, and produce precancerous progeny that migrates away from the NSC niche leading to distant tumor development.

An interesting question is how the microenvironmment influences glioma growth. The age-dependent changes in glioma growth might account, at least in part, for growth arrest or even spontaneous regression reported for low-grade glioma in children. The changes that occur normally during brain maturation in children might lead to a milieu that is no longer permissive for the growth of neoplastically transformed progenitor cells. This is in agreement with studies reporting a decrease in cancer cell proliferation with aging. The comparatively stable microenvironment in adults on the other hand may facilitate sustained growth of gliomas of adulthood.

Taken together, malignant gliomas seem to derive from distinct stem and progenitor cell populations under permissive microenvironmental conditions. Despite a certain degree of dysplasia, this cellular origin provides a plausible explanation for the ability of glioma cells to recapitulate steps of brain development. This includes the formation of communicating multicellular networks by neurite-like cellular protrusions, the integration into existing networks of the brain and the exploitation of developmental pathways to thrive.

5 | NEURONAL AND GLIAL SUBPOPULATIONS IN BRAIN TUMORS

Single cell analyses of different malignant gliomas revealed that these tumors are composed of diverse cellular subpopulations that resemble cells during neurodevelopment and in the adult brain. The diverse neuronal and glial cell populations in the brain originate from self-renewing NSCs, which reside in neurogenic stem cell niches. During both, neuro- and gliogenesis, NSCs sit at the apex of the developmental hierarchy. NSCs produce transiently amplifying progenitor cell pools, which the gradually differentiate into cells of neuronal or glial lineages.

In malignant glioma, a subpopulation of stem-like cells (cancer stem-like cells [CSCs]; brain tumor stem-like cells [BTSCs]) has been identified, which was subsequently associated with tumor resistance and recurrence. Although their significance for therapy failure in glioma is, if intriguing, an ongoing matter of debate, they represent a plausible explanation for the heterogeneous and hierarchical composition of brain tumors. These cells seem to represent the apex of the tumor cell hierarchy, are capable to undergo self-renewal and can be differentiated into neurons, astrocytes as well as oligodendrocytes in vitro, thus indicating their multipotency. Recent single cell analyses reveal that broad expression of stemness programs in human glioma and the existence of different BTSC subsets within one tumor. In addition, a mesenchymal (NSC-like) to proneural (OPC-like) hierarchy of BTSCs has been identified, with in silico lineage tracing suggesting mesenchymal BTSCs as progenitors of proneural BTSCs.

Among the cell types found in gliomas are NSC/neural progenitor cell (NPC) (neural progenitor cell-like), radial glia-like, OPC-like and different astrocytic subpopulations. The glioma subtypes identified in bulk analyses correspond to the expression profiles of cellular subpopulations and the classification depends on the relative frequency of the different cell states. Interestingly, intratumoral heterogeneity seems not to be primarily driven by different genetic subclones. Instead, in vivo lineage tracing supports a plasticity between cell states. The cellular composition might represent a steady state of subpopulations that depends on inhibition or facilitation of certain states by genetic alterations and the microenvironment.

So far, the functional implications and behavior of the heterogeneous subpopulations remain widely unresolved. It was shown that the emergence of certain astrocytic subpopulations in malignant glioma correlates with the onset of epileptic seizures. In addition, the extent of the subpopulations seems to differ between tumor regions such as the tumor core or the leading edge of tumor cell infiltration. OPCs and OPC-like glioma cells are highly migratory cells during normal brain development and in experimental models of malignant glioma. In line, OPC-like cells were enriched at the infiltrative border of human glioma. Several groups consistently reported that the OPC-like cellular population constitutes the actively proliferating fraction of glioma cells. In addition, it will be interesting to elucidate if cellular subpopulations differ in the extent of therapy resistance and network integration.

For the development of therapeutic approaches, it will be further important to identify cell type specific vulnerabilities. Several, partly antagonistic, factors have now been identified that govern glial fate diversification not only during development but also during gliomagenesis. Among others, Zfp36l1 and Sox10 promote oligodendroglial lineage transition, whereas NFIA acts antagonistically to induce astrocytic lineage differentiation.

In summary, malignant gliomas are composed of cellular subpopulations reflecting the diversity of progenitor and more differentiated cells during neurodevelopment and in the adult brain. It will be important to learn how these subpopulations evolve during tumor progression and under therapy, as well as how they contribute to different aspects of glioma biology, such diffuse infiltration and therapy resistance.
6 | NEURONAL COMPONENTS OF EXTRACRANIAL TUMORS

In light of the increasing number of studies performing single cell analysis in various tumor entities outside the CNS, it will also be fascinating to study whether at least some of them contain tumor cells with neuronal or glial features. Several studies suggest that tumorigenesis might represent a loss of the original cell identity, which can include a gain of neuronal characteristics. In prostate cancer, varying subsets of neuroendocrine cancer cells are found within the tumors, and a neuronal trans-differentiation occurring during disease progression to metastatic and hormone resistant cancer. Prostate cancer cells might even be able to fuse with nearby neuronal cells, thereby acquiring neuronal expression profiles and increasing intratumoral heterogeneity. In ovarian cancer, the expression of mRNAs associated with neurogenesis and axon extension correlated with worse outcome. In colon cancer, genes related with the nervous system increase with tumor stage.

As in GB, CSCs have now been identified in diverse cancer entities including pancreatic, colon and lung cancer, which share characteristics with embryonic NPCs. In experimental gastric and colorectal cancer, it could be demonstrated that CSCs could even give rise to neurons, thereby generating a nervous system within the tumor. In GB, tumor cells are not only attracted toward the NSC niche, but neural stem and progenitors show strong tropism toward the tumor bulk. Interestingly, it was recently described that neural progenitors leave the SVZ of the brain to populate prostate tumors, where they give rise to neurons, and promote tumor growth and metastasis. In addition, cancer tissue is strongly innervated compared to nonmalignant tissue with an increase during disease progression. This innervation by the PNS promotes tumor initiation, tumor cell growth and metastasis by direct influence on the tumor cells as well as by modulating the tumor microenvironment, as recently reviewed elsewhere.

7 | CLINICAL IMPLICATIONS

Currently, the role of the nervous system and neurodevelopmental characteristics have most extensively been studied in malignant brain tumors. Despite fundamental differences, for example, in regard to the differences of the PNS and the CNS and the cells of origin, therapeutic strategies developed for brain tumors might spearhead the development of novel therapies in other cancer types. Several novel therapeutic paradigms arise that exploit the neuronal microenvironment and neurodevelopmental characteristics: (a) Prevention of the outgrowth of neurite-like protrusions to inhibit invasion and interconnection; (b) Inhibition of tumor-tumor cell communication; (c) Inhibition of neuronal input and neurotransmitter signaling; (d) Depletion of neuronal intratumoral subpopulations and tumor-subtype specific treatments.

1. Pharmacological or genetic (eg, by antisense oligonucleotides) targeting of neurodevelopmental pathways and molecules, such as Gap43, Fez1 or Tsyh1, could inhibit the outgrowth of neurite-like protrusions. It remains to be elucidated if these protrusions also play a role for therapy resistance outside the brain, but first evidence exists that demonstrates that the inhibition of neurite-like protrusions can be used to reduce the metastatic potential. Many molecules involved during neurodevelopment seem to be of limited importance in the mature brain and might hence be suitable targets for novel tumor-specific therapies. Nonetheless, like always in Oncology, unwanted side effects need to be considered here, specifically on learning and CNS-regenerative processes. In Neuro-Oncology, one limitation of many therapeutic approaches is the limited CNS-penetration of anticancer drugs. In contrast, in the case of treatment of cancers outside the brain, this might prove beneficial: the use of a non-CNS penetrant drug could prevent side effects which are expected to result from the inhibition of neurophysiological pathways within the brain.

2. Although gap junctions are found throughout the body, gap junction inhibition as monotherapy or in combination with cytotoxic therapies might be used to decrease tumor growth and resistance by targeting communicating tumor cell networks. In brain tumors, inhibition of gap junctions might not only disrupt the growth- and resistance-promoting effects of functional interconnection but could also be used to disrupt the downstream effects of synaptic input. In preclinical models, gap junction inhibitors sensitized brain tumor cells for the effects of radio- and chemotherapy. Besides tonabersat, which is well tolerated in humans and was studied in the prevention of migraine, melcufenamate, which is used as anti-inflammatory drug in the United States, are interesting candidates to be studied in future trials. Of note, both drugs also inhibited the formation of heterocellular astrocyte-carcinoma gap junctions in a mouse model, thereby preventing brain metastasis and increasing therapy response to chemotherapy.

3. In the CNS, neuron-tumor synapses could be targeted by AMPA (in the case of glioma) or NMDA (in the case of breast cancer metastasis) receptor blockers. The AMPA receptor blocker perampanel is used as antiepileptic drug in the clinic. In a phase II clinical trial, the AMPA receptor inhibitor talampanel showed good tolerability and prolonged survival in combination with radiochemotherapy when compared to historical controls. Overall, neurotransmitter signaling might be a challenging therapeutic target due to its versatile physiological functions and a small therapeutic window of drugs interfering with it. In the case of glioma, targeting specific calcium-permeable AMPA receptors, which are otherwise just lowly expressed in the adult, is an interesting avenue. In the PNS, denervation strategies have shown promising results, but the first evidence of tumor-intrinsic neurogenesis but remodeling of existing nerves or neurogenesis within the tumor by attraction of neuronal progenitors from distant places suggests that the tumor is able to shape its own growth-enhancing micromilieu. For the development of efficient therapies, it will be important to...
decipher the tumor cell-neuron cross talk and origin of cancer-associated nerves. In glioma, it was demonstrated that specific PI3KCA variants lead to the initiation of brain hyperexcitability and synaptic remodeling,\textsuperscript{138} which might then foster brain tumor growth. In the PNS, this was illustrated recently by an elegant study,\textsuperscript{2} which showed that adrenergic neonerves foster head and neck tumor growth. Sympathectomy did not inhibit tumor growth though, as the adrenergic neonerves originated from transdifferentiation of sensory nerves.\textsuperscript{2} As an example for therapies that target nervous tumor microenvironment, first studies,\textsuperscript{136,139} including a phase II clinical trial,\textsuperscript{136} suggest potential efficacy of beta-adrenergic blockade in breast cancer. In general, organ-specific effects should be kept in mind though as, for example, cholinergic signaling promotes gastric cancer growth,\textsuperscript{140} but suppresses pancreatic cancer tumorigenesis.\textsuperscript{141}

4. Despite recent advances in the stratification of gliomas based on molecular characteristics, genomics and epigenomics, such as DNA methylation,\textsuperscript{8} which are partly linked to the cell of origin, these differences are not yet addressed by tumor type-specific treatments. A better stratification is likely a requirement for significant treatment advances in the future though. Only few hints exist that these differences could very well matter: a retrospective analysis suggested that bevacizumab, an anti-VEGF-A antibody, which did not prolong overall survival in phase III studies for the entire population of GB patients,\textsuperscript{142,143} appeared to provide a significant survival benefit for patients with proneural, IDH1 wild-type GB in a secondary retrospective analysis.\textsuperscript{83} This benefit from an antiangiogenic therapy seems rather unexpected, as proneural GB do not exhibit an upregulation of angiogenic markers (including VEGF) compared to other subtypes.\textsuperscript{83} Here, consideration of OPCs, which are thought to be the cells of origin, could again provide further clues, as VEGF-A is inter alia a potent regulator of OPC migration,\textsuperscript{144,145} and trophic coupling between endothelial and OPCs in an oligovascular niche was proposed,\textsuperscript{146} thereby making nonangiogenic effects and a selective sensitivity of these cells possible.

It will be important to investigate the biological behavior, that is, invasion, network formation and therapy resistance, as well as the cell type specific vulnerabilities of different cellular subpopulations. The plasticity of cell states\textsuperscript{106} suggests that forced transition, for example, by modulation of the switches involved in glial cell diversification,\textsuperscript{110} to a more therapy sensitive state might prove beneficial when combined with cytotoxic therapies.

In extracranial tumors, intratumoral heterogeneity with neuronal subpopulations might contribute to therapy failure. The neuronal subpopulations within epithelial tumors are very distinct with regard to gene expression and gene regulatory networks when compared to the majority of cells within a single tumor\textsuperscript{114,124} and might hence require very different therapeutic approaches. The existence of diverse subpopulations within single tumors might require combination therapies targeting individual subpopulations.\textsuperscript{105,147} As described above for the inhibition of the outgrowth of neurite-like protrusions, interference with neurodevelopmental pathways could potentially be used to prevent the acquisition of neuronal characteristics as well as interactions with the brain microenvironment during brain metastasis, thereby preventing the successful colonization of the brain.

8 | SUMMARY AND OUTLOOK

The findings reported in this article reach from molecular neuroscience to clinical aspects of oncological diseases. They highlight how the comprehension of the fundamental molecular and regulatory mechanisms of neurobiology, which provide the basis for and are recapitulated during malignant transformation, could help to appreciate and understand the heterogeneous nature of gliomas but also other cancers. In recent years, the field of Cancer Neuroscience has gained momentum,\textsuperscript{148} but deeper insights into the tumor-specific mechanisms are requisite for clinical translation.\textsuperscript{136} However, the general interest in this translation is now documented by first biotech start-ups working in the field of Cancer Neuroscience.\textsuperscript{137}

All in all, despite differences in the secreted neurotransmitters and other physiological factors, nerves and neurons are not limited to the brain, but ubiquitous throughout the body. The rapidly evolving discoveries of molecular, anatomical, functional and developmental neuronal features of cancers can provide a novel framework for a better understanding of both their fundamental biology and unexpected vulnerabilities.

ACKNOWLEDGEMENTS

This work was supported by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG: SFB 1389).

CONFLICT OF INTEREST

E. J., W. W., and F. W. report the patent (WO2017020982A1) “Agents for use in the treatment of glioma.” F. W. is cofounder of DC Europa Ltd (a company trading under the name Divide & Conquer) that is developing new medicines for the treatment of glioma. Divide & Conquer also provides research funding to F. W.’s lab under a research collaboration agreement. J. A. and H. M. declare no conflict of interest.

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**How to cite this article:** Jung E, Alfonso J, Monyer H, Wick W, Winkler F. Neuronal signatures in cancer. *Int. J. Cancer*. 2020;147:3281–3291. [https://doi.org/10.1002/ijc.33138](https://doi.org/10.1002/ijc.33138)