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Why Primary Tumours/Malignancies of the Nerve Cells Are So Rare?

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Abstract

Introduction: Primary tumours associated with nerve cells are exceptionally rare whereupon the majority of these tumours present as benign. Neurons develop oncogenic mutations less than their supporting neuroglias which are transformed into glioma tumours.

Methods and materials: Using a multi-faceted approach, search strategies were generated using specific keywords and performed on selected scientific databases. Literature searches were performed and a shortlist of seven publications was generated following a strict criteria based selection process.

Results: Reduced number of proliferating cells: Early cell cycle exit results in the inability for nerve cells to regenerate as well as preventing malignancies from developing as no DNA is required to replicate. Additionally, post-mitotic Neurons have the ability to re-enter the cell cycle without producing two daughter cells to repair damaged DNA.

Tumour suppressor proteins: A high abundancy of PTEN and TP53 are present in the CNS and PNS (higher than most other areas of the body). These act as protective mechanisms for detection of damaged DNA to mark cells for immediate apoptosis.

Inhospitable environment created by the lymphatic system: An extensive network of lymphatic vessels channel tumour cell dissemination to cervical lymph nodes. This stimulates immune responses by the high abundancy of dendritic cells and the destruction of tumour cells.

Immunity in the nervous system: Natural Killer (NK) cells, seen in high abundancy in the CNS, are the most effective response factors against tumours and viral infections. NK cells express a large range of cellular receptors to tumour ligands which stimulates NK mediated cytotoxicity.

Hereditary: Li-Fraumeni syndrome, Cowden syndrome and neurofibromatosis 1 syndrome represent three genetic conditions with associated high risks of developing tumors such as glioblastoma, schwannoma and astrocytoma.

Geographic location: There is a correlation between countries with high Human Development Index (HDI) and the incidence and mortality of brain tumors.

Conclusions and future directions: Mutations are rare in nerve cells due to their inability to proliferate and regenerate. Mutated nerve cells are marked for DNA damage repair or apoptosis preventing passing on of oncogenic mutations. The high abundancy and range of immune cells surveilling the nervous system and lymphatic system mark cancerous growths for degradation. Germline mutations account for a small proportion of nerve cell tumors.

Keywords: Early cell cycle exit • Neuron • Regeneration • Glioma • Mutation • Tumour • Nervous system • DNA damage

Abbreviations: Antigen Presenting Cells: APCs; Blood-Brain Barrier: BBB; Cancer Predisposition Syndromes: CPS; Central Nervous System: CNS; Central Nervous System Tumour: CNST; Cerebrospinal Fluid: CSF; Cyclin-Dependent Kinases: CDK; Cytolytic Lymphocyte: $CD8^+$ cell; deep Cervical Lymph Node: dCLN; Dendritic Cell: DC; Glioblastoma Multiforme (glioblastoma): GBM; Helper T cell: $CD4^+$ T cell; Human

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Development Index: HDI; Interferon Necrosis Factor Gamma: INF- γ; Interleukin: IL; Isocitrate Dehydrogenase: IDH; Li-Fraumeni Syndrome: LFS; Lymphatic Vessel: LV; Major Histocompatibility Complex: MHC; Malignant Peripheral Nerve Sheath Tumour: MPNST; Matrix Metalloproteinases: MMP; Meningeal Lymphatic Vessel: MLV; Natural Cytotoxicity Receptor: NCR; Natural Killer Cells: NK cells; Neural Progenitor Cell: NPC; Neural Stem Cell: NSC; Neurofibromatosis Type 1: NF1; Non-Homologous End-Joining: NHEJ; Peripheral Nerve Tumour: PNT; Peripheral Nervous System: PNS; Phosphatase and Tensin Homolog Deleted on Chromosome 10: PTEN; Protein Retinoblastoma: pRB; Retinoblastoma: RB; Subgranular Zone: SVG; Subventricular Zone: SVZ; T-cell Receptor: TCR; Tumour Necrosis Factor Alpha: TNF-α; World Health Organization: WHO

Introduction

Nerve cells

The nervous system of mammals is characterized by two types of nerve cells: Neurons and neuroglia (glia). Neurons have electrical excitability properties whereas neuroglia is their non-excitable supporting cells [1]. Neurons are the predominant cell type accompanied by the supporting neuroglia (glia) in both the Central Nervous System (CNS) and Peripheral Nervous System (PNS). Previous studies have claimed the ratio of glia: Neurons to be 10:1 however, novel counting methods show the real ratio to be less than 1:1 with the abundancy of neuroglia varying depending on the location in the brain [2]. Four variations of neuroglia exist in the CNS: Astrocytes, oligodendrocytes, and microglia and ependymal cells (Figure 1).

Whereas satellite and Schwann cells support the neurons in the PNS (Figure 2). Neurons assist rapid neurotransmission to transmit sensory input, process information and output of motor response by their specialized structure to dispense synapses (Figure 3) [3].

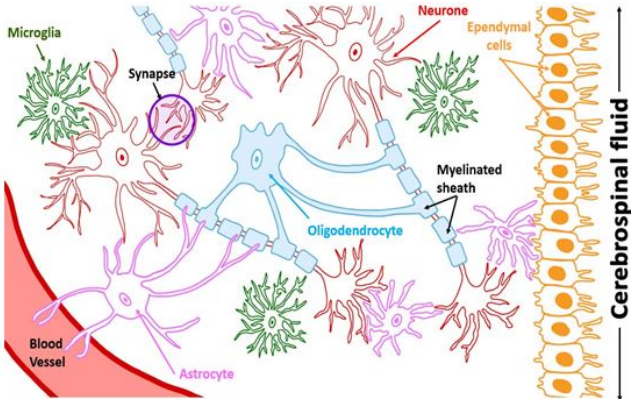

Figure 1. Original drawing of the nerve cells in the CNS and their interactions. Astrocytes (pink) play a regulatory role of the microenvironment. Oligodendrocytes (blue) make up the myelin sheath covering the axons (fibrous extensions of neurons). Ependymal cells (orange) maintain the homeostasis of the Cerebrospinal Fluid (CSF) by lining ventricles. Microglia (green) are involved in responding to infection and inflammation by playing an immunity role among the CNS environment. Neurons (red) send out multiple cellular processes from their neuronal soma to assist in paracrine cellular communication by synapses between adjacent neurons.

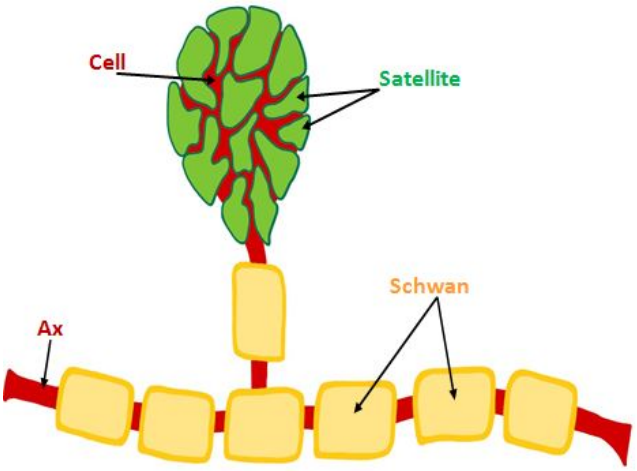

Figure 2. Original drawing of the nerve cells in the PNS and their interactions. The axon of the neuron (red) is expanded and covered in Schwann cells (yellow) play an insulating role by producing myelin to cover the peripheral axon and protect it. Satellite cells (green) cover cell bodies in peripheral ganglia, both sympathetic and parasympathetic.

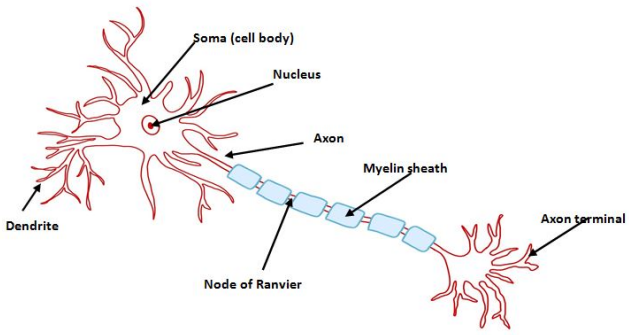

Figure 3. Original drawing of a typical neuron.

Typically, the neuron nucleus is surrounded by cytoplasm which creates the cell body, multiple dendrites which are short extending processes, and a single long process called an axon. This specialized structure aids in their function to dispense synapses.

Neurons rarely are the cells which undergo oncogenic transformation in comparison to their supporting neuroglia as the cells of origin for oncogenic transformation must be growth-competent and have differentiation capacity. Neurons undergo mitosis, proliferate and differentiate in early embryogenesis to generate the majority of neurons from Neural Stem Cells (NSCs) and Neural Progenitors Cells (NPCs) through a process called neurogenesis [4]. Gliogenesis, the generation of glial cells, succeeds neurogenesis from a pool of multi-potent NSCs shortly after birth [5]. Neurogenesis occurs in the adult brain as NSCs and NPCs have multi-potent properties to generate nerve cells. This adult

neurogenesis is con ined to two proliferative niches; the Sub-Ventricular Zone (SVZ) in the lateral ventricle and Sub-Granular Zone (SVG) in the dentate gyrus of the hippocampus [6]. Adult neurogenesis yields a low number of neurons compared to embryonic neurogenesis. Therefore, following injury to the neurons in the CNS, some level of recovery is seen. It is these NSCs and NPCs which are targeted for oncogenic transformation as the cells of origin due to their differentiation properties.

Primary tumours of the nervous system: Brain tumours have a reputation among cancer of restricted treatments available with a poor prognosis due to the high mortality rates [7]. This review focuses on primary tumours of the CNS and PNS; Table 1 de ines the differences with secondary tumours.

	Primary tumour	Secondary tumour (secondary metastasis)
Origin of tumour growth	Originates through mutations in cell's DNA, bypass the cell-cycle checkpoints and the DNA damage system to promote uncontrollable cell proliferation and grow exponentially	Originates from the original primary tumour through metastasis in order to form a macroscopic lesion
Location	Location of original DNA mutation in cell	Site where the primary tumour has metastasised to separate and distant location. Distinct from local recurrence and local invasion
Mortality rates	Longer life expectancy due to treatments available and more effective results seen	The predominant cause of cancer related death
Prevalence	Higher	Lower

Table 1. Original table clarifying the differences between primary and secondary tumours.

These differences can be characterized according to origin of tumour growth, location, mortality rates and prevalence. A primary tumour is the original tumour growth to progress in a location. This primary tumour develops from mutations in the cell's DNA which then have the ability to bypass the cell cycle checkpoints and grow exponentially. Primary tumours have been shown to release certain factors which orchestrate the formation of a pre-metastatic niche in selective locations. Metastasis involves the formation of secondary tumours in a location separate from the primary tumour and its growth to form a macroscopic lesion. It is considered distinct from local recurrence and local invasion. Metastasis also called secondary cancer and is the main cause of morbidity and mortality in cancer.

Cancer is known as an acquired genetic disorder where cells develop a growth advantage due to the accumulation of multiple gene mutations caused by DNA replication errors or exposure to genotoxic agents causing loss of regulatory functions [8]. Despite the elaborate protective mechanisms developed, numerous irreversible mutations occur preceding clinical detection of tumours. 98% of cancers are due to sporadic mutations where 90% of these are epithelial-derived carcinomas due to their rapid division rate. Overexpression mutations do not affect the germ line which means that these mutations are not heritable. Oncogenic progression in the CNS required mutations impacting cell signaling pathway with stimulating the Warburg effect to utilize energy available for tumour proliferation.

"Global Cancer Statistics 2020" reported the incidence of brain and nervous system cancer as 21st in number of new cases with 308,102 new cases where female breast cancer is the most common tumour of 2,261,419 new cases in 2020 (36 cancers analysed) [9].

CNS and PNS tumours

The CNS includes the brain and spinal cord, while the peripheral nervous system includes all of the nerves that branch out from the brain and spinal cord and extend to other parts of the body including muscles and organs. Tumours associated with the CNS are more likely to be secondary metastasis rather than primary tumours [10].

Gliomas are the predominant primary tumour group associated with the neuroglia in the CNS, accounting for 80% of malignant primary brain tumours. Brain tumours account for less than 2% of total malignant neoplasms and are responsible for a small percent of human cancers [11]. The World Health Organization (WHO) subdivides gliomas into different groups depending on their molecular biomarkers, rather than histopathology [12]. This is more bene icial as historic therapeutic target treatments were failing due to lack of molecular understanding of gliomas therefore, improved therapeutic treatment plans can be made. Mutations associated with the subgroups of glial tumours can be seen in Table 2. Gliomas are most commonly found in the very young and the elder population and are marginally more common among males (around 1.7 fold). Young adults are the most likely age group to develop low grade gliomas with the mean survival rate varying from 5.6 to 13.3 years [13]. Gliomas affect young men (20-40 years) as the second leading cause of cancer-related deaths. These statistics haven't had much change since the 1970's showing that the risk factors and treatments have not changed or improved.

Peripheral nerve tumours are a heterogenous group of mainly benign tumours which are rarer than CNS Tumours (CNSTs). They affect the nerves by being either extraneural (press against the nerve) or intraneural (grow within the nerve) (Tables 2 and 3) [14].

Central nervous cells

Name of cancer	Adult type of glioneuronal/ neuronal	Cell associations	Prevalence	Malignant or benign (WHO grade?)	Mutations in genes
Astrocytoma (*IDH*-mutant)	Adult-type diffuse gliomas	Astrocytes	12% of total	WHO grade II (diffuse astrocytoma IDH-mutant).	*IDH1, IDH2, ATRX, TP53*

			4.68 per 100,000 (10,868 cases)	WHO grade III (anaplastic astrocytoma *IDH*-mutant)	
Oligodendroglioma (*IDH*-mutant)	Adult-type diffuse gliomas	Oligodendrocytes	8%-12% of total gliomas 4%-6% of all primary CNSTs 3.57 per 100,000 (8,217 cases)	WHO grade II (oligodendrglioma *IDH*-mutant with 1p/19q co-deletion) Who grade III (anaplastic oligodendrglioma *IDH*-mutant with *1p/19q* co-deletion)	*IDH1, IDH2,* 1p/19q co-deletion, *TERT, CIC, FUBP1, TCF12, NOTCH1, PI3K.*
Glioblastoma (GBM) (*IDH*-wildtype)	Adult-type diffuse gliomas	Astrocytes, microglia	Account for 70%-75% of total diffuse gliomas Account for 2% of adult cancer deaths though, they account for 1% of adult cancer. 9.23 per 100,000 (23,327 cases)	Grade IV. Malignant and is the most aggressive type of glioma. 14-17 months of survival following diagnosis.	Overexpression of *EGFR gene* (affecting *TGF-* alpha), *IDH*-wildtype, *TERT* promoter, *TP53, NF1, MDM2* amplification, *RB1.*

Table 2. An original table explaining the types of tumours associated with the CNS and PNS with their distinctive associated characteristics.

(a). Three CNSTs (Astrocytoma (*IDH*-mutant), Oligodendroglioma (*IDH*-mutant) and Glioblastoma (GBM) (*IDH*-wildtype)) are categorised under the group adult-type diffuse gliomas. Isocitrate Dehydrogenase (*IDH*) gene is one of the most crucial genetic mutations in glioma tumours and play a key role in their diagnosis by being strong prognostic markers. *IDH*-mutant indicates the presence of *IDH* mutation. *IDH*-wild-type indicates no IDH mutation is present. These three CNSTs are among the most prevalent in the adult population with the hight incidence seen in Glioblastoma (GBM).

Peripheral nervous system

Name of cancer	Cell associations	Intra or extraneural	Prevalence	Malignant or benign (WHO Grade?)	Mutations in *genes*
Malignant Peripheral Nerve Sheath Tumour (MPNST)	Schwann, pluripotent cells in the neural crest	Extraneural and Intraneural	Very rare. 0.001% of general population.	Malignant (WHO grades II, III or IV). 63% of patients die within 2 years of diagnosis	*NF1, SUZ12, EED, TP53* and *CDKN2A*
Neurofibroma (cutaneous and plexiform types)	Schwann, perineural and fibroblasts (mixed histopathology)	Intraneural	Plexiform neurofibromas occur in 5-15% of patients with Neuro ibromatosis type 1 (NF1) syndrome. Higher rate is associated with NF1 syndrome.	Benign (WHO grade I)	*NF1*
Schwannoma	Schwann	Intraneural	8% of total intracranial tumours –most frequent is Schwannoma of the vestibular nerve with 1.3 per 100,000 incidence rate. Higher incidence rate is associated with NF2 syndrome.	Benign (WHO grade I)	Loss of chromosome 22 (22q) (*NF2, LZTR1, SMARCB1* genes are present here). This loss of 22q occurs in 61% of Schwannomas
Perineuroma (intraneural perineuroma and extraneural perineuroma)	Neoplastic perineural glia	Intraneural or extraneural	Extremely rare	Benign. Intraneural perineuroma WHO grade I. Extraneural perineuroma WHO grade I.	WD40 domain of TRAF7 Abnormalities on chromosome 22q (containing *NF2, BCR*).

Table 3. The peripheral nervous system tumours included are malignant peripheral nerve sheath tumour (MPNST), neurofibroma, Schwannoma and perineuroma.

Peripheral nerve tumours are considerably less prevalent in the general population, with higher incidences associated with neuro ibromatosis type 1 and 2 syndromes. Schwannomas are the most common type of peripheral nerve tumours. These tumours can be characterised depending on their intraneural or extraneural properties.

(a) and (b) indicate the associated nerve cells which are mutated to create the nervous system neoplasms as well as the associated mutations and prevalence among the general population. It is clear that the majority of tumours of nerve cells are benign in nature.

Nerve cell-cycles

Cancer is the accumulation of genetic mutations acquired during cell division where their regulatory properties are lost. The “normal” cell-cycle is shown in Figure 4 compared to cell-cycle exit which is characterized by nerve cells.

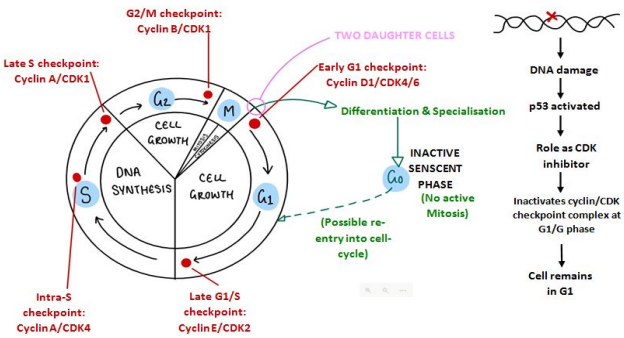

Figure 4. Original diagram incorporating the “normal” cell-cycle and neuronal cell cycle.

The average length of a "normal" cell cycle is 16 hours (15 hr for interphase, 1 hr for mitosis), but this varies depending on the type of cell. The cell progresses through the four stages G_1, S phase, G_2 and M. Genetic material is replicated in S phase before producing two daughter cells (pink) following cytokinesis. G_1 and G_2 are the gaps between S and M phase and G_0 is an inactive period where cells are in a senescent state.

Mitogens are required to induce re-entry to the cell cycle to pass the G_1 restriction point where once a cell passes this point it is irreversibly committed to progress through the cell-cycle. G_1 and G_2 checkpoints are crucial as it leads to the arrest of the cell-cycle in response to detecting damaged or un-replicated DNA. Proteins are the components of these checkpoints which act as DNA damage sensors. When these checkpoint proteins are damaged, it can lead to genomic or chromosomal instability which consequently can lead to mutations inducing carcinogenesis. Neurons are shown in green where they exit the cell cycle and differentiate into a specific phenotype. *p53* is shown to play a role as a CDK inhibitor preventing the checkpoint protein from forming when DNA damage has been detected, this prevents cancerous mutations forming in cells and being passed onto daughter cells. Adapted from Frade and Ovejero and Galderisi, et al.

Neuronal differentiation involves the two processes of completing neurite sprouting (new projection growth) and cell cycle arrest [15]. Terminally differentiated neural cells are halted in the G_0 phase followed by down expression of key cell-cycle regulators. Neural and glial differentiation is correlated with a reduction of CDK activity in the G_1 phase. This is associated with an increase in CDK inhibitors as they inhibit CDK proteins therefore; halting the progression through the cell-cycle and promoting cell-cycle exit. P27Kip1 has been shown to be playing a key role in neuronal differentiation where high expression is seen in postmitotic neurons [16].

p53, PTEN (Phosphatase and tensin homolog deleted on chromosome 10) and the Retinoblastoma (RB) family play crucial roles in cell proliferation, cell-cycle and differentiation of nerve cells in the CNS seen in Table 4.

Transcription factor	Normal role	Knockout or mutation results
TP53	Inducing cell cycle arrest prior to DNA replication in late G_1 phase, inhibiting cell proliferation, metabolic remodelling of cell, regulate the self-regeneration of neural stem cells and neural progenitor cells. The more a neural cell develops, the less it expressed p53. Contributes to oligodendrocyte differentiation. High expression is seen in response to cellular stress (DNA damage, oncogenic activation, microtubule damage, oxidative disruption) p53 activates PTEN.	Dual knockout of TP53 and PTEN in CNS led to the development of gliomas in a mouse Knockout (KO) study. The neural stem cells with KO-p53 and KO-Pten had reduced differentiation capacities, increased self-renewal and increased formation of tumours in the CNS Single mutations of TP53 in neural stem cells in the SVZ results in the proliferation of transit-amplifying progenitor-like cells, developing glioma associated mutations in the neural progenitor cells
PTEN	PTEN is a tumour suppressor gene which plays a role in apoptosis, cellular growth and arrest of cell-cycle progression at G_1.	Targeting of PTEN by tumours is likely due to its impingement on multiple signalling pathways.
RB family	The Retino Blastoma (RB) family are involved in cellular differentiation and neurogenesis. When a cell becomes terminally differentiated, it is characterised by cell cycle exit, RB family dephosphorylation and loss of E2F complexes.	The Rb family of proteins (pRB) are commonly mutated in tumours of the CNS and PNS (astrocytomas, glioblastomas and gliosarcomas) In a knockout study of RB gene where mice lack both copies of the RB gene, the results showed that pRB and pRb2/p130 are critical for neurogenesis. The mouse was shown to have neural precursor cells dividing outside the SVZ and SGZ (where normal neurogenesis occurs) in the CNS and PNS. Cells which were dividing were then found to die by apoptosis and the markers for neural differentiation were largely decreased.

Table 4. The main transcription factors in involved with neural proliferation, cell-cycle and differentiation.

The roles of *p53*, Pten and the RB family transcription factors are shown comparing the normal function to the mutated function which consequently leads to different types of neuronal tumours of the CNS.

Aims and objectives

- To accomplish the aim of exploring the reasons behind the infrequency of never cell tumours, a series of objectives were assigned:
- Evaluate why nerve cells acquire less oncogenic mutations compared to other cell types by exploring their cell-cycle arrest, regeneration capacity and proliferation abilities.
- Investigate the nervous system environment to create an inhospitable environment for tumour growth.
- Explore whether the lymphatic and immune system play roles in the removal of malignant cells in the CNS.
- Determine whether heritability and other factors have an impact on the development of nerve cell tumours.

Methods and Materials

Selection outline

Literature searches were performed on selected scientific databases to analyse publications surrounding the chosen topic. Journals and articles were screened using specific search strategies and a rigorous criteria based selection process to discard irrelevant topics and include directly relevant publications creating a shortlist of seven articles. These undergo critical analysis and create the literature analysis of the chosen topic (Figure 5).

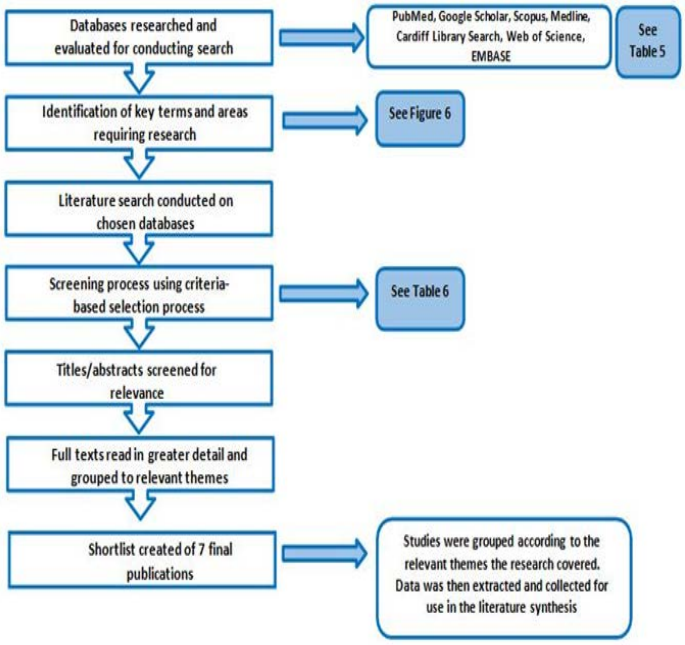

Figure 5. An original flow chart diagram indicating the selection outline of this rapid literature review in order to create a shortlist of articles.

The shortlisted publications aid in answering the research question aims in the subsequent literature analysis section.

Literature search

The scientific databases chosen to access the literature were scopus, medline (Ovid), web of science and cardiff library search. Table 5 indicates the justifications for selecting these databases. Four databases allowed access to a greater range of publications, as the literature surrounding rare nerve cell tumours is limited. Search strategies were carried out on the chosen electronic databases between 14/03/22 and 18/05/22 in a multi-faceted approach. Keywords selected to search on these databases were generalized to access more data. Although the search strategy wasn't performed on Cardiff library search, it was used to ensure the papers were peer-reviewed (Figure 6).

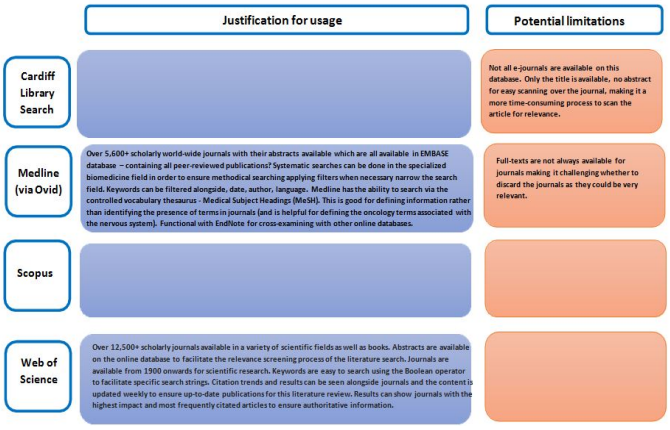

Figure 6. Justifications and limitations analysed when selecting scientific databases to conduct the literature search on cardiff library search, medline (*via* Ovid), web of science and scopus were selected as databases for performing literature searches on. Each database presents with a range of advantages in order to perform efficient searches upon ranges of available literature. However, potential limitations are mentioned alongside each database in order to establish restrictions in searching for available publications.

Considerably larger search results were seen when analysing literature of the CNS compared to the PNS. Additionally, papers associated with the CNST focused heavily on components to the CNS which were not nerve cell related. Therefore, glioma tumours were specified in the search strategy to filter out irrelevant publications with no focus to nerve cell tumours. This created a limitation as potential other nerve cell tumours could be missed when searching for gliomas specifically. Most publications studied the characterization of nerve cell tumours rather than reasons why their prevalence is so rare. Therefore, a strict criteria based selection process was used to remove irrelevant publications.

Criteria	Inclusion criteria	Exclusion criteria	Reasoning
Time period	Research published between 2000-2022	Research published before 2000	Due to the rapid advancements in literature in the last two decades, papers published after 2000 are more likely to represent up to date evidence based on the questions being asked. Due to the changes in neuroanatomy and neuro-oncology over the recent years, dated papers were excluded to prevent inaccurate information being passed on and justified in this review.
Type of publication (validity)	Published and peer-reviewed literature	Unpublished literature e.g. websites. Authors were not contacted for additional information	Peer-reviewed publications establish the validity of the research conducted by experts in the field. The research is trusted and prevents falsified conclusions from being published into scientific research. Information from websites has a higher risk of inaccurate research with no grounds for credibility and no research-based evidence. Peer-reviewed journals establish accurate conclusions drawn from the research

			conducted preventing untrustworthy work from being used in literature reviews.
Language	English language and pre-translated papers	Non-English publications without pre- translated text	English is the working language of the reviewer therefore, to prevent mistaken information used due to inaccurate translation, any non-English journals were excluded. In some cases, pre-translated journals were reviewed for relevance and unless they required involvement in contributing to the research question they were excluded.
Type of research	Primary research papers	Secondary research papers (reviews, case reports etc.)	Reviews are more likely to have an underlying biased opinion and can exclude relevant research which contradicts the pre-existing opinion of the reviewer. Primary research papers include methodology and results to support the conclusions that are established–research-based evidence. Secondary research was used to base general understanding upon, rather than base conclusions on.
Sample age	Pediatric, adult and aged patients	N/A	Explanations were required in this rapid review as to why tumours are more frequent in pediatric and geriatric patients therefore, it was relevant to include tumours associated with children even though it meant more literature research was then available for the screening process.
Relevance to research question: associated cells	Tumours associated with only the neurones and neuroglia of the CNS and PNS	Tumours associated with other components of the CNS and PNS	This prevented irrelevant information from being researched and avoided the large amount of publications available from being screened for relevance. Direct relevance to tumours of the cells was required rather than tumours associated with cells making up the environment in the CNS and PNS. This prevented time spent on irrelevant areas as other tumours of the CNS and PNS aren't associated with nerve cells, rather their supporting cells. This meant that the research maintained the aims mentioned rather than focusing on irrelevant research.
Relevance to research question: associated tumour	Primary tumours of the nervous system	Secondary tumours of the nervous system	Secondary tumours are irrelevant to the question being asked therefore, papers involving secondary metastasis of tumours into the CNS and PNS were excluded. This helped eliminate irrelevant research in order to ensure relevance to the aim and the research question.

Table 5. The inclusion and exclusion criteria applied for the relevant articles found in the literature search on the electronic databases.

This strict criteria based process was essential for creating a beneficial set of results to build a literature synthesis upon. The inclusion criteria include literature publications which form consistent, reliable and standardized results in which to include in the literature analysis. Exclusion criteria involve factors which impact and influence this uniform set of results. Exclusion criteria must be present when performing a literature search due to some of the factors affecting the reproducibility and reliance of the performed searches. The reasoning behind the inclusion and exclusion criteria is mentioned in order to create a relevant and unbiased result section. Outdated, irrelevant and unreliable publications were crucial criteria to follow when selecting literature to include in this literature review.

In terms of relevance, journals were excluded if they did not have direct relevance to the aims and research question seen in Figure 6 where themes were created. Journals were included if they provided and evaluated information in the related themes. There were three searches performed to link potential reasons why nerve cell tumours are so rare. Firstly, using textbooks and reviews to understand the anatomy of nerve cells and the different types associated with the two nervous systems. Secondly, the types of primary tumours which form from these nerve cells in the CNS and PNS to link tumour type, prevalence and associated cellular mutations. Finally, searches on the adaptations of nerve cells and their environment to prevent tumours forming were performed using the search strategy in terms of cell cycle, regeneration, immunity and lymphatic systems and risk factors. The keywords for the different themes are required to sift through the large amount of available yet irrelevant literature for this review (Figure 7). These key terms were used to create a variety of search strings to facilitate an effective systematic search technique to be performed on the databases. The same search strategy with Boolean operators were used on the different databases to ensure consistency (Appendix 1). Asterixis were used to search variation of search terms to widen the search. "OR" was used to identify journals covering similar topics and hence broaden the search. Whereas the "AND" function was used to narrow the search field by identifying specific journals which include combinations of keywords resulting in more focused and specified results. The search strategy was used to scan the title and abstract (Appendix 2 and Appendix 3).

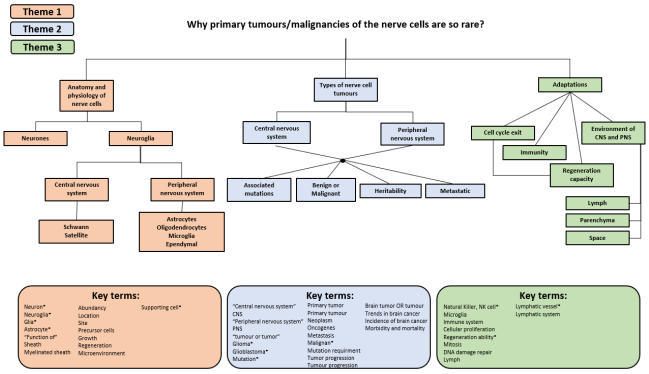

Figure 7. Relevance tree and associated keywords for creating a search strategy.

Linking the topics together in a relevance tree aided in creating key terms to create a search strategy for. This ensures effective research was performed when sourcing papers with direct relevance to the research aims and themes. The different themes can be seen correlating with different colours and their associated key terms shown below.

Screening/study selection

Figure 8 reports the results from the search strategy using the online databases and the criteria applied to exclude 507 journals to inalise 7 papers used to build the literature synthesis section. Further hand searches were completed on online sources (pubMed and google scholar) for supplementary material. Results from the literature search were imported into EndNote online library to remove duplicated journals using the "Bramer method" [17].

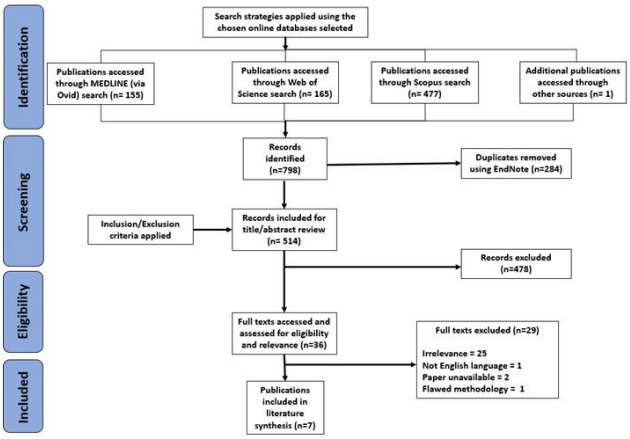

Figure 8. PRISMA flow diagram indicating the number of results at each stage of the literature search. 798 results from the databases were imported into EndNote where 284 duplicates were removed. The remaining 514 papers underwent a preliminary screen by the reviewer for relevance using the title/abstract, removing 478 references which weren't related to the themes mentioned previously. This literature search included several limits to process the publications effectively considering the large amount of irrelevant literature. The full text of the remaining 36 papers was read to make further exclusions using the inclusion/exclusion criteria. These final 7 publications were further critically appraised for quality and reliability to include into this review. A thorough methodology ensures that the papers included in this review provide novel insight into the questions being asked here.

Overall number of chosen papers: The inal number of publications following the search strategy and rigorous criteria based exclusion process was 7 to be used in the literature synthesis.

Results and Discussion

The papers chosen to include in this rapid review were categorised depending on their main aims and were grouped together. Four themes were classified from thematic analysis:

- Regeneration and proliferation ability of nerve cells.
- Statistical analysis of nerve cell tumours.
- Immune system role and environment of nerve cells.
- Risk factors associated with tumours of the nervous system.

Applying a selection process to the articles in the search strategy method, a shortlist of 7 publications was created (Appendix 3).

Literature synthesis

Cancers of the CNS and PNS represent a group of rare tumours accounting for 1.8% of new cancer cases and 2.3% of cancer-related deaths in 2012 [18]. To the best of our knowledge, this is the first review to link the powerful anti-tumour mechanisms adapted by nerve cells and the environment to the rarity of nerve cell tumours.

Reduced number of regenerating cells: The CNS is the only tissue in the human body which lacks regeneration capacities. The inability for cells of the CNS and PNS to regenerate to functional capacity following injury has often been seen as an adaptive disadvantage which has led to the paralysis, brain damage, numbness and pain in limbs. Advantages to this could be associated with fewer tumours forming in nerve cells. Genetic mutations occur during the cell-cycle of neurons and neuroglia promotes the characteristic trait of abnormal cell proliferation. Genes encoding cell-cycle regulators are frequently mutated in human tumours leading to aberrant regulation of the cell-cycle, unscheduled proliferation and carcinogenesis. 80% of human tumours are carcinomas developing from the epithelia [19]. Cells with epithelial origin require constant regeneration due to their rapid turnover rate and consequential continuous cell-cycle and proliferation where oncogenic mutations take place more regularly. There are fundamental differences between the cell-cycles of typical epithelial cells and neuronal cells.

Neurons exist in a senescent stage in G_0 remaining mitotically inactive. Therefore, neurons are generally considered post-mitotic cells with reduced opportunities of acquiring oncogenic mutations. Cardiomyocytes have limited regeneration due to early cell-cycle exit caused by Meis1 (transcription factor) and this has been assumed to contribute to the lack of malignancies forming in these cells. Neurons must dedicate their full energy to their electrochemical communication meaning no energy can be spent on their replication. Hard structures (skull, vertebrae) act as a protective mechanism surrounding the brain and spinal cord to prevent injury to neurons.

Tomashevski, et al. explored the ability for neurons to re-enter the cell-cycle following DNA damage without forming daughter cells. Terminally differentiated neurons endure high levels of genotoxic stress due to their high susceptibility of oxidative DNA damage by free radicals. Neurons are more exposed than astrocytes to conditions causing DNA damage such as ionising radiation,

suggesting that mature neurones have a deficiency in DNA damage, promoting their higher sensitivity to DNA damage. The rate of oxidative metabolism is considerably higher in neurones compared to other somatic cells resulting in increased risk of DNA damage hence, there must be mechanisms repairing damaged DNA otherwise neurones risk cell death, genomic instability and tumorigenesis [20]. Double-strand DNA breaks are the most fatal form of DNA damage which is generally fixed by Non-Homologous End-Joining (NHEJ) in mammalian cells. Postmitotic neurones showed NHEJ activation alongside retinoblastoma protein phosphorylation guided by cyclin-C kinase activity. This kinase activity is sufficient for the G_0-G_1 transition hence, the cell is able to repair damaged DNA and exit the cell-cycle without producing two daughter cells. Cell-cycle activation of terminally differentiated neurones is also associated with DNA damage-induced apoptosis whereby most neurons are induced to undergo apoptosis following re-entry to the cell-cycle. This is a process known as abortive cell-cycle re-entry, characterised by increase in cyclin D-cdk4/6 and downregulation of E2F consequently leading to apotosis, preventing development of tumorigenic mutations (Figure 9). Therefore, no daughter cell production means their mutations cannot be passed on.

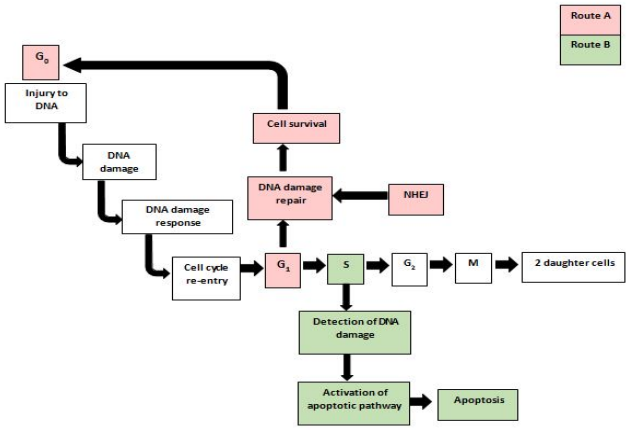

Figure 9. Adapted flow chart explaining the two routes following detection of DNA damage in terminally differentiated neurones.

Route an after detection of DNA damage utilises Non-Homologous End-Joining (NHEJ) which aids in repairing the DNA damage and the neurone is returned to G_0 without forming two daughter cells. Route B is where the DNA damage is not fixed, and the cell enters the S phase where checkpoint regulators detect the mis-replicated DNA and marks it for apoptosis. In both routes, no daughter cells are formed as the cell doesn't undergo mitosis (M) which maintains neurones at a base population.

Most neuroglia remain in a similar quiescent state where re-activation into the cell-cycle following injury to the CNS or PNS is regulated by growth factors and axonal mitogens. Losses of TP53 and NF1 function are associated with the majority of neuroglial tumours where benign tumours result from single mutations. As NF1 and TP53 are in close proximity on chromosome 11, cooperate loss of these genes on the same chromosome results in more frequent malignant tumours e.g. MPNST.

Proliferation of astrocytes (the most abundant neuroglia in the CNS) occurs predominantly during embryogenesis although, adult gliogenesis is shown following injury to the CNS e.g. breakdown of Blood-Brain Barrier (BBB). Following CNS insult, ATP levels increase triggering ibroblast growth factor-2 to increase astrocytic proliferation by stimulating the expression of cyclin D1 (key regulator of cell-cycle re-entry) and cyclin A (regulator of DNA replication), stimulating re-entry into G1. Glial pathology occurs more in the ageing brain where increased neuroglia proliferation increases risk of tumorigenic mutations.

Crocetti, et al. reported the incidence rates of CNS Tumours (CNST) where astrocytic tumours are the most frequent (Table 6). A threshold is suggested by the RARECARE project whereby rare tumours are defined as an incidence rate lower than 6 per 100,000 persons per year.

Types of tumours	Total number of cases between 1995-2002	Rate for total number of cases per 100,000	Rate of cases (per depending on gender 100,000)		Rate of cases depending (per on age in years 100,000)			
			Male	Female	0-19	20-39	40-59	60+
Astrocytic tumour	38,588	4.8	5.7	4.0	0.9	2.0	6.2	11.6
Oligodendroglia tumour	2845	0.4	0.4	0.3	0.1	0.3	0.6	0.4
Ependymal tumour	1604	0.2	0.2 No	0.2 difference	0.2	0.2 No	0.2 difference	0.2
Non-glial tumours of the CNS (embryonal tumours+choroid plexus carcinomas)	1805	0.2	0.3	0.2	0.6	0.2	0.2	<0.1
Highest group for total number of cases and rate.								
Highest group for number of cases according to gender.								
Highest group for number of cases according to age.								

Table 6. The incidence rate of tumours associated with the neuroglia.

Astrocytes, oligodendroglioma and ependymal cells compared to non-glial tumours of the CNS with rates associated to age and gender. Astrocytic tumours had the highest rate of 4.8 per 100,000 per year subsequently by oligodendroglia tumours of a 0.4 rate. Their

study also supports the evidence that glial tumours are associated more frequently with ages of 60+ years for astrocytic tumours, and incidence peaked for oligodendroglioma tumours for ages 40-59 years. The cases were diagnosed between 1995-2002 among 64 European countries and their associated cancer registries.

Tumour suppressor proteins: Every day, there are between 50-500,000 DNA damages in every cell by regular metabolic responses. Increasing age correlates with nerve cells losing their ability to respond to DNA damage offering reasons behind increased prevalence of nervous system tumours in the elder population. TP53 and PTEN are two commonly occurring mutations in nerve cell tumours. PTEN mutations are more common in primary tumours (25%) compared to secondary tumours (5%).

Loss of p53 plays a central position in developing gliomas where a single mutation in p53 is sufficient to develop malignant astrocytomas in mice model. Loss of p53 in mice is also associated with multiple oncogenic mutations in Rb and RTK pathways, both involved cellular proliferation.

Using specific monoclonal antibodies to PTEN, Gimm, et al.(2000 demonstrated PTEN levels were expressed highest in the CNS and PNS compared to other regions of the body. High PTEN expression was retained throughout the development of the CNS suggesting that PTEN plays a key role in its developmental process due to its continued expression (Gimm, et al. 2000. PTEN expression in brains begins postnatally day 0, followed by increased expression in neurones in adult brain. PTEN is also expressed in most adult neurones in the brain especially in the cell bodies of large neurones. PTEN is a negative regulator of the protein kinase mTOR which is involved in regulating cell proliferation therefore; mutations in PTEN disrupt the tightly controlled proliferation abilities of cells. PTEN is often mutated in tumours associated with the CNS particularly GBM and gliomas.

Due to the abundancy of TP53 and PTEN in adult neurones, there is a decreased likelihood of developing mutations which create a tumour. This an example of protective mechanisms put in place by adult neurones preventing the cell from proliferating with oncogenic mutations because following DNA damage detection, the cell is scheduled for apoptosis by the abundant p53 and PTEN.

Lymphatic system in nervous system: The CNS and PNS have been shown to be both inhospitable environments for tumour growth. Tumours must undergo transformation particularly to adapt to the CNS environment and grow malignantly.

For gliomas to proliferate in the CNS they must create space for their invasion. This requires "killing" neurones to facilitate their expansion. Gliomas have been reported to rarely metastasise outside the CNS although; some malignant gliomas can metastasise and form secondary tumours throughout the brain and sometimes seed into the spinal cord.

The brain lacks a classical lymphatic system although, Lymphatic Vessels (LVs) exist here in an extensive network lining the dural sinuses, draining into the deep Cervical Lymph Nodes (dCLNs). LVs play a crucial role in exchanging debris and immune cells among different tissues to remove waste before the re-entry into circulation. Lymphatics play a pivotal role in the anti-tumour response of the brain draining antigens, intratumor luid and providing immunity explored the role of Meningeal LVs (MLVs) in brain tumour pathology and Figure 10 shows their results.

For tumours to grow in the CNS there must be mutations and reprogramming to allow tumours to access the plentiful energy source. There must be metabolic reprogramming known as the Warburg effect where the cancer cells change from oxidative phosphorylation to glycolysis.

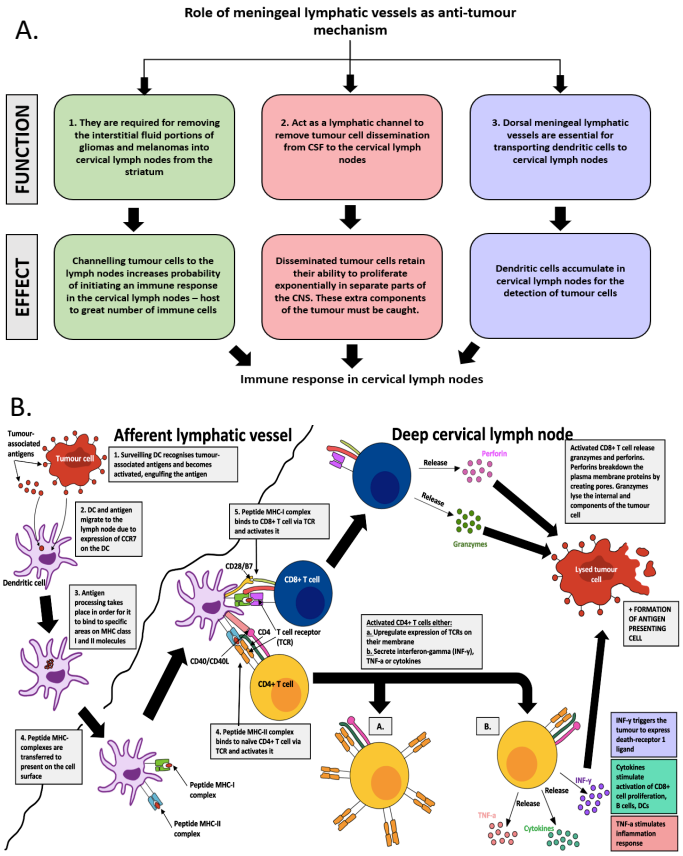

Figure 10. The role of MLVs in preventing tumour growth by channelling immune and tumour cells towards deep cervical lymph nodes in the brain.

- Indicates the roles of the meningeal lymphatic vessels.
- Indicates the role of DCs in channelling the tumour cells to the lymph node for degradation.

When the dorsal MLVs were disrupted, damage was seen in drainage of intratumour luid as well as increased dissemination of tumour cells to deep Cervical Lymph Nodes (dCLNs). Decreased DCs were seen in the dCLNs in defected dorsal MLVs. Due to the intricate immune network surveilling the CNS and lymphatic vessels, in the rare event that tumours form in nerve cells there are further protective mechanisms set in place to detect tumour cells at a manageable size and stimulate the destructive immune cells to eliminate the tumour.

Immunity in the nervous system: The immune system and CNS are highly specialised and interlinked to create an immune deficient environment. This is due to the BBB protecting the brain from the circulatory system and the lack of classic LVs with limited number of DCs in the parenchyma of the CNS. However, an adapted system in the CNS provides rigorous surveillance of the CNS performed predominantly by macrophages, microglia and Antigen-Presenting

Cells (APCs) outside of LVs. Healthy parenchyma is under constant surveillance by the resident immune cell; parenchymal microglia.

These are specialised macrophages, originating from yolk sac macrophages, migrate to the CNS in early embryogenesis and maintain their population by proliferation from local progenitors. Lymphocytes reside in the meninges and choroid plexus surrounding the brain to provide immune surveillance.

Microglia represent 5%-20% of neuroglia population and the 80%of immune cells in the CNS and present MHC class I ligands to protect themselves against the cytolytic effects of Natural Killer (NK) cells. Their predominant CNS role is to promote inflammation responses upon detection of pathogens or damage. Microglia become activated and is the predominant pro-in lammatory cytokine/ chemokine producer in neuronal tissues to activate the CNS microenvironment. Upon its activation, the BBB becomes more permeable to allow entry of peripheral immune cells such as macrophages, NK-cells and lymphocytes. This rapid immune response in the CNS prevents viruses or pathogens transforming the resident nerve cells into oncogenic cells.

NK-cells and cytolytic lymphocytes ($CD8^+$ T-cell) characterise as the most effective responsive factors against tumours and pathogens due to their role in early cytolytic protection against tumours and viral infections. NK-cells are found readily found within the CNS and have been linked to limiting the development of tumours in the CNS due to their surveillance and cytotoxic effects stimulated by the receptors on NK-cell surface (Figure 11). Healthy NK-cells will express a large range of these cellular receptors which bind and activate surface ligands on tumours *via* NK-mediated cytotoxicity. Specific cytokines (IL-2, IL-12, and IL-15) are expressed by helper T cells ($CD4^+$ T cells), DCs and macrophages which have an activating effection NK-cells. In particular IL-12 and IL-15 signal to the NK-cells to increase expression of NKG2D on the cell surface. Autologous cells are secured with a non-lytic fate due to their high expression of MHC class I molecules classifying the cell as "self" whereas, tumours are marked for a degradative fate due to their ligand expression. NK-cells bind to MHC-class I ligands and only cells with adequate numbers of these ligands are provided security against its cytotoxic nature, tumours often have insufficient MHC class I ligands in their attempt to be portrayed as "self". NK cells can destroy groups of adjacent cells following detection of oncogenic transformation, preventing the spread of disseminated tumour cells. NK-cells function by releasing lytic granules containing perforin and granzymes to induce apoptosis.

Castriconi, et al. isolated and expanded tumour cells *in vitro* from nine GBM patients to explore the properties of NK cells in destroying tumour cells. The cells were expanded in stem cell medium, implanted into immunodeficient mice and analysed for Neural Stem Cell (NSC) markers, differentiation levels and tumorigenicity. Finally, these GBM cells cultured in stem cell medium were analysed for vulnerability to lysis by NK cells (allogenic and autologous were examined) as well as assessing the interactions between NK receptors and the GBM ligands. The results from this study can be seen in Figure 11. Despite the fluctuating amounts of NCR ligands on tumour cells, NK cells can resist this by responding with sufficient combinations of receptors regardless of the up-regulating or down-regulating number of tumour ligands.

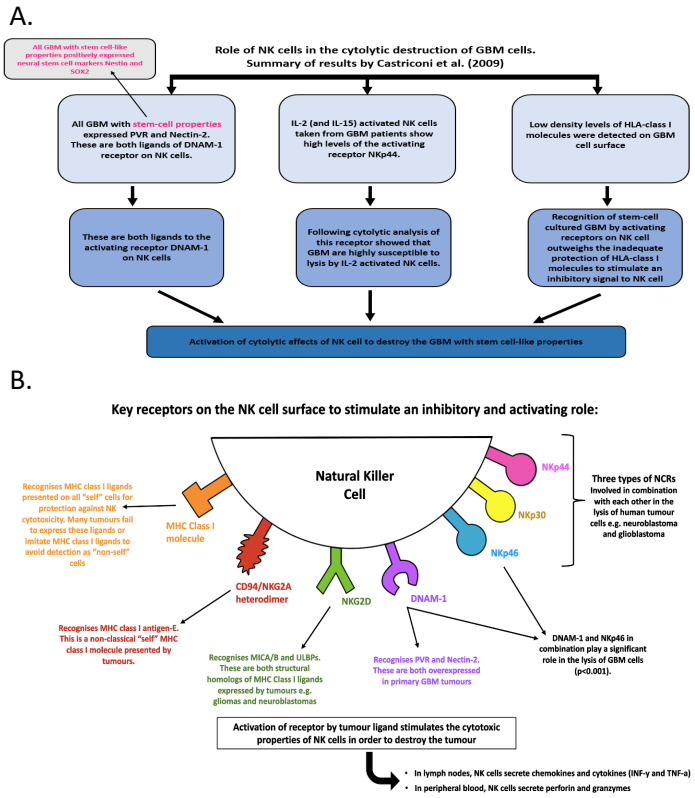

Figure 11. Results from the study by Castriconi, et al. with the cytotoxic nature of NK cells in destroying GBM tumour cells. (A) The receptors on the cell surface of NK cells, varying in numbers depending on signalling pathways impacted upon NK cell. Their associated ligands are seen which are associated with tumour cells, resulting in activation of the cytotoxic effects of NK cells in the destruction of tumour cells. (B) Flow chart showing the findings of NK-mediated lysis upon GBM cells depending on specific receptor-ligand interactions. As shown, GBM cells show insufficient amounts of MHC class I ligands as protection whereupon multiple activating ligand interactions generate NK cytotoxicity.

The immune system experiences extreme remodelling and deterioration as age increases creating an immune senescence with fluctuations in immune cell levels. The levels of functioning active NK-cells remain at only half of adult level at birth. NK-cells have a decreased response from IL-2 and IL-15 activation in neonatal NK-cells, explaining the increased number of tumours associated with childhood compared to adults due to the lack of immunity protecting and surveilling the CNS in children. CNS tumours represent 18% of total cancer diagnosed every year in children (0-19 years). With tumours occurring more frequently in the elder population, the decline in the immune system efficiency and the increased risk of cellular and genetic damage are co-factors in the increased tumorigenesis with progressing age. The CNS immune system creates an environment inhospitable to tumour growth by early detection of oncogenic cells therefore, making tumours associated with nerve cells in the CNS particularly rare.

However, the immune system can be hijacked by aggressive brain tumours (*e.g.* high-grade glioblastomas) where they incorporate the network of immune system cells into the tumour microenvironment. This creates an immune-deficient CNS causing high mortality rates in aggressive CNSTs as the body and brain become susceptible to

further metastases and the failure to respond appropriately to toxins and pathogens.

Risk factors

Mutations: Multiple mutations must take place to establish gliomas in the CNS where most characterise with dysregulation of p53. Cancer Predisposition Syndromes (CPS) represents a number of conditions where individuals are at greater risk of developing primary malignancies.

Individuals with CPS and previously diagnosed CNSTs are associated with a 10 time increased risk of developing subsequent gliomas. CPSs associated as risk factors for CNSTs include Li-Fraumeni syndrome, Neuro ibromatosis type 1 syndrome and Cowden syndrome. Germline mutations associated with CNSTs are rare as the majority of these tumours show somatic overexpression mutations. Table 7 summarises these germline mutations and their effects on developing tumours.

Genetic condition	Affected *genes*	Tumour association	How does it cause brain tumours?
Li-Fraumeni Syndrome (LFS)	*TP53* (17p13.1) Dominant 70% of LSF patients have TP53 germline mutations	• Glioblastoma (30-50% have TP53 mutations) • Other gliomas • Substantial risk of developing multiple primary cancers (60% of LSF patients are at risk)	This is a heterozygous missense mutations resulting in loss of p53 protein function. Wild-type p53 protein has disrupted function due to 1 allele of TP53 is inactivated. Loss of function mutation means p53 loses growth inhibitory and tumour suppressor roles.
Cowden Syndrome (CS)	*PTEN* (10q23.31) Dominant >80% of patients with CS develop PTEN mutations	• Oligodendroglioma • Glioblastoma • Meningioma Gangliocytoma	The PTEN gene regulates the PI3K-Akt-mTOR pathway by encoding the protein responsible for this pathways negative regulation. Mutations lead to a loss of function of this protein and therefore, loss of tumour suppressor properties.
Neurofibromatosis type 1 (NF1) syndrome	NF1 (17q11.2) Autosomal dominant 20% of patients with NF1 syndrome develop CNS tumours. Prevalence of NF1 syndrome is 1 per 2500-3000 people worldwide	• Astrocytoma • Schwannomas • Neuro ibroma (develop multiple benign plexiform or dermal neurofibromas) • MPNSTs (8%-13% of patients with NF1 syndrome develop MPNST from plexiform neuroffbromas) • Optic pathway glioma	NF1 encodes the neurofibromin protein (expressed throughout nerve cells such as neurones and astrocytes). NF1 protein regulates cell proliferation and differentiation *via* the Ras-MAPK pathway. Loss of NF1 activates RAS and inhibits cAMP signalling. RAS plays a role in regulating p16 and p53 cell-cycle control. Loss of function increases cell proliferation and increases malignancy risk in CNS and PNS.

Table 7. Summarises the impact of three hereditary conditions resulting in germline mutations which are risk factors developing tumours in the nervous system particularly glioma-prone syndromes.

Li-Fraumeni Syndrome (LSF), Cowden Syndrome (CS) and Neurofibromatosis 1 (NF1) syndrome represent three genetic conditions with associated high risks of developing tumours such as glioblastoma, schwannoma and astrocytomas. Their associated genetic mutations are shown alongside the impact of these mutations in increasing the chances of developing tumours in the CNS and PNS.

Geographic location: Khazaei, et al. studied the link between incidence and mortality of brain tumours with the impact of socioeconomic development. Their results showed that Asia was the area with the highest incidence of brain cancers reported in 2018 (156,217 cases) accounting for 52.60% of total cases. Figure 12 displays their results indicating the relationships between Human Development Index (HDI) of a country and the incidence and mortality of brain tumours.

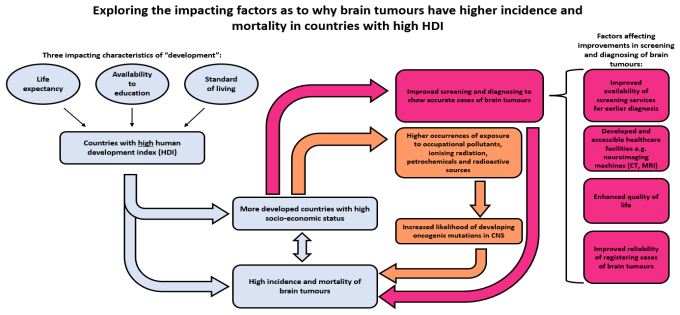

Figure 12. Summary of results by Khazaei, et al. in a study reporting incidence and mortality of brain tumours to HDI of countries.

HDI is characterised by three criteria: Life expectancy, education and standard of living. High HDI levels correlated with a high incidence and mortality of brain tumours. There are many suggested reasons why this correlation is seen such as improved availability of screening services for earlier diagnosis, developed healthcare facilities, enhanced quality of life as well as improved reliability of registering cases of brain tumours in the more developed counties. However, exposure to environmental pollutants is seen to be a risk factor associated with developing brain cancer. In countries associated with a high HDI, there is a connection with higher occurrences of exposure to occupational pollutants, radiation, and radioactive sources.

Results from this study saw a signi icant correlation between HDI with incidence ($P<0.0001$) and mortality ($P<0.001$) of brain tumours in 2018. Despite the increase over the recent decades of nervous system tumours, the question remains whether the high incidences and mortality of brain cancer is correlated with the associated high pollutants or rather, the improved healthcare services available for better screening and diagnosis indicating increased number of cases compared to other countries where many cases go undiagnosed. Prior to the improvement in diagnostics and testing, brain tumours may have been classi ied as strokes or metastatic tumours. To compare incidence of CNSTs worldwide, improvements are required by registries to record all CNST cases to provide accurate and representative comparisons of countries and ethnicities.

Conclusion

Concluding remarks

In this review, we have covered the predominant mechanisms for tumour infiltration and the protective systems put in place by nerve cells as well as the environment of the nervous system.

Mutations rarely occur in nerve cells due to their inability to proliferate and regenerate from their senescent state in G_0. Mutations are rare in the small pool of neuronal progenitor and precursor cells which are characterised with desirable regenerative and differentiation abilities due to their increased expression of DNA damage detector checkpoint proteins p53 and PTEN. Mutated nerve cells are marked for DNA damage repair or apoptosis where potential oncogenic mutations are not passed onto daughter cells and are removed from the genome. Tumorous growths which bypass these protective mechanisms are then detected by the abundancy of immune cells surveilling the nervous system and within the lymphatic system which mark them for degradation. Metastasis of nerve cell tumours is reduced by the hard bony structures and presence of the BBB. Finally, mutations which develop oncogenic transformation of cells are predominantly somatic where germline mutations account for a small proportion of nerve cell tumours. Additional risk factors have been mentioned such as ionising radiation and increasing prevalence due to increasing age and early childhood.

However, it is important to consider the disadvantageous impact of these protective mechanisms in the nervous system. The limited number of CNS and PNS regenerating cells cause other significant problems other than avoiding cancer. Following injury to the spinal cord, brain and peripheral nerves they are unable to equivalently regenerate to previous levels. The question remains whether the decreased number of nerve cell tumours is more beneficial over the vast number of degenerative nervous system diseases which stem from the inability of nerve cells to proliferate and regenerate.

Additionally, due to these cancers being so rare in nature it has resulted in less available research in therapeutic treatment compared to more common breast cancer. It also becomes a challenge for clinicians as the symptoms presented for nervous system tumours share similarities for strokes.

Therefore, these types of neoplasms could be missed in diagnostics due to the lack of research into these types of tumours and their understandings. This contributes to the issue of cancer registries listing incidence and mortality rates of neural tumours which are unrepresentative. Less developed countries correlate with decreased rates of nerve cell tumours due to the limited availability of healthcare where cases go undiagnosed. Improvements are required in reporting these cases to provide representative data to conclude risk factors based on gender, ethnicities, geographic location and age.

Limitations

As with every literature review, the associated limitations must be addressed. Research conducted into the mechanisms and adaptations underlying the rarity of nerve cell tumours is considerably limited which presented difficulties in researching and selecting relevant journals in line with the aims established in this review. Search terms were narrowed as much as possible to increase relevancy yet, some literature may have been missed which might have provided insights into areas not discussed here despite using four search engines to conduct the review. Additionally, as there are multiple different types of cells associated with the nervous systems, numerous different types of tumours are a result.

This created a limitation as nerve cell tumours couldn't be established by their specific rarity as there are too many to cover in this rapid review. Many of the literature surrounding tumours, nerve cells and CNS and PNS are review papers. It was a challenge to find original research papers rather than literature reviews on this topic. There is possible bias in this review tailored towards the CNS compared to PNS. This is due to the increased number of publications surrounding the CNS whereas; tumours of the PNS are relatively under-researched creating a challenge to find relevant literature. Finally, classifications of CNSTs have changed over time according to the WHO. This has led to a huge number of older publications using incorrect terminology to describe these tumours which associated confusion.

Future Directions

Despite establishing important conclusions underlying the rarity of nerve cell tumours, many questions remain unanswered which would provide essential insight into specific tumour rarity by generating new aims. Particularly understanding the mutations involved with nerve cell tumours and therefore, potential therapeutic targeting treatment into improving the high morbidity rate associated with these tumours.

Areas for further exploration include the triggering factors stimulating DNA repair in post-mitotic neurones which have re-entered the cell-cycle. This would provide insight into the ways in which neurones can maintain their population without inducing apoptosis following DNA damage as radiation and pollutants will continue increasing leading to heightened oncogenic mutations. Additionally, research into NSCs and NPCs in their utilisation of therapeutic potential against malignancies is required as these cells are targeted and hijacked by tumours (particularly gliomas) due to their proliferating and regenerating capacities. Development of targeted immunotherapy has been shown to be a promising avenue of treatment in more common cancers e.g. breast therefore, research into biomarkers and immune profiling of nerve cell tumours would provide improvements in treatment following diagnosis.

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