CHAPTER ONE

Pathophysiology of blood-brain barrier in brain tumor. Novel therapeutic advances using nanomedicine

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International Review of Neurobiology, Volume 151
ISSN 0074-7742
https://doi.org/10.1016/bs.irn.2020.03.001

Abstract

Glioblastoma Multiforme (GBM) is one the most common intracranial tumors discovered by Burns (1800) and Abernethy (1804) based on gross morphology of the autopsied material and referred to as "medullary sarcoma" and later "fungus medullare" (Abernethy, 1804; Burns, 1800). Virchow in 1863 was the first German pathologist using histomorphological techniques discovered that GBM is a tumor of glial origin. Virchow (1863/65) also then used the term Glioma for the first time and classified as low-grade glioma and high-grade glioma very similar to that of today according to World health organization (WHO) classification (Jellinger, 1978; Virchow, 1863/65). After almost >50 years of this discovery, Baily and Cushing (1926) based on modern neuropathological tools provide the classification of gliomas that is still valid today (Baily & Cushing, 1926).

Although, our knowledge about development of gliomas has advanced through development of modern cellular and molecular biological tools (Gately, McLachlan, Dowling, & Philip, 2017; Omuro & DeAngelis, 2013), therapeutic advancement of GBM still requires lot of efforts for the benefit of patients. This review summarizes new developments on pathophysiological aspects of GBM and novel therapeutic strategies to enhance quality of life of patients. These novel therapeutic approaches rely on enhanced penetration of drug therapy into the tumor tissues by use of nanomedicine for both the diagnostic and therapeutic purposes, referred to as "theranostic nanomedicine" (Alphandéry, 2020; Zhao, van Straten, Broekman, Préat, & Schiffelers, 2020). Although, the blood-brain barrier (BBB) is fenestrated around the periphery of the tumor tissues, the BBB is still tight within the deeper tissues of the tumor. Thus, drug delivery is a challenge for gliomas and requires new therapeutic advances (Zhao et al., 2020). Associated edema development around tumor tissues is another factor hindering therapeutic effects (Liu, Mei, & Lin, 2013). These factors are discussed in details using novel therapeutic advances in gliomas.

1. Introduction

Brain tumors (BT) are one of the most devastating diseases of the central nervous system (CNS) for which no suitable therapeutic strategies exist still today (Jellinger, 1978). The BT belongs to heterogeneous group of

primary and metastatic neoplasm of the CNS causing widespread death in patients during short survival period after diagnosis (Wirsching, Galanis, & Weller, 2016). According to new World Health Organization (WHO) classification of brain tumors based on morphological, immunological, molecular and genetic tools BT could be either as grade I or grade IV (Wesseling & Capper, 2018). Grade I BT is characterized by lesions in the brain with low proliferative properties that may be curable. Whereas grade IV BT is described as cytological malignant and mitotically active leading to extensive proliferation capabilities into the surrounding healthy brain tissues. This causes difficult to treat gliomas using available therapeutic tools (Stoyanov et al., 2018).

Glioblastoma Multiforme (GBM) stage IV is the most aggressive and proliferative BT and lethal within 6–12 months after the initial diagnosis in human cases (Cheng, Zhang et al., 2019). There are several reasons for the poor prognosis in GBM therapy. These include multidrug resistance, limited options for surgical intervention, the residual glioma cells with potentials to form another BT as well as surgical dependent malignancy (Adhikaree, Moreno-Vicente, Kaur, Jackson, & Patel, 2020; Alexander & Cloughesy, 2017). The problems get compounded further as similar treatment in different patients results in different outcomes (Stavrovskaya, Shushanov, & Rybalkina, 2016). At the moment therapeutic approaches to GBM is limited to surgical resection followed by radiotherapy and chemotherapy (Lim, Xia, Bettegowda, & Weller, 2018). These treatments results in cell damage of healthy tissues and extensive DNA damage causing serious side effects. Furthermore, repeated radiotherapy and chemotherapy is needed to prevent recurrence of BT during long-term GBM therapy causing quality of life of patients quite miserable (Anjum et al., 2017). The occurrence of GBM is largely seen in male patients with age above 45 with genetic disorders (Aliferis, Asna, Schaffer, Francis, & Schaffer, 2017; Jellinger, 1978; Lim et al., 2018).

Thus, there is an urgent need to expand our knowledge about the GBM pathophysiology and drug development to explore novel therapeutic strategic for an effective therapy for BTs. This review deals with the role of blood-brain barrier (BBB) and blood-tumor barrier (BTB) in GBM in order to expand our knowledge for development of suitable therapeutic strategies and to enhance the quality of life of patients.

1.1 History of glioblastoma

Glioblastoma was first described by Burns (1800) and Abernethy (1804) in Britain as Medullary Sarcoma based on gross morphology on autopsy

materials (Abernethy, 1804; Burns, 1800). This is because of the diffuse tumor formation in the CNS lacking a clear border with the healthy tissues (Jellinger, 1978; Virchow, 1863/65). French pathologists termed them as Encephaloide while German scientists called it Fungus Medullare (see Jellinger, 1978; Scherer, 1940c). These terminology of gliomas prevailed before the advent of light microscopy.

With the advent of Light Microscopy, Virchow was the first to analyze glial tumors using histopathological investigations (Jellinger, 1978; Virchow, 1863/65). Virchow clearly described that these malignant tumors are originating from glial cells of the CNS with clear demarcation between healthy tissues. He was the first to use the term "Glioma" for this brain tumor (Virchow, 1863/65). Virchow also differentiated gliomas into two distinct identity as Low Grade Gliomas (now Grades I and II) and High Grade Gliomas (now Grades III and IV by WHO Classification 2016 (Jellinger, 1978; Virchow, 1863/65; Wesseling & Capper, 2018).

At that time there was no distinct differentiations between glial cells of various types but the glia or Glue was considered as a homologous entity (Virchow, 1858). With the discovery of neurons in the cerebellum by Purkinje (1837) followed by Golgi (1873) and Cajal in 1887–1888 (Cajal, 1888a, 1888b) using silver stain changed the fundamentals of CNS anatomy and pathology. The astrocytes were first discovered by Von Lenhossek (1893) and microglial cells and oligodendrocytes were described by Hortega in (1913–1916) (Ramón y Cajal, 1913; Río-Hortega, 1916). This was postulated that each glial cell has distinct function in the CNS.

In 1926 neuropathologist Bailey and neurosurgeon Cushing provides first detailed modern classification of Gliomas that formed the base of WHO recent classification (2016) of different grades of Gliomas (Baily & Cushing, 1926; Omuro & DeAngelis, 2013; Wesseling & Capper, 2018). Bailey and Cushing based on histopathological evidences called gliomas as Spongioblastoma Multiforme because of multiform appearances of different cells within the same type of tumor samples (Baily & Cushing, 1926). They also mention astrocytoma for those tumors that originates from astrocytes (Baily & Cushing, 1926; Jellinger, 1978). Later on the term Spongioblastoma and the astrocytoma was replaced with Glioblastoma Multiforme (GBM). This was later confirmed by Scherer (1938, 1940a, 1940b) that GBM and astrocytoma originated from the same precursor cells (Scherer, 1940c). Scherer then used the term primary GBM and secondary GBM. These two types of GBM described by the Scherer have distinct clinical manifestation and biological properties (see Scherer, 1940c).

Thus primary GBM is extremely aggressive whereas secondary GBM has slower progression and better prognosis. Scherer also examined in details neovascularization around GBM also known as Scherer formation (Scherer, 1940c; Stoyanov & Dzhenkov, 2018).

2. The blood-brain barrier and brain tumors

The blood-brain barrier (BBB) strictly regulates that homeostasis of the CNS under normal conditions (Sharma, 2009; Sharma & Westman, 2004). The BBB is slightly more permeable around tumor microvessels (Arvanitis, Ferraro, & Jain, 2020; Quail & Joyce, 2017). However, this doesn't allow enough drugs or therapeutic agents to enter into the core of the tumor tissues (Sarkaria et al., 2018; van Tellingen et al., 2015). Thus, therapeutic strategies in BT did not yield desired results so far.

The BBB is a complex structure comprising the continuous endothelial cells that are joined by tight junctions that consists the main anatomical site (Arvanitis et al., 2020; Quail & Joyce, 2017; Sharma, 2009; Sharma & Westman, 2004). The endothelial cells are more than 85% covered by astrocytic end feet and associated with pericytes (Arvanitis et al., 2020). Recent evidences suggests that cerebral endothelial cells together with pericytes and astrocytic end feet constitute the greater BBB function that regulates the passage of materials from blood to brain and vice versa (Arvanitis et al., 2020; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015).

The BBB is disrupted during the BT development process and generally known as blood-tumor barrier (BTB) (Da Ros et al., 2018). The BTB is heterogeneously permeable to small and some large molecules but is not enough open to allow high drug concentrations from periphery in accumulating within the BT (Arvanitis et al., 2020). Thus, the BBB is still the major limiting factor in treating BT effectively (Arvanitis et al., 2020; Sharma & Westman, 2004).

2.1 The blood-brain barrier structure and function

The blood-brain barrier (BBB) is a physiological regulating system for exchanges of cells and molecules between the blood and brain interface (Sharma, 2012; Sharma & Sharma, 2017, 2019) (Fig. 1). Large molecules such proteins normally do not cross the BBB from the vascular compartment to the cerebral compartment (Sharma, 2009; Sharma, Westman, & Nyberg, 1998). However, for essential nutrients specific transport system works to maintain healthy brain cells within a strict limit (Kiyatkin & Sharma, 2019;

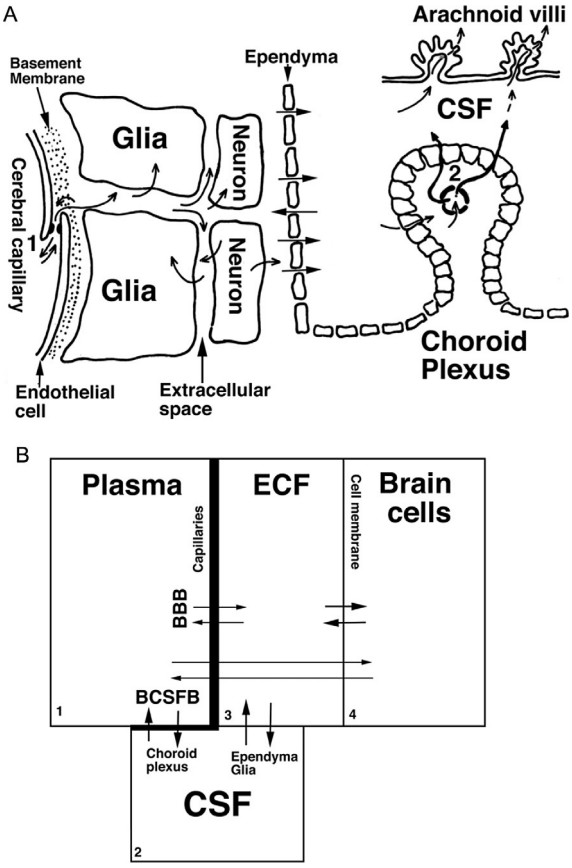

Fig. 1 Diagrammatic representation of route of exchange of essential materials across the blood-brain (1) and blood-CSF (2) barriers (A). (B) Tightness of barrier function represented by thickness of black lines within the blood brain (1), blood-CSF (2), ependyma and extracellular fluid (3) and extracellular fluid and brain cells (4) compartments of the fluid microenvironment of the brain (arrows). The barrier between the blood and brain is the tightest whereas barrier between blood and CSF is comparatively less tight to regulate exchange of essential materials. The barriers between extracellular fluid and ependymal or extracellular fluid and brain cells are not very tight and exchange of substances occur between them quite easily up to some extent (B). Likewise free exchange can occur between neurons, glia and ependymal cells for maintenance of fluid microenvironment of the brain (A, arrows). BCSFB, blood-cerebrospinal fluid barrier, CSF, cerebrospinal fluid, ECF, extracellular fluid. *Data modifies after Sharma, H. S. (2009). Blood–central nervous system barriers: The gateway to neurodegeneration, neuroprotection and neuroregeneration. In A. Lajtha, N. Banik & S K. Ray (Eds.),* Handbook of neurochemistry and molecular neurobiology: Brain and spinal cord trauma *(pp. 363–457). Berlin, Heidelberg, NY: Springer Verlag; Sharma, H. S. (2004a). Blood-brain and spinal cord barriers in stress. In H. S. Sharma &*

Nation et al., 2019; Sweeney, Zhao, Montagne, Nelson, & Zlokovic, 2019). Likewise, toxic and metabolic molecules are excluded from the BBB from brain to blood in order to keep cerebral microenvironment healthy (Sharma, 2004a, 2004b).

Under physiological conditions, the anatomical site of the BBB is the cerebral endothelial cells (as mentioned above) that are connected with tight junctions (Arvanitis et al., 2020; Sharma, 2009; Sharma & Westman, 2004) (Fig. 2). The endothelial cells in brain are thickly covered by the basal lamina that is in contact with pericytes and astrocytic end feet (Arvanitis et al., 2020). Neuronal contacts also occur on the endothelial cells together with pericytes and astrocytic end feet (Arvanitis et al., 2020; Nation et al., 2019; Sweeney et al., 2019). During development of the cerebral endothelial cells inputs of astrocytes, neuron and pericytes are responsible for BBB induction (Arvanitis et al., 2020; Nation et al., 2019; Sharma, 2009, 2012; Sharma et al., 2017, 1998; Sharma & Sharma, 2019; Sharma & Westman, 2004; Sweeney et al., 2019). In adult situation, these neuronal, glial, and vascular elements together in synergy regulate cell and molecular transport across the brain and vice versa to maintain homeostasis (Arvanitis et al., 2020; Sharma, 2009; Sharma & Westman, 2004).

2.1.1 The BBB microenvironment

The BBB microenvironment includes macrophages and fibroblasts apart from neurons, basal membrane and microglia (Arvanitis et al., 2020). Moreover, several enzymes present within the endothelial cells are able to degrade drugs and chemicals in entering the brain fluid microenvironment (Kiyatkin & Sharma, 2019; Nation et al., 2019; Sharma, 2012; Sharma et al., 2017; Sharma & Sharma, 2019; Sweeney et al., 2019). Endothelial cells efflux mechanisms including P-glycoprotein (PGP) also inversely affects the blood-brain transport of cells and molecules into the cerebral microenvironment in healthy conditions (Arvanitis et al., 2020; Hoosain et al., 2015;

J Westman (Eds.), The blood-spinal cord and brain barriers in health and disease *(pp. 231–298). San Diego: Elsevier Academic Press; Sharma, H. S. (2004b). Pathophysiology of the blood-spinal cord barrier in traumatic injury. In H. S. Sharma & J. Westman (Eds.),* The blood-spinal cord and brain barriers in health and disease *(pp. 437–518). San Diego: Elsevier Academic Press; Sharma, H. S. (1999). Pathophysiology of blood-brain barrier, brain edema and cell injury following hyperthermia: New role of heat shock protein, nitric oxide and carbon monoxide. An experimental study in the rat using light and electron microscopy.* Acta Universitatis Upsaliensis, 830, *1–94; Sharma, H.S. (1982).* Blood-brain barrier in stress *(Ph D Thesis). Varanasi, India: Banaras Hindu University Press.*

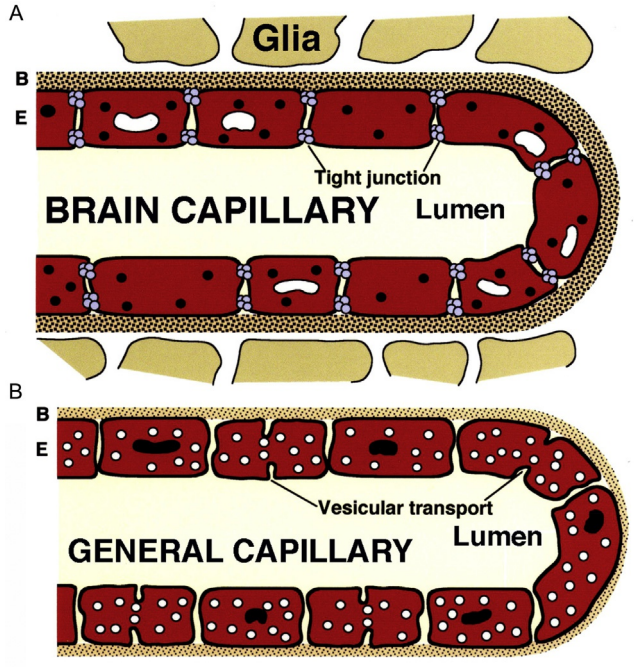

Fig. 2 Diagrammatic representation of a brain capillary (A) and a general capillary (B) for comparison. The endothelial cells (E) of brain capillary are connected with the tight junctions and covered with a thick basal lamina (B). The brain capillary is also covered by the glial end feet (Glia). In addition, the brain capillary endothelial cells do not show microvesicles for vesicular transport under normal conditions. On the other hand, general capillary do not contain tight junctions between the endothelial cells and exhibit lots of microvesicles for vesicular transport (B). The basal lamina (B) is very thin around the general capillary. *Data modified from Sharma, H.S. (2012). New perspectives of central nervous system injury and neuroprotection.* International Review of Neurobiology, 102*, xv–xx. doi: 10.1016/B978-0-12-386986-9.00013-2 (No abstract available); Sharma, H. S. (2004a). Blood-brain and spinal cord barriers in stress. In H. S. Sharma & J. Westman (Eds.),* The blood-spinal cord and brain barriers in health and disease *(pp. 231–298). San Diego: Elsevier Academic Press.*

Sharma, 2004a, 2004b; Ueno, 2009) (Fig. 3). Since endothelial cells of the BBB represent an extended plasma membrane, passive diffusion across the barrier depends on lipophilicity and molecular weight of the material (Arvanitis et al., 2020; Fu, 2018; Tajes et al., 2014). In addition the ability of the molecules to form hydrogen bonds further limits their passive diffusion across the BBB (Bickel, 2005; Pardridge, 2005). Drug molecules less

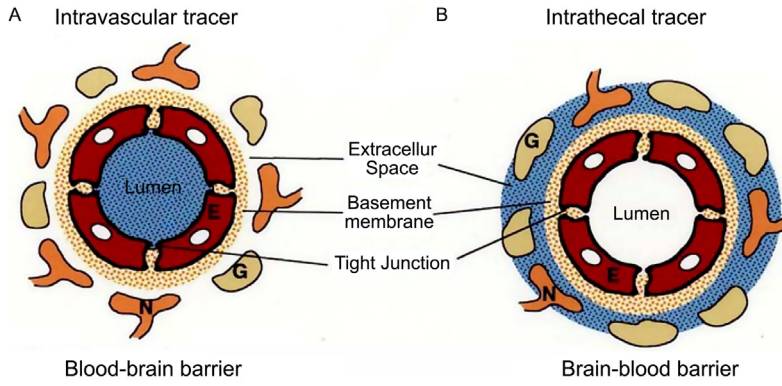

Fig. 3 Diagrammatic representation of normal cerebrovascular influx (A) and efflux (B) mechanisms to Evans blue albumin (Blue). Cerebrovascular barrier between blood and brain is composed of endothelial cells (E) surrounded by thick basement membrane and covered by glial cells (G) and neuronal (N) connections. The endothelial cells are connected with tight junctions making a continuous cell membrane. In normal conditions, Evans blue albumin does not permeate the luminal side of the endothelia cell (A) constituting the effective blood-brain barrier (BBB). Likewise, the abluminal endothelial cell membrane is also impermeable to intracerebral or intracerebroventricular administration of Evans blue albumin (B) under normal conditions representing brain-blood barrier (bbb). Thus, under normal physiological conditions, the influx and efflux mechanisms at the cerebrovascular endothelium are quite effectively regulating the brain fluid microenvironment. In glioblastoma, both the influx (BBB) and efflux (bbb) mechanisms are jeopardized resulting in leakage of blood or cancer cells leading to tumor development or metastasis. For details see text. *Data adapted from Sharma, H. S. (2004a). Blood-brain and spinal cord barriers in stress. In H. S. Sharma & J. Westman (Eds.),* The blood-spinal cord and brain barriers in health and disease *(pp. 231–298). San Diego: Elsevier Academic Press; Sharma, H. S. (2004b). Pathophysiology of the blood-spinal cord barrier in traumatic injury. In H. S. Sharma & J. Westman (Eds.),* The blood-spinal cord and brain barriers in health and disease *(pp. 437–518). San Diego: Elsevier Academic Press.*

than 400 Da that forms less than eight hydrogen bonds can cross in small fraction across the BBB depending on their lipid solubility (Arvanitis et al., 2020; Sharma, 2009; Sharma & Westman, 2004). Large molecules such as proteins, enzymes, monoclonal antibodies and/or gene therapy are totally excluded from the blood to brain transport at the BBB (Arvanitis et al., 2020; Kiyatkin & Sharma, 2019; Nation et al., 2019). Passage of exogenous molecules through brain diffusion is also limited due to ATP-binding cassette

(ABC) transporters (Gomez-Zepeda, Taghi, Scherrmann, Decleves, & Menet, 2019; Leandro, Bicker, Alves, Falcão, & Fortuna, 2019) and efflux transport proteins that are largely located at the luminal side of the endothelial cell membranes (Abdul Razzak, Florence, & Gunn-Moore, 2019; Erdő & Krajcsi, 2019). Thus, the healthy brain consists of a powerful BBB function that regulates the exchange processes across the vascular compartment strictly within a narrow limit (Arvanitis et al., 2020; Sharma, 2009; Sharma & Westman, 2004; Wu, Lee, Chou, Chern, & Lin, 2019).

2.1.2 Adsorptive mediated BBB transport

Macromolecules could be transported from luminal to abluminal side of the endothelial cells through intracellular membrane bound vesicles (Sharma, 2009; Sharma & Westman, 2004). This is a nonspecific process called vesicular transport or adsorptive-mediated transport (AMT) (Lossinsky & Shivers, 2004; Lu, 2012; Matsumoto, Stewart, Banks, & Zhang, 2017) (Fig. 4). This process does not involve any specific membrane receptors (Arvanitis et al., 2020; Sharma & Westman, 2004). In some cases electrostatic interaction between positively charged molecules and negatively charged BBB could be used for therapeutic purposes (Lockman, Koziara, Mumper, & Allen, 2004; Yuan, Li, Gil, Lowe, & Fu, 2010). Surface charge can interact with nanoparticles for the drug transport. However, these electrostatic charges are not always consistent (see Lockman et al., 2004).

2.1.3 Carrier mediated BBB transport

Small biomolecules such as glucose, amino acids, hormones, bile salts and other monocarboxylic acids are transported from blood to brain using specific carrier mediated transport (Arvanitis et al., 2020; Nation et al., 2019; Pardridge, 2005; Sweeney et al., 2019; Tega, Yamazaki, Akanuma, Kubo, & Hosoya, 2018). The transport rate is dependent on the magnitude of occupation by the carrier (Pardridge, 2005). More than eight different transport systems are so far recognized that are active at the BBB interface (Arvanitis et al., 2020; Nation et al., 2019; Sweeney et al., 2019). These include glucose transporter (GLUT) (Espinoza-Rojo, Iturralde-Rodríguez, Chánez-Cárdenas, Ruiz-Tachiquín, & Aguilera, 2010), Amino acid transporter (AAT) (Helms, Nielsen, Waagepetersen, & Brodin, 2017), neutral amino acid transporter (NAAT) (Nation et al., 2019; Pardridge, 2005; Sweeney et al., 2019), cationic amino acid transporter (CAAT) (Pardridge, 2005), beta amino acid transporter (βAAT) (Nation et al., 2019), choline transporter (ChT) (Geldenhuys & Allen, 2012), peptide transporter (PT)

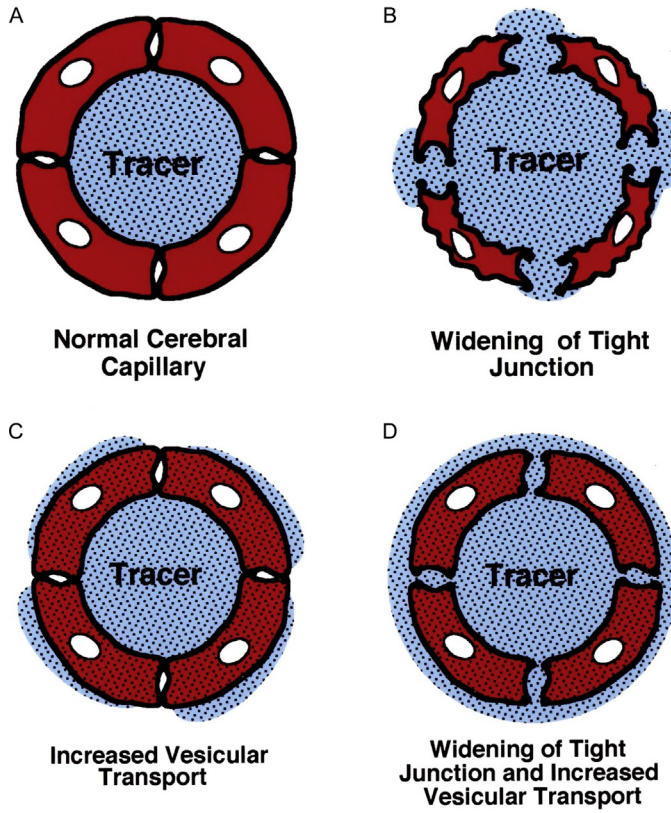

Fig. 4 Diagrammatic representation of blood-brain barrier (BBB) leakage under pathological conditions including brain tumor and gliomas. Leakage of the BBB under disease processes could occur due to widening of the tight junctions (B) when the tight junctional proteins are lost or the endothelial cells are deformed by drugs, chemicals or cellular damage. In most neurodegenerative cases, the tight junctions may not be compromised but the endothelial cell membrane becomes leaky allowing passage of blood-borne substances to enter into the brain parenchyma (C). Whereas, in some cases of vascular diseases including chronic hypertension the tight junctions are widened enough to allow large molecules such as proteins together with the leakage of endothelial cell membrane (D). It is also likely that under such pathological or neurodegenerative diseases or circumstances both influx and efflux mechanisms of the normal BBB (A) is compromised. In glioblastoma, all kinds of the BBB leakage are present where heterogeneity of the cerebral microvessels is prominent. For details see text. *Data modified from Sharma, H. S. (2004a). Blood-brain and spinal cord barriers in stress. In H. S. Sharma & J. Westman (Eds.),* The blood-spinal cord and brain barriers in health and disease *(pp. 231–298). San Diego: Elsevier Academic Press; Sharma, H. S. (2004b). Pathophysiology of the blood-spinal cord barrier in traumatic injury. In H. S. Sharma & J. Westman (Eds.),* The blood-spinal cord and brain barriers in health and disease *(pp. 437–518). San Diego: Elsevier Academic Press.*

(Keaney & Campbell, 2015), fatty acid transporter (FAT) (Tiwary et al., 2018) and nucleoside transporter (NT). These transporters are expressed within the BBB endothelial cells (Arvanitis et al., 2020; Nation et al., 2019; Sweeney et al., 2019). Drugs that closely mimic these endogenous carriers are thus normally transported within the brain using carrier-mediated transport (CMT) (Arvanitis et al., 2020; Nation et al., 2019).

2.1.4 Receptor mediated BBB transport

Receptor-mediate transcytosis (RMT) is highly selective and specific transport for molecules that bound with high affinity to the transmembrane receptors located to the luminal side of the endothelial cells (Choudhury et al., 2018; Nation et al., 2019; Pulgar, 2019). Some of the receptors expressed at the endothelial cells for RMT include transferrin receptor (TfR) (Choudhury et al., 2018; Pulgar, 2019), the low-density lipoprotein receptor (LDLR) (Sagare, Deane, & Zlokovic, 2012; Zhao, Li, Zhao, Song, & Zhao, 2016), insulin receptor (IR) (Banks, Owen, & Erickson, 2012; Rhea, Raber, & Banks, 2020) and nicotine-acetylcholine receptors (nAChRs) (Damaj, Wiley, Martin, & Papke, 2005; Zhan et al., 2011).

Apart from that cell penetrating peptides (CPP) (Gallo, Defaus, & Andreu, 2019; Raucher, 2019; Silva, Almeida, & Vale, 2019) are also able to transport proteins and peptides in a non-specific receptor-independent manner (Arvanitis et al., 2020; Nation et al., 2019). CPP could be classifies as cationic, hydrophobic and amphipathic based on their ability to bind ligands (Arvanitis et al., 2020).

2.1.5 The blood-brain barrier function in physiological conditions

The endothelial cells in brain are surrounded by basal lamina or extracellular matrix (ECM) that is mainly composed of glycoproteins (Arvanitis et al., 2020; Nation et al., 2019). The ECM is significantly altered in diseases of the CNS (Henrich-Noack et al., 2019; Reed, Damodarasamy, & Banks, 2019). In addition, the endothelial cell functions are also regulated by pericytes and astrocytes in activating multiple signaling pathways to regulate the BBB function (Langen, Ayloo, & Gu, 2019; Villabona-Rueda, Erice, Pardo, & Stins, 2019; Xu, Nirwane, & Yao, 2018). Pericytes at the abluminal surface of the endothelial cells regulate vascular functions during neuroinflammation and age related degeneration in the microvasculature (Laredo, Plebanski, & Tedeschi, 2019; Rustenhoven, Jansson, Smyth, & Dragunow, 2017; Sweeney, Ayyadurai, & Zlokovic, 2016).

Astrocytes cover the abluminal side of the endothelial cell surface regulate the cell signaling pathways and maintain the tightness of the junctional complex together with the basal lamina (Buskila, Bellot-Saez, & Morley, 2019; Hamm et al., 2004; Thomsen, Routhe, & Moos, 2017). Astrocytes could also work as connecting with the gap junctions and the tight junctional complexes (Figs. 1–4). This forms additional barrier in the CNS that is normally known as glia limitans (Gimsa, Mitchison, & Brunner-Weinzierl, 2013; Rutka et al., 1997; Sofroniew, 2015). However, removal of astrocytes using laser technologies in adult mouse brain did not induce greater BBB permeability (Alvarez, Katayama, & Prat, 2013; Skaper, 2017). This suggests that pericytes and astrocytes might influence or induct BBB properties during the development processes (Nation et al., 2019; Sweeney et al., 2019).

In addition to cellular contacts of the endothelial cells, the BBB function is also influenced by several circulating factors, hormones and stressors (Sharma, 2004a, 2004c, 2004d; Sharma & Alm, 2004; Sharma, Patnaik, Ray, & Dey, 2004). The mechanisms by which circulating factors affect BBB dysfunction is not well known (Arvanitis et al., 2020; Sharma, 2009). However, it appears that microglia that is abundant immune cells in the CNS could influence BBB function during neuroinflammation (Liebner et al., 2018; Ransohoff, 2016; Xiong, Liu, & Yang, 2016). This is evident from the findings that activation of microglial disrupts the BBB function during neuroinflammation (Yoshida et al., 2018). Likewise the peripheral immune cells such as leukocytes can increase the BBB permeability via interleukin-1β (IL-1β) secretion (Su et al., 2017). Alternatively, leucocytes could also stimulate through intracellular adhesion molecule 1 (ICAM1), VCAM1 or E-selectin (Jia, Lu, Martin, & Jiang, 2014).

Apart from humoral and neurogenic factors could also regulate the cerebrovasculature (Johansson & Auer, 1983; Stolp & Molnár, 2015). The cerebral endothelial cells are also innervated by synaptic endings of GABAergic, serotonergic, noradrenergic and cholinergic neurons that could regulate cerebral blood flow, neurovascular coupling and the BBB permeability (Edvinsson & MacKenzie, 1976; Halvorsen, Sharma, Basu, & Wiklund, 2015; Semenas, Sharma, & Wiklund, 2014; Sharma, Nyberg, Cervos-Navarro, & Dey, 1992; Sharma, Olsson, & Dey, 1990; Sharma, Westman, Cervós-Navarro, Dey, & Nyberg, 1997).

Thus, the function of the BBB is complex and is regulated by several cellular, neuronal and humoral factors under physiological conditions (Arvanitis et al., 2020; Sweeney et al., 2019). Disturbances in this functional regulation could result in disease processes that require further investigations (Arvanitis et al., 2020; Sharma, 2009; Sharma & Westman, 2004).

3. The blood-tumor barrier structure and function

Development of brain tumor (BT) in closed cranium results in compression of microvessels in the peritumoral regions impairing the local cerebral blood flow (CBF) (Noh & Walbert, 2018; Seano et al., 2019; Van Roost, Hartmann, & Quade, 2001). Growth and expansion of BT alters the microvasculature within the core of the tumor as compared to peritumoral healthy tissues (Noh & Walbert, 2018; Van Roost et al., 2001). With further progression of the primary BT and brain metastasis the microvasculature of BT becomes heterogeneous (Arvanitis et al., 2020). Expansion of neoplastic lesion alters neuronal viability and drastic changes in the vascular properties within the local and remote tumor areas (Noh & Walbert, 2018; Seano et al., 2019). Due to high metabolic demand and increased nutritional needs of cancer cells, BT alters the existing microvessels and creates new blood vessels via angiogenesis (Broekman et al., 2018; Di Tacchio et al., 2019; Nowak-Sliwinska et al., 2018).

Interestingly, BT microvessels are tortuous and differ widely anatomically in same kind of BT or related tumors (Di Tacchio et al., 2019; Guo et al., 2019; He et al., 2018). Vascular alterations in BT are primarily due to dysregulation of angiogenic factors expression, e.g., vascular endothelial growth factor (VEGF) causing hypoxic or acidic microenvironment (Guo et al., 2019). This leads to further progression of BT by hypoxia-inducible factor 1a (HIF1a) transcription (Eyrich, Potts, Robinson, Maximov, & Kenney, 2019; Kinali et al., 2019; Tang et al., 2016). Inhibition of VEGF signaling pathways is able to transiently prevent leaky microvessels in BT (Cheng, Chen et al., 2019b; Ziegler et al., 2019). However; adverse effects of blocking VEGF signaling pathways are hypoxia and greater invasion of cancer cells (Krishnan et al., 2015; McIntyre et al., 2012; Sugimoto, Ishibashi, Nakamura, Yachie, & Ohno-Shosaku, 2017). A reduction in BBB permeability in BT microvessels by anti-VEGF treatment could also hamper effective drug delivery (Arvanitis et al., 2020).

3.1 The blood-tumor barrier

Due to changes in the properties of the tumor microvasculature, the BBB is comparatively leaky in BT as compared to normal BBB in healthy brain (Arvanitis et al., 2020) (Fig. 5). Using magnetic resonance imaging (MRI) and positron emission tomography (PET) techniques disruption of the BTB is seen in glioblastoma (Arvanitis et al., 2020; Swanson et al., 2009).

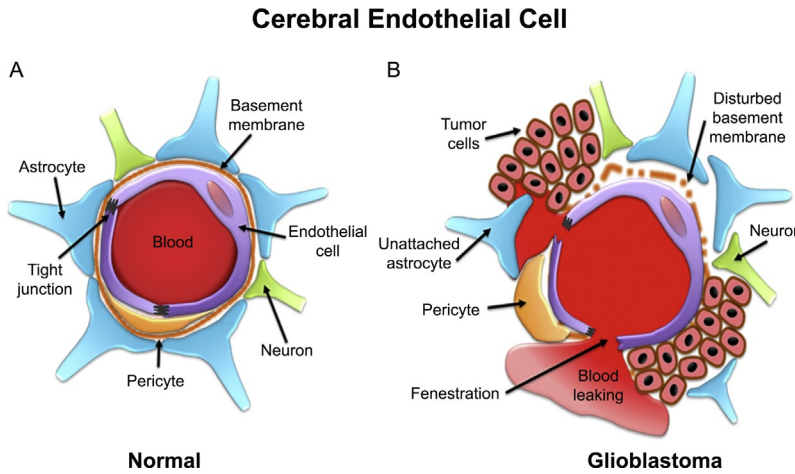

Fig. 5 Diagrammatic representation of cerebral capillary showing endothelial cell in normal (A) and in glioblastoma (B). Compact endothelial cells connected with tight junctions surrounded by thick basement membrane and pericytes covered with astrocytic end feet and neuronal connections are evident (A). In glioblastoma the cerebral capillary function is severely distorted (B). This is evident from the leaky endothelial cells with and/or widening of the tight junctions, degeneration of basement membrane and pericytes together with loss of connections to astrocytic end feet and neurons. This structural deformity allows leaky capillary to the blood and cancer cells causing brain pathologies (B). For details see text.

However, despite a leaky barrier in BTB the core of glioblastoma still has the intact BBB properties (Arvanitis et al., 2020; Sarkaria et al., 2018). Due to this reason, drugs delivery to glioblastoma is still limited for effective therapy (see Arvanitis et al., 2020; van Tellingen et al., 2015).

The leaky BTB in periphery of GBM is largely due to altered pericytes structure together with loss of astrocytic end feet and neuronal connections (Aldape, Zadeh, Mansouri, Reifenberger, & von Deimling, 2015; Berges et al., 2018; Matias et al., 2018). Moreover, it is quite likely that invasion of cancer cells may distort astrocytic end feet; pericytes and neuronal connections resulting in partial disruption of the BBB in BT (Arvanitis et al., 2020; van Tellingen et al., 2015) (Fig. 5). There are evidences of abnormal transport of T-cells and monocytes in BT indicating that permeability of the BTB is increased to peripheral circulating immune cells (Quillien et al., 2019; Wang et al., 2017). A significant decrease in tight junctional proteins in BT microvessels is seen whereas intra-tumoral microvessels do not show full features of the BBB (Arvanitis et al., 2020; Shevchenko et al., 2019; Wen et al., 2017; Zhou et al., 2017). However, the BTB still shows active

expression of efflux transporters that hinders drug delivery to the core of BT (Bao et al., 2019; Dréan et al., 2018). Several investigations suggests that oligodendrocyte transcription factor 2 (OLIG2) together with WNT-β-catenin signaling strengthen the BTB integrity (Arvanitis et al., 2020; Shevchenko et al., 2019; Wen et al., 2017).

3.2 The blood-tumor barrier heterogeneity

The BTB shows great heterogeneity in BBB disruption in tumor areas (Arvanitis et al., 2020; Stark et al., 2002). This is evident from the fact that low molecular weight lipophilic molecules when injected systemically exhibit increased heterogeneous distribution in metastatic brain lesions as compared to the surrounding healthy tissues (see Arvanitis et al., 2020). Furthermore, sphingosine-1-phosphate receptor 3 (SIPR3) that is expressed in reactive astrocytes and brain cancer cells could increase the BTB permeability through astrocytic-IL-6 and CC-chemokine ligand 2 (CCL2) release (Arvanitis et al., 2020; Nation et al., 2019; Stark et al., 2002). This is also evident in GBM that apart from reduced tight junctional proteins, loss of pericytes and astrocytic end feet coverage is also responsible for increased permeability of the BTB in diverse areas (Papadopoulos, Saadoun, Davies, & Bell, 2001; Xiao et al., 2019). Leaky microvessels in GBM causes water and metabolic proteins and waste accumulation in the brain parenchyma resulting in edema formation (Papadopoulos et al., 2001). Brain metastatic cells show higher expression of proteases like cathepsin S that degrades tight junctional adhesion molecule JAM2 thereby decreasing the BBB integrity in BT (Arvanitis et al., 2020; Liu, Mei, & Lin, 2013; Papadopoulos et al., 2001; Xiao et al., 2019).

4. Therapeutic strategies for brain tumor

The incidences of brain tumor across the world is about 5–6 cases per 100,000 people per year out of which 80% of cases are malignant gliomas. In the United States about 3 cases per 100,000 populations per year of brain tumor is reported (Barnholtz-Sloan, Ostrom, & Cote, 2018; McNeill, 2016; Ostrom, Wright, & Barnholtz-Sloan, 2018). Thus, more than 10,000 cases of glioma are diagnosed annually in the United States (Barnholtz-Sloan et al., 2018; Davis et al., 2019). Out of which ca. 54% cases are malignant glioma (Barnholtz-Sloan et al., 2018).

The etiological risk factors for that are linked to gliomas include exposure to therapeutic ionizing radiation, vinyl chloride, pesticides, smoking,

petroleum refining and synthetic rubber manufacturing industries (Batash, Asna, Schaffer, Francis, & Schaffer, 2017; Davis, 2016; Omuro & DeAngelis, 2013). On the other hand, residential electromagnetic field, formaldehyde, diagnostic irradiation or cellphone exposure is not linked to GBM. Some genetic factors also susceptible in human populations for development of BT or GBM (Ahmadi-Zeidabadi et al., 2019; Arvanitis et al., 2020; Ouadah et al., 2018).

Standard current therapy for GBM is maximal surgical resection along with radiotherapy and adjuvant temozolamide or Carmustine wafers in newly diagnosed patients lower than 70 years of age (Hirono et al., 2019; Nassiri et al., 2020). Recent advancement in GBM therapy is concentrated to expand our knowledge on the pathogenesis of GBM induced cellular signaling pathways, occurrence of resistance to therapy and to explore methods to enhance penetration of drugs across the BBB for effective therapy (Eskilsson et al., 2018; Huang, Zhang et al., 2017; Sasmita, Wong, & Ling, 2018).

4.1 Glioma stem cell and resistance and BT therapy

Glioma stem cells (GSC) constitute a subpopulation of GBM responsible for enhanced resistance to current therapies and recurrence of the glial tumor (Bahmad et al., 2020; Lathia, Mack, Mulkearns-Hubert, Valentim, & Rich, 2015; Ludwig & Kornblum, 2017; Ma et al., 2018). The GSCs are very similar to normal stem cells except being oncogenic in their host cells and induce heterogeneous cell population of the tumor mass (Bahmad et al., 2020). GSCs are highly proliferative with self-renewal with multi-differential potentials and strong tumorigenic capabilities (Lathia et al., 2015; Ma et al., 2018). GSCs contribute resistance for radiotherapy through preferential activation of DNA-damage-response pathways (Lathia et al., 2015; Ludwig & Kornblum, 2017; Ma et al., 2018). These cells provide resistance to chemotherapy of GBM via O^6-methylguaninie-DNA-methyltransferase (MGMT) pathways along with inhibition of apoptosis and upregulation of multidrug resistance genes (Begicevic & Falasca, 2017; Huang & Rofstad, 2017; Jin, Jin, & Kim, 2017).

4.1.1 Pathogenesis of glioblastoma

Some populations of patients develop GBM due to certain kinds of hereditary syndromes (Broekman et al., 2018; Degl'Innocenti, di Leo, & Ciofani, 2020). Pathogenesis of gliomas results from genetic alterations and abnormal regulation of growth factor signaling pathways (Broekman et al., 2018).

This is largely mediated through vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) (Bag et al., 2019; Li et al., 2018; Nicolas, Abdellatef, Haddad, Fakhoury, & El-Sibai, 2019), hepatocyte growth factor (HGF) (Cruickshanks et al., 2017; Tabouret et al., 2016; Yu et al., 2019), platelet derived growth factor (PDGF) (Liu et al., 2018; Yang, Dodbele et al., 2019) and loss of phosphotensin analogue (PTEN) (Banasavadi-Siddegowda et al., 2017; Benitez et al., 2017; Luo, Lei, Xiang, & Ye, 2018). In such cases, downregulation of growth signaling pathways, e.g., PI3K/AKT are activated. In low-grade gliomas mutations in p53 gene and overexpression of PDGF-α and its receptors are quite frequently seen (see Arvanitis et al., 2020). On the other hand, in high-grade gliomas inactivation of retinoblastoma gene (RB1) and increased expression of human double minute 2 (HDM2) is identified (Arvanitis et al., 2020; Huang, Zhang et al., 2017; Sasmita et al., 2018).

Primary GBM amplifies the mutated EDGF receptor (EGFR) to EGFRvIII whereas secondary GBM has increased signaling through PDGF-A receptor (Benitez et al., 2017; Yang, Dodbele et al., 2019a). These mutations lead to increased tyrosine kinase receptor (TKR) and subsequently activate RAS and PI3K pathways (Sadahiro et al., 2018). Primary GBM also amplifies MDM2 gene, PTEN mutations homozygous deletion of CDKN2A (Banasavadi-Siddegowda et al., 2017; Luo et al., 2018). On the other hand secondary GBM has more mutations in p53 and IDH1 together with MET amplification and overexpression of PDGFR-A (Benitez et al., 2017; Liu et al., 2018; Yang, Dodbele et al., 2019a). Progression and persistence of GBM to high grade is further associated with RB1 inactivation and increased activity of HDM2 genes (see Arvanitis et al., 2020). These aberrations affect significantly the growth factor-mediated cell signaling pathways and induce increased cell proliferation, inhibition of apoptosis and activate angiogenesis.

4.2 Bacterial toxins and viral vectors for novel glioma therapy

As early as in the beginning of the 19th century Coley believed that bacterial or viral pathogens help in spontaneous tumor remission (see Hoption Cann, van Netten, & van Netten, 2003). This idea was further substantiated in 1891 when Coley found that malignant recurrent sarcoma in a young child disappeared during a superficial streptococcal infection (erysipelas) (Coley, 1891). Further investigation into case studies, Coley found 38 cases of carcinomas and sarcomas went into remission during concomitant erysipelas infection (Coley, 1893).

Based on these evidences, Coley initiated treatment of sarcomas patients with inoculations of Streptococcus with varying successes (Coley, 1894). However, the efficacy and safety of this treatment appears to be highly variable. Although Coley's method continued further during the middle of the 20th century when it was found that cytokines particularly tumor necrosis factor and interleukins facilitated better therapeutic efficacies in treating tumors (Coley, 1914). Later on Coley use heat killed bacterial endotoxin instead of live bacteria to achieve tumor remission in patients (Coley, 1894, 1912, 1913, 1914, 1915). These findings prompted wider investigation on molecular characteristics of pathogens in tumor progression and immunotherapy. Based on these findings Coley is regarded as the father of immunotherapy.

4.2.1 Viral infections and cancer

A link between viral infection and cancer was observed when one leukemia patient went into spontaneous remission after an influenza outbreak in 1904 when it was not known that influenza is a virus (De Pace, 1912; Dock, 1904a, 1904b; Shah, Jusué-Torres, Ivan, Komotar, & Kasahara, 2018). In 1912 regression of cervical carcinoma was observed after Pasteur's vaccination for rabies (De Pace, 1912). This finding further conforms a link between virus and cancer treatment (see Shah et al., 2018). Furthermore several cases of hematological malignancies were reduced or disappear during viral infections (Dock, 1904b; Hoption Cann et al., 2003; Huebner, Rowe, Schatten, Smith, & Thomas, 1956; Shah et al., 2018). Thus, hematological malignancies were treated with systemic viruses, e.g., varicella, measles, mumps, feline panleukopenia and New Castle disease virus (Bierman et al., 1953; Dock, 1904b; Huebner et al., 1956). Based on these studies National Cancer Institute in 1956 used wild adenovirus for the treatment of cervical cancer that resulted in tumor regression in greater than 50% of patients (Hoption Cann et al., 2003; Huebner et al., 1956; Shah et al., 2018). However, the treatment effect was short lasting (Huebner et al., 1956). These early studies open new areas of viral vectors therapy where viruses are genetically modified for their better selectivity and specificity to destroy tumor cells. This opens a new era in developing modern nano-biotechnological tools for effective tumor therapy (Arvanitis et al., 2020; Hoption Cann et al., 2003; Shah et al., 2018).

4.2.2 Bacterial infection and cancer

In the middle of 20th Century it was found that malignant tumor tissues if inoculated with spores of nonpathogenic Clostridium butyricum (M55)

results in liquefactive necrosis (Bierman et al., 1953; Moese & Moese, 1964). Based on this observation, 49 glioblastoma patients were treated with intracarotid M55 spores with the idea to induce oncolysis and abscess formation that would be easy for surgical removal. However, 19 of 49 patients died after surgical ablation of the abscess or encephalitis. Many other patients died during recurrence or surgery of glioblastoma (Heppner & Möse, 1978; Marth, Ascher, Pavelka, & Möse, 1989).

In spite of these tremendous failures, uses of M55 in glioblastoma continue after 30 years to explore it oncolytic properties (Staedtke et al., 2015). However, development of malignant edema, increased intracranial pressure and abscess formation further restricted using this type of therapeutic procedures.

In the past 22 years, pathogenic bacterial infections and increased survival of patients of malignant glioma is further corroborated by several studies (Kapp, 1983; Staedtke et al., 2015). These cases showed spontaneous regression of glioma during infections and enhanced the survival of patients. In three patients infected with *Enterobacter aerogenes* oncolytic effects in glioma was clearly seen together with improved immune responses (Bowles & Perkins, 1999). Likewise increased survival of 18 patients was seen in glioma that developed post-operative infections (Bohman et al., 2009). Improvement in survival of patients with gliomas is also reported in cases that developed pathogenic infections after surgery (Bohman et al., 2009; De Bonis et al., 2011). However, Food & Drug Administration (FDA) in United States does not approve this kind of treatment till date (Shah et al., 2018).

4.2.3 Viral genome modification and glioblastoma treatment

With advancement of genetic modification of virus technology, first bioengineered oncolytic herpes simplex virus was generated (Martuza, Malick, Markert, Ruffner, & Coen, 1991) and used for the treatment of malignant glioblastoma (Markert et al., 2000). After that several viruses were genetically modified for glioblastoma treatment. These include adenovirus, New Castle Disease virus, measles, and poliovirus and vaccinia virus (Markert et al., 2000; Martuza et al., 1991). Since glioblastoma is highly proliferative with lack of metastasis and is largely confined within the postmitotic cells thus, it limits the spread of viruses to nonneoplastic tissues (Shah et al., 2018; Wollmann, Ozduman, & van den Pol, 2012). Oncolytic virus therapy uses specifically the tumor cells for replication, lysis and dissemination (Huebner et al., 1956; Markert et al., 2000; Wollmann et al., 2012). This makes them unique to target cancer cells because of their oncological signaling pathways.

Many of these viral therapies are undergoing Phase I and II clinical trials for glioblastoma treatment (Broaddus et al., 1999; Horowitz, 1999; Pan et al., 2010; Wollmann et al., 2012). These viruses are administered intraparnechymally into the tumor area (Horowitz, 1999; Pan et al., 2010; Wollmann et al., 2012).

4.2.4 *Viral vectors and glioblastoma treatment*

Apart from genome modification of viruses, viral vectors for gene therapy are also employed for the treatment of glioblastoma (Caffery, Lee, & Alexander-Bryant, 2019; Manikandan, Kaushik, & Sen, 2019). Gene therapy using adenoviral vectors are primarily used in restoring tumor suppression by additional delivery of genes like p53 or cycline-dependent kinase pathways (Broaddus et al., 1999; Horowitz, 1999; Li et al., 1999; Pan et al., 2010). These early results did not enhance survival of patients beyond 10 months after the diagnosis of gliomas (Lang et al., 2003). However, further studies using new technology resulted in tailored gene therapy in glioblastoma for suppression of angiogenesis, elimination of drug resistance capacity and enhance anti-tumor immunological activation (Nanda et al., 2001; Perez et al., 2012). In 2000 viral vectors are used to induce suicidal genes for glioblastoma cells (Hossain, Riecken, Miletic, & Fehse, 2019). Thus, the suicidal genes, e.g., thymidine kinas or cytosine deaminase could be incorporated into the tumor genome to induce toxicity with the help of prodrugs, e.g., ganciclovir or 5-fluorocytosine (Lee et al., 2019; Niu et al., 2013). These therapies are currently in practice and helps in preventing recurrence of glioblastoma up to some extent (see Arvanitis et al., 2020).

4.3 Enhanced drug delivery through the blood-brain and blood-tumor barriers

For effective treatment strategies for brain tumors or GBM there is a need to enhance permeability and retention (EPR) of drugs using modification of the drug delivery system (de Paula, Primo, & Tedesco, 2017; Ganipineni, Danhier, & Préat, 2018; Gutkin, Cohen, & Peer, 2016). Although, for normal functioning of the brain an intact BBB is needed to maintain homeostasis but this aspect is hindering the most in drug delivery to the brain tumors for effective therapy (Arvanitis et al., 2020; Sharma, 2009; Sharma & Westman, 2004). Peritumoral BBB is leaky but drugs after their systemic delivery could not reach to the tumor core tissue because several efflux and transporter mechanisms are still working to prevent EPR (Arvanitis et al., 2020; Šamec, Zottel, Videtič Paska, & Jovčevska, 2020).

Studies have clearly shown that despite a leaky BTB at the periphery of the tumor, the microvasculature of tumor exhibit profound heterogeneity in BBB permeability (Arvanitis et al., 2020; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015). This is because of the fact that the anatomy and physiology of the BT microvasculature is altered as compared to healthy surrounding brain tissues (Sarkaria et al., 2018). Thus, pericytes population is altered with desmin-positive pericytes in brain metastasis that are permeable to low molecular weight drugs at BTB (Arvanitis et al., 2020; Hosono, Morikawa, Ezaki, Kawamata, & Okada, 2017). Reactive astrocytes showed loss of connections with the endothelial cells that results in reduction in lipid transporter NLS1 expression (Betsholtz, 2015; Tiwary et al., 2018). In addition, SIPR3 expression in reactive astrocytes and brain cancer cells enhanced the BTB permeability via astrocytic IL6 and CC-chemokine ligand 2 (CCL2) secretion (see Arvanitis et al., 2020; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015).

During tumor progression in glioblastoma reduced tight junctional proteins together with significantly less coverage of stem cell derived pericytes on the endothelial cells is seen that is responsible for the altered BTB integrity (Arvanitis et al., 2020; Li, Liu, Ma, Wang, & Xue, 2015; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015). Leaky microvessels results in water and waste retention in the brain parenchyma together with increase in interstitial and intracranial fluid pressure causing cerebral edema in malignant BT (Arvanitis et al., 2020; Liu et al., 2013). This functional heterogeneity of BT microvessels in brain tumor microenvironment could be modulated for developing effective drug delivery system for therapeutic purposes (Sarkaria et al., 2018).

Systemic drugs for BT therapy are restricted to enter tumor tissues by multiple barriers at the BTB such as paracellular transport for hydrophilic molecules, transcytosis and efflux transporters (Sarkaria et al., 2018; van Tellingen et al., 2015). In addition, ABC transporters further decrease the uptake of drug molecules at the BTB to enter tumor tissues (Arvanitis et al., 2020). Thus, in recent years several strategies are used to either bypass or alter the BBB function for EPR to treat BT (see below).

4.3.1 Modulation of influx transport at BTB/BBB

Modulating receptor mediated transcytosis through transcellular route at the endothelial cells is one of the promising approach for drug transport across the BTB/BBB in BT (Arvanitis et al., 2020; Bhowmik, Khan, & Ghosh, 2015; On & Miller, 2014; Sarkaria et al., 2018). Receptor-mediated transport at the BTB/BBB could be modulated by targeting the

monoclonal antibody to its receptor to induce endocytosis (Arvanitis et al., 2020; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015). This process utilizes vesicular trafficking system to transport drugs or molecules to the abluminal surface (Bhowmik et al., 2015). Drugs or molecules are linked to the antibody for transport across the BTB/BBB (Arvanitis et al., 2020). For this purpose transferrin, insulin or insulin like growth factor-1 receptors are commonly used (Arvanitis et al., 2020; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015). This mode of transport is very well functioning for drugs or molecules up to 80 nm in diameter used for the treatment of BT (Arvanitis et al., 2020). Other approach in this direction is to employ endogenous expression of BTB/BBB low density lipoprotein receptor related protein 1 (LRP1) (Orthmann et al., 2012; Quail & Joyce, 2017). Evidences suggest that LRP1-targeted peptide chemotherapy conjugates of 3-paclitaxel molecules linked to angiopep-2 results in 50 fold higher transport into brain metastasis and improved survival (Arvanitis et al., 2020; Orthmann et al., 2012; Quail & Joyce, 2017; Sarkaria et al., 2018; Stavrovskaya et al., 2016; van Tellingen et al., 2015).

Another way to enhance transfer at BTB/BBB is to SLC proteins on the endothelial cells for EPR (Dickens et al., 2018; Kou et al., 2018). This is seen for glucose transporter (GLUT1) that is responsible for glucose transport through endothelial cell membrane as well as LAT1 transporter that bidirectionally transport neutral amino acids at the BBB (Bao et al., 2019). Overexpression of GLUT1 is associated with poor survival of cells in glioblastoma. Likewise, LAT1 overexpression is associated with proliferation of gliomas that is sensitive to hypoxia-induced cell death (Aoki et al., 2019; Arvanitis et al., 2020).

4.3.2 Modulation of efflux transporters at BTB/BBB

Efflux transporters within the cytoplasm of the endothelial cells work actively to pump drug and waste materials out from brain to blood and thus results in poor brain to blood drug ratio (Arvanitis et al., 2020; Gomez-Zepeda et al., 2019; Leandro et al., 2019; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015). Almost all pharmacological active molecules approved by FDA have high binding affinities to these efflux transporters at the endothelial cells of then BBB/BTB (see Arvanitis et al., 2020). Efflux transporters include ABC (P-gp) and BCRF that has high affinity to several drugs and chemotherapeutic agents (Li et al., 2015). These efflux transporters are often overexpressed in tumor microvessels as compared to healthy brain endothelial cells (Gomez-Zepeda et al., 2019; Leandro et al., 2019). These tumor efflux transporters bind to therapeutic agents and thus

keep the levels of the drug much below within the tumor tissues affecting effective therapy (Arvanitis et al., 2020; Gomez-Zepeda et al., 2019; Leandro et al., 2019; Li et al., 2015; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015). In order to attain high levels of drug transport into the tumor tissues, co-administration of drugs with efflux transport inhibitors resulted in high concentration of therapeutic agents into the BT (Arvanitis et al., 2020). Using these techniques several fold higher drug concentration of temozolomide (1.5-fold), poly (ADP ribose) polymerase (PARP) inhibitor SBT-888 (fivefold) and mutant BRAF inhibitor vemurafenib (50-fold) in tumor tissues has been achieved (Becker et al., 2018; de Gooijer et al., 2018; Tangutoori, Baldwin, & Sridhar, 2015).

Another approach is to make structural changes in molecular targets such as kinase inhibitors PI3K and mTOR to reduce their affinities to efflux transporters like ABC and BCRF transporters leading to EPR in tumor tissues is quite promising for BT therapy (Keppler-Noreuil, Parker, Darling, & Martinez-Agosto, 2016; Li et al., 2016; Venkatesh et al., 2017). This technique not only enhances drug penetration across the BTB/BBB but also assist in improved cancer cell uptake (Arvanitis et al., 2020; Gomez-Zepeda et al., 2019; Leandro et al., 2019).

4.3.3 Stem cell induced drug delivery at the BTB/BBB

Using stem cells for drug delivery is another option for EPR in BT therapy. Stem cells could disseminate within the tumor cells causing specific delivery of drugs for BT (Dührsen et al., 2019;). In addition, stem cell delivery may lead to slowly releasing drugs or chemotherapeutic agents into the tumor tissue for effective therapy (Arvanitis et al., 2020; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015). In this regards neural stem cells (NSC) and mesenchymal stem cells (MSC) as preferred carriers are utilized for drug delivery across the BTB/BBB for primary BT or brain metastasis (Bagó, Sheets, & Hingtgen, 2016; Dewari et al., 2018; Dührsen et al., 2019; Li, Bonamici et al., 2018; Zhao, van Straten, Broekman, Préat, & Schiffelers, 2020). It appears that stem cells cross the BTB/BBB similar to immune cells infiltration (Li, Bonamici, et al., 2018).

Stem cell delivery of therapeutics agents to BT further emphasized the role of genetic modification of the cells to secrete antitumor proteins, antiangiogenic factors and immunosupportive elements for better anticancer treatment (see Arvanitis et al., 2020; Bagó et al., 2016; Erdő & Krajcsi, 2019; Gomez-Zepeda et al., 2019; Zhao et al., 2020). Additional research using nanoparticles for stem cell delivery loaded with drug could further advance BT therapies for enhanced survival (Sharma, Feng et al., 2015).

5. Nano-drug delivery for brain tumor therapy

As mentioned above, therapeutic agents reaching to the core of tumor tissues are prevented by an active BBB, heterogeneity of the BTB, resistance to chemotherapy and various efflux transporters (Arvanitis et al., 2020; Erdő & Krajcsi, 2019; Hoosain et al., 2015; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015). Thus, the need of the hour is to find suitable therapeutic strategies to enhance the permeability of the drug within the tumor core tissues for longer time to have superior therapeutic effects (Sharma et al., 2016; Sharma, Feng et al., 2015; Sharma, Muresanu, Castellani et al., 2019; Sharma, Muresanu, Lafuente, Patnaik et al., 2018; Sharma, Muresanu, Lafuente, Sjöquist et al., 2018; Sharma, Muresanu, Ozkizilcik et al., 2019; Sharma & Sharma, 2012).

Recent investigations on GBM clearly show that the genetic profile and glioma stem cells are the leading causes of resistance to temozolomide (TMZ) therapy and radiation (Grek et al., 2018; Howard et al., 2017; Johannessen, Bjerkvig, & Tysnes, 2008; Triscott, Rose Pambid, & Dunn, 2015). Thus, the major obstacle for the GBM treatment is the lack of suitable drug delivery across the BBB/BTB (see Arvanitis et al., 2020; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015). Since drug delivery across the brain tissues could be further advanced using nanobiotechnology (Sharma et al., 2016; Sharma, Muresanu, Lafuente, Sjöquist et al., 2018). A possibility exists that nano-drug delivery could enhance therapeutic efficiency in GBM (Sharma et al., 2016; Sharma, Feng et al., 2015; Sharma, Muresanu, Lafuente, Patnaik et al., 2018; Sharma, Muresanu, Lafuente, Sjöquist et al., 2018; Sharma & Sharma, 2012).

Several nanomaterials such as liposomes, polymer micelles, iron oxide nanoparticles (IONP) and nanoemulsions are investigated recently for the better treatment options in GBM (Mahmoudi, Bouras, Bozec, Ivkov, & Hadjipanayis, 2018; Michael, Lee, Zhang, & Yu, 2018; Ung & Yang, 2015). In most of the studies, these nanomaterials exhibited better therapeutic effects of the drugs in GBM (Cano, Espina, & García, 2020; Kwon, Yoo, Sym, & Khang, 2019; Rezaei, Rabiee, & Khademi, 2020; Tang et al., 2019). This is evident from the fact that drugs delivered using these nanomaterials enhanced permeability and retention (EPR) of the compounds within the tumor tissues and showed better therapeutics outcomes (see Arvanitis et al., 2020; Quail & Joyce, 2017; Rezaei et al., 2020; Sarkaria et al., 2018; van Tellingen et al., 2015).

Several techniques with nanomaterials of the treatment of tumor and EPR are applied currently (Rezaei et al., 2020). These include active

targeting to increased drug delivery to the tumor tissues (Arvanitis et al., 2020; Cano et al., 2020). Convection-enhanced delivery (CED) is also used to increase the uptake of the nanomaterials into the BT (Elenes & Rylander, 2017; Jahangiri et al., 2017; Singleton et al., 2017). Recently; nanomaterials is also used with siRNA to alter gene expression that alters GBM proliferation and remission (Huang, Jiang et al., 2017; Xu et al., 2020; Yang, Gao, Liu, Pang, & Qi, 2017). Also the nanomaterials are employed with chemotherapeutic agents to tumor tissue that would reduce toxicity to other organs and healthy cells (see (Arvanitis et al., 2020)).

5.1 Nanodelivery of drugs and enhanced permeability and retention

In gliomas and other BT loss of endothelial cells tight junctions with alterations in pericytes and coverage of astrocytic end feet allow increase in the peritumoral BTB to small molecules (Laredo et al., 2019; Rustenhoven et al., 2017; Sweeney et al., 2016). Angiogenesis together with increased VEGF production enhances the BTB breakdown resulting in infiltration of cancer cells in the brain parenchyma (Di Tacchio et al., 2019; Krishnan et al., 2015; Nowak-Sliwinska et al., 2018; Ziegler et al., 2019). Proliferation of GBM into the brain cells further disrupts the lymphatic system. (D'Alessio, Proietti, Sica, & Scicchitano, 2019; Nistal & Mocco, 2018; Song et al., 2020). These two factors play key roles in enhancing the drug permeability and retention within the tumor tissues (Adhikaree et al., 2020; Stavrovskaya et al., 2016). Nanodelivery of drugs in GBM use these advantages of porous BTB and reduced outflow of lymphatic system resulting in enhanced drug concentration and retention into the tumor tissue for long time (Michael et al., 2018; Rezaei et al., 2020; Ung & Yang, 2015). Several nanoformulation is currently being used for the treatment of gliomas mentioned below.

5.1.1 Active tumor targeting by nanoparticles

Active or direct targeting of tumors by nanoparticles associated with drugs or chemotherapeutic agents is one of the most important therapeutic advances for BT treatment (Pant et al., 2019; Rizwanullah, Alam, Harshita, Rizvi, & Amin, 2020; Vanderburgh et al., 2020). Several kinds of nanoparticles are used for this purpose.

(a) Liposome nanoparticles

Using liposome nanoparticles for drug or chemotherapeutic agents results in an increased delivery of these molecules within the tumor tissue with high retentions capabilities (Formicola et al., 2019; Joshi et al., 2016).

Combination of liposomes with polyethylene glycol (PEG) is used to attach functionalization of drugs and ligands for specific targeting the tumor tissues and preventing in accumulating in other tissues (Grahn et al., 2009; Wehbe et al., 2017). Using these principles IL-13 was conjugates with liposome containing doxorubicin (DOX) because high-grade astrocytoma contains IL-13Rα2 in most of tumor tissues (Madhankumar et al., 2009; Yang et al., 2012a). Thus, in this case liposomal nanoparticles actively targets GBM cancer cells bypassing the efflux pump (ABC transporter) induced chemotherapeutic resistance (Gomez-Zepeda et al., 2019; Leandro et al., 2019; Munoz, Walker, Scotto, & Rameshwar, 2015). Similarly, when liposome nanoparticles conjugated with DOX and atherosclerotic plaque-specific peptide-1 (AP-1) then it binds to IL-4 receptor that is overexpressed in BT cells and transported within the tumor cell by endocytosis (Yang, Wong et al., 2012). Likewise conjugation of endotoxins to the surface of liposome nanoparticles increases nanoparticles delivery and enhances cell death in GBM tissues (Dührsen et al., 2019).

Direct targeting tumor tissues by convection-enhanced delivery (CED) where drugs are delivered using a Microinfusion pump into the BT with nanoformulations results in superior therapeutic effect (Elenes & Rylander, 2017; Jahangiri et al., 2017). Using this CED method delivery of CPT-11/irinotecan liposomal nanoparticles in to the brain parenchyma resulted in much lower systemic toxicity as compared to the same delivered without CED (Haryu et al., 2018; Mehta, Sonabend, & Bruce, 2017; Souweidane et al., 2018). This suggests that both nanoparticles delivery into the tumor and CED could be used in future for better therapeutic effects.

(b) Polymeric nanoparticles

Further evidences showed that polymeric nanoparticles, i.e., poly (lactide-co-glycolide) PLGA conjugated with chemotherapeutic agent paclitaxel (PTX) and delivered directly into tumor tissues using CED technique resulted in much less systemic toxicity with high EPR of the drug (Di Mauro et al., 2018; Wang et al., 2018). When PLGA nanoparticles is delivered using CED technique with PTX through intracranial root in a rat glioma model this resulted in longer survival period as compared to free PTX treatment under identical conditions (Di Mauro et al., 2018). Interestingly, PLGA-nanoparticles with PTX when given without CED technique the survival period is shorter than using CED method (Saucier-Sawyer et al., 2016).

(c) Polymeric micelles

In rat and mice glioma model when DOX is delivered with polymeric micelles nanoparticles that have both hydrophilic and hydrophobic

characters resulted in longer survival period if administered using CED method (Arvanitis et al., 2020; Gao et al., 2017). Thus, conjugation of DOX to aspartic acid residue of PEG copolymer and then used CED to deliver polymeric micelles into the brain parenchyma in a rat or mice tumor models resulted in long survival period as compared to free DOX (Arvanitis et al., 2020; Fang et al., 2017; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015). This indicates future potentials of nanoparticles conjugated drugs for better therapeutic approaches in GBM.

5.1.2 Nanoparticles for treating brain tumor stem cells

Cancer stem cells initiate phenotypically human GBM that originates from GSCs (Shevchenko et al., 2019; Wen et al., 2017; Zhou et al., 2017). Thus, this is imperative that therapies directed against these stem cells could alleviate GBM development or resection (Bahmad et al., 2020; Lathia et al., 2015; Ludwig & Kornblum, 2017; Ma et al., 2018). However, the main problem is to exactly locate the involvement of GSCs in GBM (Ma et al., 2018). This makes treatment strategies very difficult (Ludwig & Kornblum, 2017). It is still not certain whether GSCs reside in the perivascular area or the hypoxic environment of the tumor cells (Arvanitis et al., 2020). There are evidences that CD133+/−Nestin+cells are located within the perivascular areas of the tumor where growth factors are secreted by the endothelial cells to maintain the population of the GSCs (García-Blanco, Bulnes, Pomposo, Carrasco, & Lafuente, 2016; Milkina et al., 2018). On the other hand, hypoxic microenvironments of the tumor cells cause upregulation of hypoxia-inducible factor 1-alpha (HIF-1α) and hypoxia-inducible factor 2-alpha (HIF-2α). It is likely that both these factors induce angiogenesis (Mohapatra et al., 2019; Tamura et al., 2019). Interestingly, HIF-2α could further maintain tumor GSCs phenotype and also convert non-GSCs cells to stem cells in GBM (Yao et al., 2015). However, other evidences also suggest a role of hypoxic environment of the GBM further promotes angiogenesis through HIF-2α. Thus, downregulating HIFs could be crucial for novel therapeutic approaches to GBM (Tamura et al., 2019; Valencia-Cervantes et al., 2019; Yao et al., 2015).

Since HIFs are associated with reactive oxygen species (ROS) production activated further by hypoxia, one possibility is to reduce or control the production of ROS in GBM (Deveci, Akyuva, Nur, & Nazıroğlu, 2019; Shimada et al., 2018). During hypoxic microenvironment intracellular concentrations of ROS increases surpassing the levels of glutathione, the endogenous antioxidant that could neutralize ROS toxic effects on the cells (Deveci et al., 2019; Shimada et al., 2018). Increased ROS activity further

stabilizes the HIF concentration that is responsible for transcription of VEGF and angiogenesis (Arvanitis et al., 2020; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015). Thus, bevacizumab—a humanized monoclonal antibody that inhibits the VEGF activity is useful in treating recurrence of GBM in clinical situations (Diaz et al., 2017; Kaka et al., 2019; Kim, Umemura, & Leung, 2018; Romani, Pistillo, Carosio, Morabito, & Banelli, 2018). This effect of anti VEGF is further enhanced when bevacizumab is combined with a topoisomerase 1 inhibitor irinotecan (Lu et al., 2019; Seystahl et al., 2019). Thus, inhibiting VEGF-induced angiogenesis appears to be important in treating GBM. However, attenuating or abolishing HIF stabilization using nanoparticles targeting could be a future strategies for effective therapy for GBM (see Arvanitis et al., 2020; Lu et al., 2019). In this line experimental evidences show that intracerebral treatment with an ROS scavenger tempol together with TMZ chemotherapy is quite effective in suppressing tumor growth with increased survival (Ravizza, Cereda, Monti, & Gariboldi, 2004).

When these agents were delivered through nanoemulsion, TMZ get better access to the GBM due to EPR effect and acts as ROS scavenger (Castilho-Fernandes, Lopes, Primo, Pinto, & Tedesco, 2017; Desai, Vyas, & Amiji, 2008). As a result the ROS concentration is reduced in the cytosol and attenuate the stabilization of HIFs (Luo et al., 2018). When nanoemulsion delivery of an inhibitor of DNA topoisomerase 1 CPT was given in GBM the ROS activity is significantly decreased (Castilho-Fernandes et al., 2017; Ravizza et al., 2004). However, CPT is not a water-soluble compound thus its intravenous delivery is not possible (Grisanti et al., 2019). Some water-soluble derivatives of CPT such as irinotecan or topotecan were developed but further research is needed in this direction using nanotechnology.

To overcome these difficulties CPT prodrug was developed where tetraethylene glycol (TEL) linked to CPT and α-lipoic acid (ALA) was used. This combination of CPT-TEL-ALA when administered is degraded in the biological system to release CPT in active form within the GBM that enhances ROS scavenging (Lee et al., 2010). In addition, when stable nanoparticles in combination with a-tocopherol; vitamin E with CPT-TEL-ALA the combination was more effective in reducing ROS and HIF production (Kang et al., 2004; Lee et al., 2013; Schwartzbaum & Cornwell, 2000). However, further research using nanodelivery of active ROS scavenging compounds are needed to inhibit GSCs induced angiogenesis making GBM less aggressive in future.

5.1.3 Nanoparticles and glioma resistance factor

One of the main problems in GBM therapy is the drug resistance of therapeutic agents (Arvanitis et al., 2020; Stavrovskaya et al., 2016). There are reasons to believe that use of nanoparticles may reduce the drug resistance phenomena in GBM (Kou et al., 2018; Rizwanullah et al., 2020; Sharma & Sharma, 2012; Silva et al., 2019; Vanderburgh et al., 2020; Wen et al., 2017). The therapeutic response to chemotherapy has allowed more insight to the GBM in which genetic marks CPT plays an important landmark discovery (Lu et al., 2019). The recently identified gene isocitrate dehydrogenase 1 (IDH1) is one of the crucial genetic factors that differentiate between the primary GBM and secondary GBM (Miller, Shih, Andronesi, & Cahill, 2017). This ability of IDH1 gene in identifying the secondary GBM led to genetic mutation of IDH1 that allowed significantly enhanced survival from 1 year to ca. 4 years (Chen, Yao, Xu, & Qin, 2016; Kaminska, Czapski, Guzik, Król, & Gielniewski, 2019).

One of the key chemotherapeutic agents in GBM is TMZ that allowed us to expand our knowledge in understanding of TMZ resistance in GBM (Arvanitis et al., 2020; Tang et al., 2016; van Tellingen et al., 2015). TMZ mode of action in GBM is largely due to alterations in the DNA repair gene O^6-alkylguanine-DNA-alkyltransferase (MGMT) by removal of adducts at the O^6-position of quinine and O^4-position of thymine (Ciechomska, Marciniak, Jackl, & Kaminska, 2018; Johannessen et al., 2018). Furthermore, methylation of CpG islands in the MGMT promoter area results in gene silencing by blocking the enzyme production responsible for tumor cell to repair DNA damage (Fukushima et al., 2018; Zhang et al., 2020). MGMT gene is also a biomarker for understanding the responsiveness of the tumor therapy by TMZ and other agents (Mansouri et al., 2019; Wu et al., 2018). Elevated MGMT levels in the cytosol correlates well with increase in survival and slowing progression of the disease (Jesionek-Kupnicka et al., 2019; Li, Guo, Wang, & Wang, 2017). Interestingly, when the two genes IDH1 and MGMT are combined resulted in better GBM survival than either gene alone (Arita et al., 2016; Bani-Sadr et al., 2019; Marton et al., 2020).

The GSCs are known to elevate the levels of MGMT expression (Lizarte Neto et al., 2019). However, the ability of GSCs in hypoxic microenvironment of the GBM makes it almost impossible for several traditional chemotherapeutic agents to enter into the GBM cells enhancing survival (Sak et al., 2019). Use of liposomal nanoparticles to deliver TMZ into

the GBM core tissues resulted in reduced resistance to drug delivery (Arcella et al., 2018). This observation led to develop nanotechnologies to treat GBM targeting the specific biomarkers of the tumor tissues for better survival (Arvanitis et al., 2020; Quail & Joyce, 2017; Sarkaria et al., 2018; van Tellingen et al., 2015). Accordingly, cationic liposome associated with antibody to transferrin receptor known as slC-nanocomplex is used to target the GBM (Joshi et al., 2016). In this set up, transferrin receptor allowed enhanced BBB permeability to GSCs and the liposome nanoparticles become carrier of the chemotherapeutic agents through siRNA (Voth et al., 2015). Recent evidences showed positive effects of slC-TMZ and slC-p53 for GBM treatment. The slC-TMZ is found to be quite efficient in killing GBM cancer cells as compared to TMZ alone (Aliferis et al., 2017; Arvanitis et al., 2020). The slC-p53 is able to downregulate MGMT expression thus blocking MGMT methylation and reducing TMZ resistance (Arvanitis et al., 2020; Von Lenhossek, 1893). These observations suggest future use of nanotechnologies in GBM therapy.

6. Theranostic nanomedicine for brain tumor therapy

Nanotechnological tools are not only employed to enhance drug delivery into the GBM tissues, but nanotechnology also assist in diagnosis of the tumor cells in the brain (Alphandéry, 2020; d'Angelo et al., 2019). In many cases same nanoparticles could serve for diagnostic purposes and at the same time offer great therapeutic effects (Dufort et al., 2019). This has led to the development of a new discipline called "Theranostic" technology (d'Angelo et al., 2019; Dufort et al., 2019; Gholami, Tafaghodi, Abbasi, Daroudi, & Kazemi, 2019). Theranostic as the word suggests a combination of two terms "Therapeutics" and "Diagnostics" and include both diagnostic and therapeutic technology using nanoparticles (d'Angelo et al., 2019).

Several types of nanoformulations and nanoplatforms are used to enhance drug delivery for increased therapeutic efficacy in BT (Shahein et al., 2019). Nanoplatforms often combine nanoparticles with drugs or molecular probes for imaging; and therapy (d'Angelo et al., 2019). These include polymer drugs or conjugates, micelles, liposomes or dendrimers (see Arvanitis et al., 2020; d'Angelo et al., 2019). These nanoplatforms have several advantages over conventional drugs, e.g., conjugation or entrapment of drugs and nanoparticles within the target tissues (Arvanitis et al., 2020).

Drug delivery using nanoparticles are able to enhance drug solubility, reduce cytotoxicity and improves pharmacokinetic profiles of the drugs used (Gutkin et al., 2016; Kim et al., 2019; Séhédic, Cikankowitz, Hindré, Davodeau, & Garcion, 2015). Nanoplatforms thus increase the drug half-life in the biological system, deliver drugs to the target sites and could control the drug release in high quality for better efficiency (d'Angelo et al., 2019; Séhédic et al., 2015). The amount of drug release from nanoplatforms could be controlled by various additional factors such as light, ultrasound, enzymatic activity, pH or temperature. Increased half-life of drugs from nanoplatforms desired drugs would accumulate in tumor tissues due to EPR effect (Betzer et al., 2019; Hameed, Zhang, Bhattarai, Mustafa, & Dai, 2019; Lian, Wei, & Ma, 2019). However, this EPR effect varies in patients between tumor types and metastases within the same patient (d'Angelo et al., 2019).

The theranostic approach requires usage of molecular imaging tools and a combination of different drug delivery systems (d'Angelo et al., 2019). In addition, the efficacy of drug effects in tumors can also be easily monitored. This will help in the development of novel drug targeting and to explore new therapeutic combinations to treat GBM more effectively (Arvanitis et al., 2020; Betzer et al., 2019; d'Angelo et al., 2019; Hameed et al., 2019; Kim et al., 2019; Lian et al., 2019).

6.1 Multifunctionalized nanoplatforms

In recent years, multifunctionalized nanoplatforms combining several therapeutic and diagnostic agents to drug delivery system for treating BT has emerged (Bechet et al., 2015; Duan, Li, Zhao, & Xu, 2018; Locatelli et al., 2014; Tang et al., 2019; Yang, Song et al., 2019). Some of the benefits of these nanoplatforms include biocompatibility, selective delivery as well as maximum tolerable drug concentration with low cellular toxicity (see Arvanitis et al., 2020; d'Angelo et al., 2019). In addition multifunctionalized nanoplatforms prevents early degradation or inactivation during intravascular transport of drugs to the target tissues (d'Angelo et al., 2019; Duan et al., 2018; Locatelli et al., 2014). Use of multifunctionalized nanoplatforms is advantageous for drug and tracer imaging, targeting ligands or therapeutic drugs and also to avoid interference with the immune system (d'Angelo et al., 2019).

Magnetic iron oxide nanoparticles (MIONPs) are one good example in this direction (Abakumov et al., 2019; Del Sol-Fernández et al., 2019;

Rego et al., 2019; Sharma et al., 2011; Shi, Mi, Shen, & Webster, 2019). These MIONPs are coated human serum albumin that can be attached with a chemotherapeutic agent and photosensitizers (Del Sol-Fernández et al., 2019; Rego et al., 2019; Shi et al., 2019). Drug delivery system could then be directed to the target sites using light or external magnets to achieve high concentration of the drugs for effective therapy (Abakumov et al., 2019; d'Angelo et al., 2019; Del Sol-Fernández et al., 2019; Rego et al., 2019; Shi et al., 2019). Multifunction theranostic nanoplatforms using contrast agent encapsulated within the liposomes could simultaneously detect early stage of disease and drug delivery (d'Angelo et al., 2019; Liu et al., 2019, 2016).

It remains to be seen whether multidrug delivery using other nanoplatforms such as nanowire scaffolds with stem cells and enzymes could also enhance better therapeutic effects in GBM. This is a subject that requires further investigation.

7. Our experiments with nanowired delivery of drugs in experimental glioma

As evident from the above description that GBM is quite complex and so far no effective therapy has been worked out. This is due to the fact that several factors in GBM play crucial role such as changing microvascular structure and function, drug resistance to glioma, lack of drug delivery to the GBM core tissue, as well as differences in the metabolism of GBM within the same tumor cells and responsiveness of same drug to different stages of the cancer even or in same patient (Arvanitis et al., 2020; Gately, McLachlan, Dowling, & Philip, 2017; Gokden, 2017; Liao et al., 2019; Quail & Joyce, 2017; Rezaei et al., 2020; Sarkaria et al., 2018; Stavrovskaya et al., 2016; van Tellingen et al., 2015).

Thus, there is an urgent need to explore new suitable therapeutic strategies using nanomedicine to reduce some of the anatomical and chemical barriers of drug delivery to the tumor cells for better treatment. For this, good animal models of GBM are needed for drug testing to achieve better therapeutic goals.

In this direction, several models of rat brain glioma are established since the last 40 years for the drug development for GBM (Agnihotri et al., 2013; Chen & Hambardzumyan, 2018; Miyai et al., 2017). Each model has some specificity with regard to GBM and thus could be used to study some aspects of glioma in adult art brain (see Arvanitis et al., 2020). As early as 1971 the

first rat brain tumor model was described using single or multiple weekly administrations of *N*-methylnitrosourea (NMU) intravenously (Koestner, Swenberg, & Wechsler, 1971; Swenberg, Koestner, & Wechsler, 1972). These models of rat brain tumor models were quite reproducible (Barth & Kaur, 2009). However, these rat brain tumor models in no way could be simulated with human GBM cases. Nevertheless these tumor models are used for exploration of therapeutic strategies using pharmacological approaches and provided new insights in GBM pathology and therapy.

7.1 Induction of primary glioma

We used standard methods to induce rat brain glioma by injection of 5 mg/kg, i.v. MNU per week for 26 weeks. After 17–21 weeks of termination of MNU injections glioma in the brain develops quite similar to that of clinical cases (Bilzer, Reifenberger, & Wechsler, 1989). The rat brain glioma can largely be classifies as low to middle grade astrocytoma and seen in more than 70% of rats. Only 10% cases did not survive for 26 weeks injection. About 4% of rats showed moribund stages or died after 11–16 weeks after completing 26 weeks of MNU injections (Sharma HS, Unpublished observation). All experiments were carried out according to National Institute of Health Guidelines for care and handling of experimental animals and approved by the local Institutional Ethics committee.

7.1.1 Plasma biomarker of rat brain glioma

As mentioned above GBM is the most vascularized BT with numerous microvascular proliferations (cf Arvanitis et al., 2020). Furthermore, hypoxic environment around tumor cells alters GSCs and induces release of several pro-angiogenic factors that contribute to the tumor growth and complexity (Kim et al., 2018; Tamura et al., 2019). In this regards vascular endothelial growth factor-A (VEGF-A) is the most prominent factor in causing microvascular proliferation and promoting cell migration (Martini et al., 2018).

Several isoforms of VEGF are identified in GBM that has different biological function and molecular sizes such as VEGF-121, VEGF-189, VEGF-165 and VEGF-206 (D'Alessandris et al., 2015; Martini et al., 2018). Out of these isoforms, VEGF-121 present in circulation is the main factor in GBM although it has low mitogenic potential. Recent studies show that IN GBM VEGF-121 can be detected in peripheral blood samples and correlates with GBM severity and susceptible to treatment outcome (Martini et al., 2018). Thus, VEGF-121 measurement in plasma samples could reflect status of GBM and its therapeutic effects.

This idea is supported by the findings that in human cases of GBM, the level of VEGF-121 in plasma is very high (Martini et al., 2018). Treatment with a potent monoclonal antibody of VEGF bevacizumab in these patients significantly lowered the plasma VEGF-121 that corresponds to better clinical outcome (Martini et al., 2018).

7.1.2 Measurement of VEGF-121 in plasma of rat brain glioma

We measured VEGF-121 in plasma of rats 13–17 weeks after termination of MNU injections using enzyme-linked immunoabsorbent assay (ELISA) using commercial protocol. For this purpose, about 1 mL heparinized blood sample was collected from right jugular vein through a poly-ethylene (PE 10) catheter inserted before the experiment. The blood samples were centrifuged (15 min at 900 × *g* at 4 °C) to collect plasma and stored at −80 °C for later VEGF determination. VEGF-121 was measured using VEGF-121 ELISA Kit (My Bio Source, San Diego, CA, USA, MBS-702523 VEGF-121 ELISA Kit, sensitivity 39 pg/mL) according to standard protocol (see Martini et al., 2018). The control and experimental samples were measured in triplicate in a spectrophotometer (Beckman DU-650 UV-Vis, Rochester, NY, USA). Quantification of VEGF-121 was done in identical manner using standard curve.

7.1.3 Nanodelivery of drugs using TiO_2 nanowires for rat glioma

We used nanowired delivery of the following drugs to induce neuroprotection in rat glioma model (Fig. 6).

(a) Cerebrolysin (EverNeuro Pharma, Oberburgau, Austria): Cerebrolysin- a balanced composition of several neurotrophic factors and active peptide fragments and is remarkable neuroprotective in CNS injuries, neurodegeneration, hyperthermia and drug induced neurotoxicity (Ozkizilcik, Sharma, et al., 2018; Ozkizilcik, Williams et al., 2018; Sharma, Muresanu, Castellani et al., 2019; Sharma, Muresanu, Lafuente, Patnaik et al., 2018).

(b) H-290/51 (Astra Zeneca Mölndal, Sweden): This compound is a chain breaking antioxidant and highly neuroprotective in CNS Injuries caused by trauma, hyperthermia, nanoparticles intoxication and psychostimulants abuse (Sharma et al., 2009; Sharma, Muresanu et al., 2015; Sharma, Muresanu, Lafuente, Sjöquist et al., 2018; Sharma, Sjöquist, & Ali, 2007).

These drugs are nanowired separately according to standard protocol as described earlier. Nanowired cerebrolysin was delivered in dose of

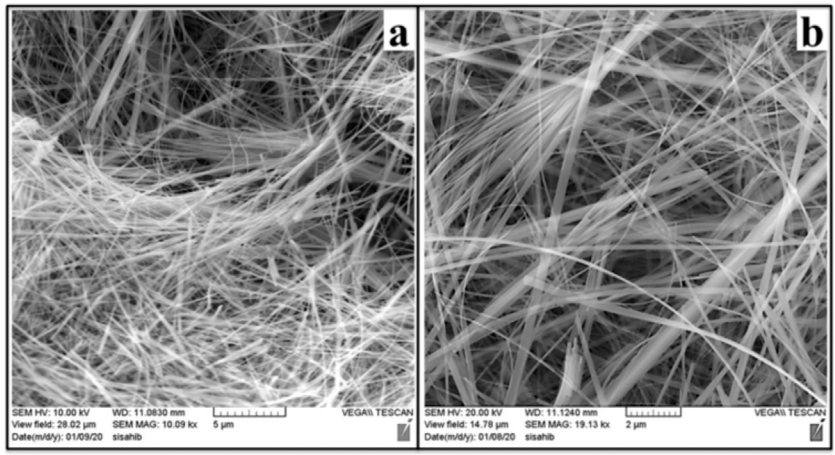

Fig. 6 Scanning electron microscope (SEM) images of titanate nanowires for Cerebrolysin or H-290/51 drug loading for nanowired delivery. TiO_2 nanowires are shown at low (A) and high (B) magnification used for glioblastoma nanomedicine therapy. For details see text.

5 mL/kg, i.v. after termination of MNU injections every week for 15 weeks in the rat Glioma model. Nanowired H-290/51 was delivered in a dose of 50 mg/kg, i.v. in separate group of rats with glioma in identical manner every week after termination of MNU injections for 15 weeks. Saline treated control group instead of MNU is also treated with these nanowired drugs in identical manner for comparison.

7.1.4 Nanodelivery of drugs reduces pathophysiology of rat brain glioma

Using MNU administration of 26 weeks resulted in glioma development in the brain after 17–21 weeks exhibited remarkable tumor development. Thus, the tumor diameters ranged from 1.5 to 2.3 mm in control groups located largely within the cerebral cortex of one or both hemispheres. The tumor like growth can be found on different parts of the cerebral cortex some predominates on the occipital or parietal cortices whereas some are found on the temporal cortex (results not shown).

These animals with tumor showed loss of motor co-ordination as examined using RotaRod treadmill. Thus, glioma rats are unable to stand over RotaRod of 16 RPM for more than 30–35 s as compared to control group that manages to stay over 120 s cut off time. This suggests that our rat glioma model has some clinical similarities on behavioral functions.

To further find out the relevance of rat brain glioma we measured VEGF-121 in plasma. Our observation showed a close parallelism between tumor diameter and plasma VEGF-121 level (Sharma H et al., Unpublished observations).

Measurement of VEGF-121 in plasma of rats with glioma exhibited a very high level (280 ± 18 pg/mL) as compared to saline treated control group (44 ± 8 pg/mL). This suggests that rat brain glioma is also associated with significant rise in plasma VEGF-121 level. Regression analysis shows a close correlation between tumor diameter and rise in plasma VEGF-121 level (correlation coefficient $R^2 = 0.9$, $P < 0.001$) (Fig. 7).

Repeated treatment with nanowired cerebrolysin (NWCBL) or nanowired H-290/51 (NWH290/51) resulted in significant downregulation of plasma VEGF-121 (102 ± 8 pg/mL NWCBL; 128 ± 12 pg/mL NWH290/51) indicating successful treatment of rat glioma very similar to that observed with VEGF-monoclonal antibody treatment in human cases.

The development of tumor in these NWCBL or NWH290/51 treated rats showed marked reduction in tumor diameter (NWCBL 0.51 ± 0.03 mm; NWH290/51 0.73 ± 0.04 mm). Also these drug treated rats improved staying at the RotaRod treadmill (NWCBL 85 ± 8 s; NWH290/51 78 ± 5 s with 120 s cut off time for controls).

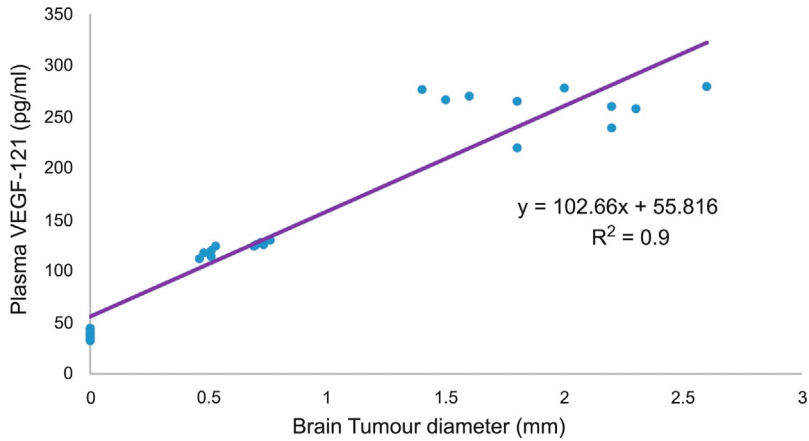

Fig. 7 Regression analysis showing close correlation between tumor diameter and plasma vascular endothelial growth factor 121 (VEGF-121) in control, untreated and nanowired cerebrolysin or H-290/51 treated group. Correlation coefficient $R^2 = 0.9$, $P < 0.001$.

Measurement of water content around tumor tissues showed significant increase in edema formation ($1.23 \pm 0.34\%$) that was reduced by NWCBL ($0.43 \pm 0.05\%$) and NWH290/51 ($0.52 \pm 0.07\%$) indicating excellent therapeutic efficacy of nanowired delivery of drugs.

Interestingly TiO_2 nanowired delivery without drugs did not influence tumor diameter, edema formation, VEGF-121 levels and RotaRod performances (results not shown).

8. Possible mechanisms of nanowired drug delivery on neuroprotection in rat glioma

Our observations are the first to show that cerebrolysin when administered using nanowired delivery weekly for 15 weeks in MNU induced rat brain glioma showed profound neuroprotective effects in terms of reduction in tumor diameter and VEGF-121 plasma levels. Also, the peritumoral edema formation is significantly reduced. Obviously, these factors also improve cognitive function on the RotaRod treadmill by the cerebrolysin (Menon, Muresanu, Sharma, Mössler, & Sharma, 2012; Muresanu et al., 2019; Ruozi et al., 2015; Sharma et al., 2007; Sharma, Muresanu, Mössler, & Sharma, 2012). This observation opens up a novel therapeutic strategy using cerebrolysin for the treatment of GBM in clinical conditions. Cerebrolysin is currently being used clinically for stroke, traumatic brain injuries and other neurodegenerative diseases such as Alzheimer's and Parkinson's diseases (Alvarez et al., 2011; Brainin, 2018; Ghaffarpasand et al., 2018; Requejo et al., 2018). Thus, use of cerebrolysin in GBM therapy could further help in alleviating some of the pathophysiological aspects of BT patients that could enhance their quality of life.

Our observations with NWCBL showed marked reduction in peritumoral edema formation in rat glioma. This indicates that cerebrolysin is able to reduce BTB permeability that is somehow responsible for adverse tumor proliferation and metastasis. This effect is possibly due to the drugs neurotrophic effects on fenestrated microvessels and normal healthy brain cells around the tumor formation (Alvarez et al., 2011; Menon et al., 2012; Muresanu et al., 2019; Ruozi et al., 2015; Sharma et al., 2012).

Previous research shows that cerebrolysin is a potent antioxidant drug capable to reduce oxidative stress in a variety of neurodegenerative diseases, stroke, hyperthermia and drugs of abuse (Boshra & Atwa, 2016; Ozkizilcik, Sharma, et al., 2018; Ozkizilcik, Williams et al., 2018; Sharma, Muresanu et al., 2015). There are also evidences that cerebrolysin could attenuate hypoxic insults to the cells and induce neuroprotection

(Węgrzyn, Kutwin-Chojnacka, Bilski, Mroszczyk, & Węgrzyn, 2019). Thus, it is quite likely that NWCBL is inducing most pronounced effects on rat glioma in attenuating oxidative stress and hypoxic insults during the formation of chemical induce tumorogenesis. Since hypoxic environment around tumors is responsible for proliferation, resistance to treatment and tumor growth, reduction in hypoxia by NWCBL could reduce tumor size and peritumoral edema formation causing brain pathology.

A reduction in VEGF-121 in plasma in cerebrolysin reflects these antioxidant and anti-hypoxic effects of the drug together with neuroprotective ability of the nanodelivered cerebrolysin (Requejo et al., 2018). These observations suggest that nanowired delivery of cerebrolysin is able to reduce some of the crucial parameters of rat glioma inducing neurological problems. Since normal cerebrolysin in the identical doses or TiO_2 nanowires alone did not show significant reduction in tumor size, VEGF-121 levels, edema formation and cognitive function (results not shown), it appears NWCBL is needed to induce neuroprotection in rat glioma model.

That antioxidant property of nanodelivered drugs is important in reducing tumor size, VEGF-121 level, edema formation and enhancing cognitive functions is further supported by the results obtained with a potent chain-breaking antioxidant compound H-290/51. H-290/51 is a powerful antioxidant and strongly neuroprotective in a wide variety of noxious insults to the CNS (Westerlund, Ostlund-Lindqvist, Sainsbury, Shertzer, & Sjöquist, 1996; Wiklund, Nilsson, Sjöqvist, & Berggren, 1994). Thus, treatment with H-290/51 induced neuroprotection in brain and spinal cord injury, hyperthermic insults to the CNS; psychostimulants induced brain pathology and following nanoparticles intoxication (Sharma et al., 2009; Sharma, Muresanu, Lafuente, Sjöquist et al., 2018). These neuroprotective effects of the compound H-290/51 are further enhanced when this is delivered through nanowired technology (Sharma, Kiyatkin et al., 2015; Sharma, Muresanu et al., 2015).

In this investigation, NWH290/51 is able to markedly reduce tumor size, VEGF-121 in plasma, peritumoral edema formation and enhanced cognitive functions. This suggests that antioxidant property of the therapeutic compound is necessary to reduce glioma induced brain pathology and functional impairment. As mentioned above, TiO_2 nanowires alone or normal H-290/51 has almost no effects on rat glioma model (Sharma, Kiyatkin et al., 2015; Sharma, Muresanu et al., 2015). This indicates that nanowired delivery of H-290/51 is needed to reduce the tumor size and other elated brain pathologies.

It would be interesting to combine NWCBL and NWH290/51 therapy for rat glioma after full tumor formation to see whether this combination of nanomedicine could also alleviate tumor induced brain pathology and reduction in the tumor sizes (Sharma, 1982, 1999; Sharma, Kiyatkin et al., 2015). This is a feature that requires additional investigation.

Nanodelivery of compounds are able to better penetrate the brain tissue in good quantity and maintain their higher concentration within the tumor cells for longer time period (cf Sharma et al., 2017). This is because of the fact that their metabolism is reduced due to nano-drug complex formulation (Sharma, Muresanu, Lafuente, Sjöquist et al., 2018; Sharma, Muresanu, Castellani et al., 2019). This could be one of the main reasons that normal CBL or H-290/51 could not have significant effects on rat brain glioma (Sharma HS, Unpublished observations). Also, the nanowires alone could not alter the tumor pathophysiology indicating that nanomaterial alone are unable to induce any positive effects on tumor pathology (see Sharma et al., 2017).

Our laboratory is engaged to understand a suitable combination of drugs, antibodies to VEGF and stem cells using nanowired technology to study killing potentials of tumors at advanced stages in a rat model of glioma. This is the feature that is currently being investigated in our laboratory.

9. Conclusion and future direction

In conclusion, GBM is a complex and various factors are responsible for tumor progression and persistence. Nanomedicine is the need of hour to develop suitable therapeutic strategies to treat BT patient in future. Our observations suggests that nanowired delivery of neuroprotective confounds may have some future integrating GBM. It would be interesting to see a combination of several drugs, antibodies, stems cells together with chemotherapy and radiotherapy could advance therapeutic benefits to GBM patients and enhance their quality of life.

Acknowledgments

This investigation is supported by grants from the Air Force Office of Scientific Research (EOARD, London, UK), and Air Force Material Command, USAF, under grant number FA8655-05-1-3065; Grants from the Alzheimer's Association (IIRG-09-132087), the National Institutes of Health (R01 AG028679) and the Dr. Robert M. Kohrman Memorial Fund (R.J.C.); Swedish Medical Research Council (Nr 2710-HSS), Göran Gustafsson Foundation, Stockholm, Sweden (H.S.S.), Astra Zeneca, Mölndal, Sweden

(H.S.S./A.S.), The University Grants Commission, New Delhi, India (H.S.S./A.S.), Ministry of Science & Technology, Govt. of India (H.S.S./A.S.), Indian Medical Research Council, New Delhi, India (H.S.S./A.S.) and India-EU Co-operation Program (R.P./A.S./H.S.S.) and IT-901/16 (J.V.L.), Government of Basque Country and PPG 17/51 (J.V.L.), J.V.L. thanks to the support of the University of the Basque Country (UPV/EHU) PPG 17/51 and 14/08, the Basque Government (IT-901/16 and CS-2203) Basque Country, Spain; and Foundation for Nanoneuroscience and Nanoneuroprotection (FSNN), Romania. Technical and human support provided by Dr. Ricardo Andrade from SGIker (UPV/EHU) is gratefully acknowledged. Dr. Seaab Sahib is supported by Research Fellowship at University of Arkansas Fayetteville AR by Department of Community Health; Middle Technical University; Wassit; Iraq, and The Higher Committee for Education Development in Iraq; Baghdad; Iraq. We thank Suraj Sharma, Blekinge Institute Technology, Karlskrona, Sweden and Dr. Saja Alshafeay, University of Arkansas Fayetteville, Fayetteville AR, USA for computer and graphic support. The U.S. Government is authorized to reproduce and distribute reprints for Government purpose notwithstanding any copyright notation thereon. The views and conclusions contained herein are those of the authors and should not be interpreted as necessarily representing the official policies or endorsements, either expressed or implied, of the Air Force Office of Scientific Research or the U.S. Government.

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