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Review Article

The role of microglia and P2X7 receptors in gliomas

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ABSTRACT

Gliomas are the most prevalent tumours of the central nervous system and present with high morbidity and mortality. The most common and most aggressive form of glioma is glioblastoma multiforme, of which patients have a median survival time of only 12 to 15 months. Current treatment options are limited and have a small impact on clinical outcome and prognosis. There is accumulating evidence that microglia, the immunocompetent cells of the central nervous system, and the purinergic P2X7 receptor (P2X7R) may contribute to tumour progression and pathology. Importantly, P2X7R on both tumour cells and infiltrating microglia is overexpressed in animal and human glioma cultures. Factors released by glioma cells and P2X7R activation recruit microglia into the largely immunosuppressive tumour microenvironment where they have been demonstrated to contribute to either tumour proliferation or tumour suppression. It is likely that P2X7R mediates a range of microglia effector functions in the glioma setting, potentially increasing tumour growth and proliferation. This review evaluates current evidence on the roles of microglia and P2X7R in glioma pathogenesis. Understanding the nature, mechanisms and outcomes of microglia and P2X7R activation in gliomas is necessary for the development of more therapies with increased efficacy and specificity.

1. Introduction

Gliomas are glial cell malignancies characterised by high histological heterogeneity and tissue invasiveness (Wen and Kesari, 2008). These neoplasms predominantly develop as diffuse tumours that extensively infiltrate the brain parenchyma (Perry and Wesseling, 2016). Non-diffuse gliomas are less common and are typified by decreased growth-rate and infiltrative capacity (Perry and Wesseling, 2016). The World Health Organization (WHO) further classifies gliomas based on a combination of histological and molecular characteristics (Louis et al., 2016; Louis et al., 2007). Histologically, diffuse gliomas include low-grade astrocytomas (WHO grade II) with low mitotic and necrotic potential, anaplastic gliomas (WHO grade III) with increased vessel density, mitotic activity and nuclear pleomorphism, and glioblastomas (WHO grade IV) that are mitotically active and present with significant neovascularisation and necrosis (Perry and Wesseling, 2016; Louis et al., 2007). WHO grade I gliomas are commonly non-diffuse, pilocytic astrocytomas with lower infiltrative potential (Perry and Wesseling, 2016). Glioblastoma (WHO grade IV) is the most common form of glioma and presents with the worst prognosis (Goodenberger and Jenkins, 2012).

Although several genetic and environmental factors are reportedly linked to glioma development, the aetiology of most cases is unknown (Goodenberger and Jenkins, 2012). Ionising radiation is the most strongly linked environmental risk factor (Wen and Kesari, 2008). However, little evidence suggests a definitive link between mobile phone use, smoking or alcohol and glioma development (Cardis et al., 2010; Bondy et al., 2008). There is considerable research focusing on

Abbreviations: ATP, adenosine triphosphate; BBG, brilliant blue G; BzATP, 2′3′-O-(4-benzoylbenzoyl)-ATP; Ca^{2+}, calcium ion; CNS, central nervous system; CXCR4, CXC chemokine receptor 4; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FasL, Fas ligand; VEGF, vascular endothelial growth factor; GME, glioma microenvironment; HIF-1α, hypoxia-inducible factor 1-alpha; iNOS, inducible nitric oxide; IDH, isocitrate dehydrogenase; IL, interleukin; K^+, potassium ion; M-CSF, macrophage colony stimulating factor; MCP-1, monocyte chemoattractant protein-1; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; MMP-2, matrix metalloprotease-2; MST, median survival time; Na^+, sodium ion; nfP2X7, non-functional P2X7 receptor; NLRP3, NOD-like receptor protein 3; OxATP, oxidized ATP; P2X7R, P2X7 receptor; PD-L1, programmed death-ligand 1; SDF-1α, stromal cell-derived factor 1-alpha; TGF-β, transforming growth factor-beta; TME, tumour microenvironment; TNF-α, tumour necrosis factor-alpha; Treg cells, regulatory T cells; WHO, World Health Organization

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several genetic factors and glioma oncogenesis, as reviewed by Goodenberger and Jenkins (Goodenberger and Jenkins, 2012) and Reifenberger et al. (Reifenberger et al., 2016). Among these, isocitrate dehydrogenase (IDH) 1 and 2 mutations have made the greatest impact on glioma classification and diagnosis, forming the basis of the updated WHO 2016 glioma classification (Louis et al., 2016). IDH enzymes regulate cellular redox reactions and are important in cellular defence against oxidative stress (Cohen et al., 2013). IDH mutations occur in over 80% of low-grade gliomas and secondary glioblastomas (Molenaar et al., 2018). Characteristic of these mutations is the extensive hypermethylation of CpG islands, which ultimately promote glioma oncogenesis (Cohen et al., 2013). Patients harbouring IDH 1/2 mutations have improved survival and clinical outcome, compared to those without IDH mutations (Yan et al., 2009; Houillier et al., 2010).

Current treatment options for gliomas are limited. Maximal safe surgical resection is often performed on newly diagnosed gliomas; however, due to the high infiltrative capacity of these malignancies, complete elimination is not possible (Coniglio and Segall, 2013; Wen and Kesari, 2008). Tumour resection has been reported to modestly increase survival time by several months (Lara-Velazquez et al., 2017), although this observation remains controversial (McGirt et al., 2009; Chaichana and McGirt, 2012; Sanai and Berger, 2008; Bloch et al., 2012). The current treatment regimen also includes radiotherapy, often in conjunction with the alkylating agent, temozolomide (Johnson and Chang, 2012). Use of temozolomide chemotherapy has been shown to increase survival by a modest 2.5 months, compared to radiotherapy alone (Stupp et al., 2005). However, the majority (60–75%) of glioblastoma patients receive no therapeutic benefit with temozolomide administration, and there is minimal therapeutic efficacy in patients with recurrent glioblastoma (Chamberlain, 2010). For low-grade gliomas, the chemotherapeutic agents used include procarbazine, lomustine and vincristine (Buckner et al., 2016). Genetic and molecular changes associated with glioma pathogenesis also inherently increase glioma radioresistance (Han et al., 2017; Johnson and Chang, 2012; Marumoto and Saya, 2012). A further concern with current mainstay of treatment is the risk and adverse side effects that include the potential for immunosuppression and pancytopaenia, leading to an increased risk of infections and bleeding (Nagane et al., 2009). Radiotherapy can also induce significant cognitive changes in low-grade glioma patients, which impose lifelong implications on both the individuals affected and their families (Klein et al., 2002; Pendergrass et al., 2018). The cognitive effects of radiotherapy in cases of high-grade glioma should be elucidated.

Both morbidity and mortality of malignant gliomas is extremely high. Despite vigorous treatment efforts, patients with glioblastomas have a median survival time (MST) of 12 to 15 months (5-year survival rate of 5%), while patients with anaplastic astrocytomas have a MST of 2 to 5 years (5-year survival rate of 30%) (Wen and Kesari, 2008; Goodenberger and Jenkins, 2012). The progression to high-grade gliomas is common among patients with lower-grade tumours (Perry and Wesseling, 2016).

The purinergic P2X7 receptor (P2X7R) has been a recent topic of interest in glioma research. P2X7R is expressed on many immune cells of haematopoietic origin and the central nervous system (CNS) (Sperlágh and Illes, 2014). In gliomas, P2X7R is expressed on both glioma cells and glioma-associated microglia (Volonte et al., 2012; Ryu et al., 2011). Microglia are immunological mediators of the CNS and constitute the largest infiltrating cell subpopulation in the glioma microenvironment (Quail and Joyce, 2017). These cells have been reported to serve contradictory roles that either promote (Komohara et al., 2008; Ellert-Miklaszewska et al., 2013) or hinder (Sutter et al., 1991; Galarneau et al., 2007) glioma cell proliferation. The mechanisms of microglial activation and function within the tumour site are unclear, although many of these appear to be mediated by P2X7R (Monif et al., 2016; Wang et al., 2008). There is also controversy on the action of P2X7R *per se* in the glioma microenvironment – receptor activation has been associated with both trophic (Ryu et al., 2011; Wei et al., 2008) and cytolytic (Tamajusuku et al., 2010; Fang et al., 2013) effects. Furthermore, it is known that microglial P2X7R expression is upregulated in gliomas (Monif et al., 2014), but the receptor activation state and function within the tumour milieu remains unclear. A deeper understanding of the roles of microglia and P2X7R in glioma progression will aid the development of more effective and targeted therapies for human gliomas. Here, the current literature on the role of microglia and P2X7R in gliomas is evaluated. This review discusses, briefly, the neuroimmunology of glioma pathogenesis, with an emphasis on the role of parenchymal microglia. A further focus is on the reputed functions of P2X7R in malignant gliomas of both animal models and in humans. The roles of P2X7R in other neoplastic diseases are not reviewed here in detail.

2. Microglia-macrophages of the brain

Microglia are the primary effector cells of the CNS, comprising of 10% of non-neuronal cells (Salter and Stevens, 2017). Recent fate mapping analyses suggest that microglial cells originate from primitive yolk sac progenitors that migrate into and colonise the CNS in the early stages of embryogenesis (Ginhoux et al., 2010). This speculation remains controversial, with earlier studies revealing that these cells share a close lineage relationship with peripheral macrophages derived in the bone marrow (Williams and Hickey, 1995). Flow cytometric analyses have also indicated an overlap in cell surface markers of microglia and macrophages (Wei et al., 2013; Lorger, 2012; McLarnon, 2017). However, recent evidences have defined a series of microglial-specific biomarkers that uniquely distinguish these cells from parenchymal macrophages; these include signature microRNA expression patterns (Butovsky et al., 2014), cell surface markers (Bennett et al., 2016) and distinct epigenomic and transcriptomic phenotypes (Gosselin et al., 2017).

Nevertheless, microglia are potent homeostatic mediators of the CNS parenchyma. Under normal conditions, these ‘resting’ cells are morphologically characterised by ramified protrusions that stem from the cell body. These branches constitutively communicate with neurons and glial cells in the surrounding environment (Wei et al., 2013; Nimmerjahn et al., 2005). Upon activation by various pathological stimuli, microglia have the unique ability to be polarised from a resting state towards a spectrum of either a ‘pro-inflammatory’ or an ‘immunosuppressive’ phenotype (Wei et al., 2013; Tarique et al., 2015). Microglia that are largely pro-inflammatory release large amounts of mediators that formulate effective immune responses (Gieryng et al., 2017). Furthermore, expression of both MHC class I and MHC class II suggest roles in antigen presentation and T cell activation (Lorger, 2012; Graeber et al., 2002). Conversely, immunosuppressive microglia predominantly secrete ‘anti-inflammatory’ factors that promote immune suppression and tissue repair (Gieryng et al., 2017). Sustained microglial activation has been associated with pathological neuroinflammation, which can fuel the development of neurodegenerative and neoplastic diseases (Perry et al., 2010; Streit et al., 2005; Salter and Stevens, 2017).

2.1. Glioma-associated microglia-macrophages

The role of microglia in tumour architecture and growth was historically neglected. Our previous work (Monif et al., 2014) and research from other laboratories (Hussain et al., 2006; Yi et al., 2011) have shown that microglia are an integral part of the tumour microenvironment (TME). In fact, microglia are now known to be one of the largest infiltrating cell subpopulations in human gliomas (Hussain et al., 2006; Quail and Joyce, 2017). Glioma cells release various microglia-recruitment/activation factors into the glioma microenvironment (GME), including macrophage chemoattractant proteins, colony stimulating factors, growth factors, hypoxia-induced factors, cytokines

and ATP (Lorger, 2012; Graeber et al., 2002; Wang et al., 2008; Pellegatti et al., 2008). The large numbers of infiltrating microglia are also likely due to accumulating hypoxia in the necrotic TME. For example, the hypoxic GME has been shown to increase CXC chemokine receptor 4 (CXCR4) on the surface of microglial cells by activating hypoxia-inducible factor 1-alpha (HIF-1α) (Wang et al., 2008). Binding of CXCR4 to its ligand, stromal cell-derived factor 1-alpha (SDF-1α) then facilitates microglial migration to the TME (Wang et al., 2008). There is robust evidence supporting the origins of glioma-associated microglia from both local precursors in the CNS parenchyma and peripheral blood monocytes/macrophages (Graeber et al., 2002; Glass and Synowitz, 2014; Dello Russo et al., 2017; Arcuri et al., 2017).

Intratumoural microglia numbers have been reported to positively correlate with histological tumour grade (Nishie et al., 1999; Yi et al., 2011). This relationship also seems to be consistent with microglial phenotype and level of malignancy, with higher-grade gliomas having an increased proportion of immunosuppressive microglia, relative to lower-grade tumours (Komohara et al., 2008). However, on a new perspective, nanostring expression profiling has revealed that glioma-associated microglia might in fact, express an immunological profile similar to that of unpolarised, quiescent macrophages (Gabrusiewicz et al., 2016). The microglia activation state in gliomas requires further elucidation.

2.1.1. Tumour-promoting roles of microglia-macrophages

Accumulating evidence describes various functions of microglia that either support or suppress an anti-tumour response. In gliomas, microglia are common infiltrators of both tumoural and peritumoural mass (tissue composition surrounding the tumour) (Hoelzinger et al., 2007). Within the GME, microglia have been considerably reported to skew towards an immunosuppressive phenotype that supports tumour growth and angiogenesis (Hussain et al., 2006; Komohara et al., 2008). This transition is largely influenced by the presence of anti-inflammatory cytokines, interleukin (IL)-10 and transforming growth factor-beta (TGF-β), in the GME (Gieryng et al., 2017; Nduom et al., 2015). Macrophage colony stimulating factor (M-CSF) released by glioma cells also polarise microglia into an immunomodulatory state. Immunomodulatory microglia *per se* are important producers of immunosuppressive cytokines and growth factors that fuel glioma progression (Huettner et al., 1997; Wagner et al., 1999; Wei et al., 2013). Microglia in glioblastoma samples were shown to have upregulated expression of genes associated with immunosuppression and tissue repair (Li and Graeber, 2012). Despite the opposing results of earlier studies (Graeber et al., 1994; Morris and Esiri, 1991), immunosuppressive microglia reportedly express lower levels of MHC II (Taniguchi et al., 2000). This suggests a potential reduction in tumour antigen-presentation in high-grade gliomas. Interestingly, a study by Hussain and colleagues demonstrated the presence of MHC II in glioma-infiltrating microglia, but also revealed significant down-regulation of CD80/86 co-stimulatory molecules necessary for effector T cell activation (Hussain et al., 2006). Hence, microglia in high-grade gliomas may induce T cell anergy (inactivation occurring in the absence of a co-stimulatory signal), preventing the generation of T cell-mediated anti-tumour responses.

An important pro-tumourigenic factor secreted by microglia is matrix metalloprotease-2 (MMP-2), which catalyses pro-MMP-2 (inactive form) from glioma cells into active MMP-2, promoting tumour invasion by degrading the extracellular matrix (Markovic et al., 2005). Microglia are also potent sources of Fas ligand (FasL), which induces apoptosis in infiltrating Fas-expressing effector lymphocytes to promote immunosuppression (Badie et al., 2001). Other tumour-promoting mediators secreted by glioma-associated microglia include vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and prostaglandin E2, which respectively foster tumour angiogenesis, proliferation and immunosuppression (Lorger, 2012; Hoelzinger et al., 2007). Microglia-secreted IL-10 and TGF-β further inhibit the anti-tumour response (Gieryng et al., 2017). An interesting observation is the tumour-promoting activity of the pro-inflammatory cytokine, IL-1-beta (IL-1β), released by glioma-associated microglia (Hoelzinger et al., 2007). Importantly, IL-1β release into the GME is dependent on P2X7R (Monif et al., 2016), which will be discussed in detail in Section 3. IL-1β has been shown to stimulate TGF-β transcription in glioma cells, resulting in the upregulation of VEGF, EGF receptor (EGFR) and MMP-9, which ultimately increases tumour proliferation and invasion (Hoelzinger et al., 2007). IL-1β also exerts its effects in an autocrine manner, being a potent trophic activator of microglia (Monif et al., 2016). The tumour-promoting effects of IL-1β might also be attributed to the activation of P2X7R, required for IL-1β release (Franceschini et al., 2015; Monif et al., 2016). However, the comparison of IL-1β mRNA levels in human glioblastoma samples with clinical data drew an association between increased IL-1β mRNA levels and longer glioblastoma patient survival (Cuny et al., 2002). Few clinical studies have investigated the link between IL-1β levels and glioblastoma survival. While the results of the study by Cuny et al. suggests a potential IL-1β-mediated anti-tumour response consistent with the pro-inflammatory properties of the cytokine, the study also demonstrated a positive correlation between inducible nitric oxide synthase (iNOS) levels and IL-1β mRNA levels. It is known that IL-1β induces iNOS expression (Kleinert et al., 2003). However, it has been well documented that iNOS serves important roles in malignant glial transformation *in vivo* and the promotion of tumour proliferation and invasion (Jahani-Asl and Bonni, 2013; Tran et al., 2017; Fahey et al., 2018). Collectively, these results and contradictions prompt the need for more research on intra-tumoural IL-1β levels and glioblastoma survival.

2.1.2. Tumour-inhibiting roles of microglia-macrophages

Microglia may also be involved in tumour inhibition. Contrary to the pro-tumourigenic role of microglia-released EGF, earlier research demonstrated microglia-mediated lysis of glioma cells expressing EGFR in the presence of an EGFR-specific monoclonal antibody (Sutter et al., 1991). However, whether this lysis mechanism occurs naturally *in situ* in the absence of EGFR-mAb, should be investigated. Furthermore, microglia have been shown to secrete TNF-α into the GME (Roessler et al., 1995; Hoelzinger et al., 2007). In gliomas, TNF-α potentiates anti-tumour immunity, rather than tumour growth (Roessler et al., 1995), but also interestingly further recruits microglia to the tumour site (Villeneuve et al., 2005). The latter observation highlights a potential dual role of microglia in glioma, likely influenced by the diversity of pro- and anti-inflammatory mediators present within the complex GME.

On a new perspective, a recent study led by Lisi et al. characterised the distribution of distinct microglial phenotypes in high-grade glioma specimens (Lisi et al., 2017). An analysis of 41 surgically resected human glioblastoma samples demonstrated that microglia of the amoeboid phenotype were primarily situated towards the tumour centre, while ramified microglia were distributed around the periphery. Additionally, glioma-associated microglia were found to express both pro- and anti-inflammatory activation markers (Lisi et al., 2017). Continual research to elucidate the contribution and activation states of infiltrating microglia in the GME is much needed.

3. P2X7R

Adenosine triphosphate (ATP) is quintessentially recognised as a potent energy source that fuels biological reactions vital for cell survival (Khakh and Burnstock, 2009), but of increasing prominence is its alternative role as a universal signalling molecule. ATP is important, not only in cellular metabolism, but also in mediating neurotransmission, cell migration and proliferation, inflammation and the immune response (Volonte et al., 2003; McLarnon, 2017). Under normal physiological solutions, it is present in low (nanomolar) amounts extracellularly and larger (5–10 millimolar) amounts intracellularly. ATP

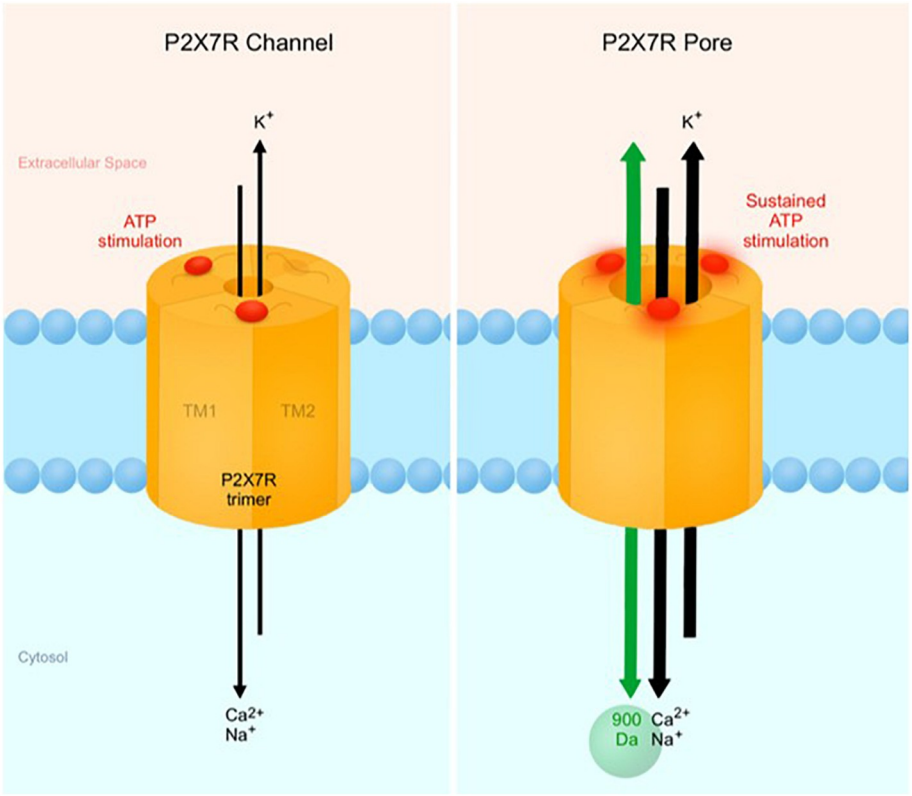

Fig. 1. P2X7 receptor (P2X7R) has two conductance states – a schematic diagram. (Left) Basal P2X7R stimulation in lower adenosine triphosphate (ATP) concentrations mediates the opening of an ion-selective channel, enabling calcium (Ca^{2+}) and sodium (Na^{+}) influx and potassium (K^{+}) efflux. (Right) Alternatively, sustained stimulation with ATP induces the formation of a large, non-selective pore, allowing massive influx and efflux of ions, as well as entry and exit of aqueous solutes of up to 900 Da (Da) in size.

within the intracellular space is released upon various stimuli, including stress, inflammation and cell death (Gehring et al., 2012; Di Virgilio et al., 2017; Kojima et al., 2017).

Notably, it is the primary agonist of P2X purinoceptors (Burnstock, 2006), which are trimeric ion channels that modulate transmembrane ion movement (Di Virgilio et al., 2017). Unique among this subfamily is P2X7R, which is generally activated at high ATP levels, over the 200 micromolar range (Sperlágh and Illes, 2014). This low-affinity ATP receptor is widely expressed in cells of haematopoietic origin, including microglia, macrophages and lymphocytes (Volonte et al., 2012). P2X7R has two conductance states (Fig. 1). Stimulation in low extracellular ATP environments formulates a channel with increased cation selectivity, enabling calcium (Ca^{2+}) and sodium (Na^{+}) influx and potassium (K^{+}) efflux (Adinolfi et al., 2005; Monif et al., 2009). Alternatively, P2X7R forms a large, non-selective membrane pore upon sustained ATP stimulation (Adinolfi et al., 2005; Savio et al., 2018). In addition to a substantial increase in cation fluxes, the altered conductance of the pore facilitates permeability to aqueous solutes of up to 900 Da (Di Virgilio et al., 2017; Franceschini et al., 2015). Although the transition from P2X7R channel to pore is well documented, the mechanisms of pore formation remain unclear and require further elucidation. Several pore formation theories have been proposed, with the two most common being (1) the progressive dilatation of the P2X7R channel following sustained ATP stimulation (Alves et al., 2014) and (2) the recruitment of an extrinsic accessory molecule, such as pannexin, following receptor activation (Pelegrin and Surprenant, 2006). The P2X7R pore was recognised as a cytolytic entity (Tamajusuku et al., 2010; Fang et al., 2013; Greig et al., 2003). However, recent reports are on the contrary, highlighting a trophic role (Monif et al., 2014; Giannuzzo et al., 2015; Bergamin et al., 2015).

3.1. The dual role of P2X7R in cancer

P2X7R serves immunomodulatory functions (Di Virgilio et al., 2017) that are implicated in a range of pathological conditions. For example, they have been extensively described in various cancers (White et al., 2005; Li et al., 2006; Zhang et al., 2009; Adinolfi et al., 2012; Boldrini et al., 2014; Zheng et al., 2014). ATP concentration in the TME measures in the hundreds of micromolar range, which is beyond the threshold required for P2X7R activation (Pellegatti et al., 2008; Roger et al., 2015). Exogenously applied ATP has been shown to suppress tumour cell proliferation by arresting cell cycle progression (Rapaport, 1983) – this is likely related to the pro-apoptotic/necrotic effects of P2X7R overstimulation (Mackenzie et al., 2005; Adinolfi et al., 2005), which may not represent a physiological scenario and rather being the by-product of disrupted membrane homeostasis and subsequent cell death. Nonetheless, the cytolytic functions of P2X7R in cancer have been demonstrated in several studies. P2X7R stimulation with high concentrations of ATP (1000–5000 μM) and 2′3′-O-(4-benzoylbenzoyl)-ATP (BzATP), a potent experimental P2X7R agonist, substantially reduced tumour growth in a human cutaneous squamous cell carcinoma line (Greig et al., 2003). Furthermore, Feng et al. (Feng et al., 2011) speculated direct P2X7R-mediated anti-proliferative and death-inducing activity on melanoma and colon cancer cells. In this study, prolonged exposure to 2.5 mM ATP inhibited tumour cell proliferation and decreased cell count and confluency. The anti-tumour effects were subsequently blocked by co-incubation with a P2X7R antagonist. P2X7R-mediated inflammatory cell recruitment and IL-1β production in a mouse model of melanoma and colon cancer was also significantly reduced following P2X7R ablation (Adinolfi et al., 2015). These results highlight the importance of P2X7R in generating effective inflammatory and anti-tumour immune responses.

On a different note, P2X7R may also serve trophic roles in the TME. While the underlying mechanisms are still unclear, an increasing amount of studies are reporting on the pro-tumourigenic effects of P2X7R stimulation (Adinolfi et al., 2012; Amoroso et al., 2015; Giannuzzo et al., 2015; Giannuzzo et al., 2016; Xia et al., 2015). Indeed, P2X7R is overexpressed in a range of cancers, including pancreatic ductal adenocarcinoma (Giannuzzo et al., 2015), thyroid papillary cancer (Solini et al., 2008) and leukaemia (Zhang et al., 2004).

Moreover, P2X7R expression in some neoplasms may be associated with a worse prognosis (Qian et al., 2017; Liu et al., 2015a; Liu et al., 2015b). This evidence signifies the importance of P2X7R in the progression and infiltrative potential of certain cancers. P2X7R antagonism inhibited proliferation of pancreatic ductal adenocarcinoma cells, and increased receptor expression positively correlated with the degree of tumour cell survival, migration and invasion (Giannuzzo et al., 2015; Giannuzzo et al., 2016). The metastatic potential of breast cancer was also shown to be reduced *via* silencing of P2X7R expression (Xia et al., 2015). Another study reported that P2X7R expression in human embryonic kidney cells induced a more anaplastic and tumourigenic phenotype with decreased apoptosis (Adinolfi et al., 2012). Furthermore, Amoroso and associates demonstrated P2X7R-mediated tumour promotion in human neuroblastoma cells (Amoroso et al., 2015). In this study, P2X7R stimulation with ATP and BzATP potentiated the oncogenic PI3K/Akt signalling pathway, essential for neuroblastoma progression. VEGF production was also lowered by P2X7R downregulation. The above data summarise the growth-promoting roles of P2X7R in the TME. It is clear that P2X7R activation is coupled to two distinct responses in the context of cancer. Although the detailed mechanisms mediating this dual role are vague, these differences are likely to be dependent on cell line, mechanisms of cell death and ATP concentration (Burnstock and Di Virgilio, 2013; Roger et al., 2015).

3.2. P2X7R in gliomas

While there is extensive literature on P2X7R in non-CNS cancers, the roles of P2X7R in gliomas have only recently been described. Current literature reflects contradictory results. As previously discussed, the GME is one that is highly complex, comprised of intricate cellular networks and a myriad of immunological mediators. In the glioma milieu, P2X7R is known to be expressed on both glioma cells (Ryu et al., 2011; Tamajusuku et al., 2010; Wei et al., 2008) and infiltrating microglia (Monif et al., 2014). Hence, in this context, it is likely that these cells harbour the P2X7R-mediated effects. Moreover, there is lowered expression of ATP hydrolysing enzymes present in the GME, resulting in prolonged effects of ATP and therefore increased P2X7R stimulation (Wink et al., 2003).

P2X7R suppression *via* antagonism or genetic silencing stimulated C6 glioma cell proliferation (Fang et al., 2013). This effect was mediated by the resultant upregulation of EGFR in a mechanism modulated by a P2Y receptor. Downstream release of HIF-1α and VEGF fostered glioma growth and angiogenesis. In another *in vitro* model of glioma, the GL261 mouse glioma cell line, P2X7R stimulation with BzATP resulted in tumour cell death, which was prevented with receptor silencing or antagonism with oxidized ATP (OxATP) (Tamajusuku et al., 2010). This study also observed that ATP-P2X7-induced glioma cell death was primarily necrotic in nature – evidence supporting this included cell shrinkage, membrane permeabilization and limited caspase-1 activity. Necrosis, characteristic of high-grade glioblastomas, prompted by P2X7R activation could therefore also contribute to the hypoxic microenvironment; the subsequent release of hypoxia-induced growth-promoting factors has additionally been reported to recruit microglia (Wang et al., 2008). While these results may be significant, experimental conditions often involve prolonged, maximal P2X7R stimulation, which disrupts the homeostatic ionic membrane gradient, leading to a mitochondrial catastrophe that inevitably results in cell death (Di Virgilio et al., 2017). Whether this cytolytic response is reciprocated in a physiological setting is unclear (Monif et al., 2009) and requires further elucidation.

Interestingly, P2X7R expression and activation may be implicated in enhancing the effects of conventional treatment (D'Alimonte et al., 2015; Gehring et al., 2015). *In vitro* P2X7R stimulation with ATP and BzATP induced longer-lasting cytotoxicity of temozolomide (D'Alimonte et al., 2015). It has previously been shown to significantly increase in radiosensitive human glioma cells after irradiation and subsequently induce death in these cells (Gehring et al., 2012). Building from this, a study led by Gehring et al. irradiated GL261 and human M059 J glioma cells and observed a reduction in cell numbers for both cell lines (Gehring et al., 2015). This cytotoxic effect was mediated by P2X7R activation, as P2X7R antagonism and silencing inhibited this radiation-induced cell death after 24 h. The same study also linked P2X7R upregulation to a positive glioma prognosis. Data from human glioma biopsies and over 300 glioma patients associated a drastically higher MST in patients with increased P2X7R expression (MST of 80 months), compared to patients with decreased P2X7R expression (MST of 14 months) and response to radiotherapy positively correlated with this observation. Patients with amplified P2X7R mRNA levels also had substantially higher MST. From these data, it seems that the P2X7R gene may be silenced with increasing glioma malignancy; however, studies have reported P2X7R upregulation in glioma (Ryu et al., 2011; Monif et al., 2014) and a positive correlation between increasing tumour grade and receptor expression (Ji et al., 2018). In face of the controversy, P2X7R agonists may synergistically enhance the effect of current anti-glioma therapies.

Alternatively, rat C6 glioma cell culture experiments and calcium-sensitive spectrofluorescence recorded pro-tumourigenic P2X7R pore activity – P2X7R agonism with BzATP increased cell motility and P2X7R expression (Wei et al., 2008). BzATP agonism also increased VEGF, monocyte chemoattractant protein-1 (MCP-1) and IL-8 production (Wei et al., 2008). Of note, MCP-1 and IL-8 are chemokines that recruit microglia/macrophages and neutrophils, respectively (Deshmane et al., 2009; Bergamin et al., 2012). Both cell types are thought to be immunostimulatory in the neuropathological context. However, in gliomas, certain anti-inflammatory mediators in the GME seem to polarise these cells into a pro-tumourigenic, immunosuppressive state (Quail and Joyce, 2017; Nduom et al., 2015). These growth-promoting results are also consistent with the finding that sustained P2X7R activation, as opposed to current dogma, did not induce apoptosis/necrosis in C6 glioma cells (Wei et al., 2008; Ji et al., 2018). Another C6 glioma study speculated tumour reduction after P2X7R antagonism with brilliant blue G (BBG), although this observation was only associated with receptor blockage in glioma cells and not microglia (Ryu et al., 2011). Further animal studies have revealed tumour inhibition and reduced microglia release of anti-inflammatory mediators following P2X7R antagonism with BBG and OxATP (Fang et al., 2011; Bergamin et al., 2015). In an autocrine manner, these mediators induce microglia polarisation towards the immunosuppressive phenotype (Bergamin et al., 2015; Nduom et al., 2015). Hence, these studies (Fang et al., 2011; Bergamin et al., 2015) suggest the importance of P2X7R-mediated immunomodulatory microglial polarisation on glioma progression.

Despite the important roles of microglia in the GME and expression of P2X7R in these cells, there is little literature on microglial P2X7R in glioma. We have previously shown that P2X7R is expressed not only on glioma cells, but also on surrounding microglia in human glioma tissue cultures (Monif et al., 2014). P2X7R was also found to be higher in directly infiltrating microglia than peritumoural microglia, but the opposite was true for glioma cells. Importantly, P2X7R pore was found to be trophic in human glioma cultures and inhibition of P2X7R resulted in a reduction of glioma cell numbers (Monif et al., 2014). Massive K^+ efflux by the P2X7R pore is a crucial activator of the NOD-like receptor protein 3 (NLRP3) inflammasome, a multi-protein complex involved in the production of IL-1β *via* a caspase-1-dependent mechanism (Franceschini et al., 2015). IL-1β release has recently been demonstrated to be dependent on P2X7R pore formation (Monif et al., 2016; Barbera-Cremades et al., 2012; Ferrari et al., 1997; Hide et al., 2000). The cytokine also serves as a trophic activator of microglia (Monif et al., 2016). This activation, coupled with further immunosuppressive microglia polarisation by immunosuppressive factors in the GME, might be a possible mechanism for the overall P2X7R-mediated trophic effects on the glioma culture. More research is needed

to clarify this. Importantly, P2X7R antagonism with BBG (7 μM) decreased tumour cell number (Monif et al., 2014). These data further potentiate the use of P2X7R antagonists in glioma therapy and prompt the need for additional research on P2X7R and its effects on microglia in the GME.

4. P2X7R as a therapeutic target for gliomas

The relationship between P2X7R activation and glioma progression is a relatively recent field of research. Despite this, there is much potential for P2X7R to be established as a therapeutic target in the near future. We have presented a range of data in support of this. Currently, there are few advancements in the therapeutic development of P2X7R-targeting agents for human gliomas. The use of P2X7R agonists and antagonists including BzATP, BBG and OxATP, have shown varying results in both animal and human glioma cells (see Section 3.2. above). Furthermore, the A-740003 P2X7R antagonist successfully inhibited the release of inflammatory cytokines by macrophages exposed to glioma conditioned medium that was mediated by P2X7R activation (Bergamin et al., 2015). Collectively, the ability of these agents to successfully target P2X7R *in vitro* shine light into the development of P2X7-targeting agents that will be effective *in situ*. The challenge is to establish compounds that will surpass the blood brain barrier and target P2X7R in the GME.

Several P2X7R-targeting compounds have been developed for a range of cancers. A detailed review has been conducted by Burnstock and Knight (Burnstock and Knight, 2018). Notably, there has been a recent development of antibodies targeting a non-functional form of P2X7R (nfP2X7), which does not have capacity to form the pore conductance state (Barden et al., 2014). This is a result of the loss of two out of three ATP binding sites in nfP2X7 – the binding of ATP to all three ATP binding sites is required for pore formation (Barden et al., 2014). Of note, Barden and colleague's study is based on the hypothesis that activation of the P2X7R pore induces cytolytic effects that result in cell death (Tamajusuku et al., 2010; Fang et al., 2013; Greig et al., 2003). This hypothesis should be further investigated in *in vivo* experiments, as *in vitro* experiments that often involve maximal P2X7R stimulation inevitably resulting in cell death, may not entirely represent true physiological scenarios. In the study, the nfP2X7 receptor was expressed and successfully targeted in a range of cancers, including gastrointestinal stromal tumour, pituitary cancer, Hodgkin's lymphoma, colon adenocarcinoma, pancreatic cancer, and a range of lung cancers. Following this study, a phase I clinical trial involving 21 participants has also been initiated (Gilbert et al., 2017). The trial evaluated the safety of a topical ointment containing sheep anti-nfP2X7 antibodies for the treatment of basal cell carcinoma. After 28 days of treatment, 65% of participants demonstrated a reduction in lesion area, 15% showed an increase in lesion area and 20% exhibited no change in lesion size. Continual, larger-scale trials are required to assess the efficacy of anti-nfP2X7 antibodies. However, in gliomas, studies have demonstrated the presence of the P2X7R pore (Wei et al., 2008; Monif et al., 2014), providing evidence of a functional P2X7R in gliomas. Functionality of P2X7R remains a topic of continual research.

5. Conclusions

There is considerable evidence of microglia and P2X7R involvement in gliomas. P2X7R has been reported to serve both tumour-promoting and tumour-inhibiting roles in human and animal models of glioma, although many of these mechanisms require elucidation. Importantly, the receptor regulates the release of cytokines, chemokines and growth factors that potentiate the migration of local and peripheral immune cells into the GME. These factors ultimately prevent or facilitate tumour immune evasion and hence, modulating the extent of P2X7R activation could impact glioma growth. It is clear that microglia infiltrate the GME in large amounts, but whether these cells limit tumour growth or alternatively contribute to tumour proliferation and invasion, is unknown. Elements of microglia recruitment and function also appear to be mediated by P2X7R activation in the GME. Moreover, P2X7R is highly expressed on glioma-associated microglia. Studies have reported positive correlations between both microglia and P2X7R numbers and increasing glioma malignancy. This presents a likely crosstalk between microglia and P2X7R on glioma progression, but the extent of this interplay has been sparsely investigated. Multiple studies have focused on P2X7R pore within the GME, but further research is required to clarify both pore and channel effector activity of the receptor in the context of gliomas. The paradox of microglia and P2X7R involvement in gliomas strongly prompts the need for further investigation. Experiments on *in vivo* glioma animal models and human glioma tissue samples are essential to broaden advancements in this field. Subsequent investigations should additionally focus on the relationship of P2X7R with a range of components in the GME, including microglia. Finally, the peripheral immunological phenotype of glioma patients and the efficacy of temozolomide and other agents used in standard glioma treatment in relation to P2X7R stimulation or inhibition, should be assessed. Nonetheless, preliminary research suggests that targeting P2X7R may be an effective therapy or co-therapy for human gliomas in the near future.

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