REVIEW ARTICLE

Cellular and Molecular Biology

The importance of RHAMM in the normal brain and gliomas: physiological and pathological roles

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Although the literature about the functions of hyaluronan and the CD44 receptor in the brain and brain tumours is extensive, the role of the receptor for hyaluronan-mediated motility (RHAMM) in neural stem cells and gliomas remain poorly explored. RHAMM is considered a multifunctional receptor which performs various biological functions in several normal tissues and plays a significant role in cancer development and progression. RHAMM was first identified for its ability to bind to hyaluronate, the extracellular matrix component associated with cell motility control. Nevertheless, additional functions of this protein imply the interaction with different partners or cell structures to regulate other biological processes, such as mitotic-spindle assembly, gene expression regulation, cell-cycle control and proliferation. In this review, we summarise the role of RHAMM in normal brain development and the adult brain, focusing on the neural stem and progenitor cells, and discuss the current knowledge on RHAMM involvement in glioblastoma progression, the most aggressive glioma of the central nervous system. Understanding the implications of RHAMM in the brain could be useful to design new therapeutic approaches to improve the prognosis and quality of life of glioblastoma patients.

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INTRODUCTION

The receptor for hyaluronan-mediated cell motility (RHAMM), also called hyaluronan-mediated motility receptor (HMMR), HIABP or CD168, is codified in the long arm of human chromosome 5 in a small cluster which also includes *NUDCD2* (NudC domain-containing protein 2), *CCNG1* (cyclin G1), and *MAT2B* (methionine adenosyltransferase 2B) genes [1]. The RHAMM gene contains 18 exons and mainly generates four different isoforms by alternative splicing. These isoforms were named A-D (or 1–4), being A the full-length RHAMM and D the shortest isoform lacking exons 1 to 4 [2, 3].

Briefly, RHAMM was originally identified as a 56–58 kDa hyaluronan-binding protein in murine fibroblast supernatants [4]. Then, a first cDNA which contained an open reading frame encoding a 52 kDa polypeptide was isolated using a polyclonal antibody generated against the first isolated RHAMM protein. Subsequently, 70 kDa and 72 kDa proteins were cloned. The overexpression of the largest protein, designated RHAMM1v4 because it contained exon 4 (actually exon 8), leads to malignant transformation and metastases on murine fibroblasts. Later, using three new antibodies recognising different RHAMM epitopes, only one protein was detected at 85 kDa for human cells and at 95 kDa for murine line cells and primary tissues suggesting that previous reports had mistaken full-length RHAMM for a truncated non-native version of the protein. All in all, and despite the doubts about its structure, its history reveals the complexity of RHAMM and that the isoform RHAMM1v4 (isoform D) encodes an N-terminally truncated protein [5]. The RHAMM structure consists mainly of an N-terminal microtubule-binding domain and a coiled-coil axis responsible for its interaction with actin microfilaments. Moreover, it contains a projection domain that binds to calmodulin in a Ca^{2+}-dependent way and a basic leucine-zipper motif in its carboxy-terminal domain, which is responsible for RHAMM targeting to the centrosome and binding to hyaluronan (HA) [6, 7]. RHAMM isoform D, which lacks the N-terminal domain, becomes diffuse in the cytoplasm and upregulated in the cell nucleus and is associated with neoplastic initiation and/or metastasis [2, 6, 8, 9]. On the whole, these data reinforce the complexity of this protein and the heterogeneity of its functions.

The role of RHAMM as a putative cell surface receptor

RHAMM was firstly described as interacting with HA and heparin associated with wound repair [1, 10]. These interactions occur

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through ionic bonds along two regions of basic amino acids separated by a leucine zipper localised in the C-terminus of RHAMM [11]. Interestingly, the leucine zipper between two basic alpha helices suggests the possibility of dimerisation which could affect RHAMM binding to HA [2]. Considering that HA is an extracellular matrix component, RHAMM/HA contact requires that both molecules colocalize at the cell surface. The expression of RHAMM in the cell membrane has been reported [4, 12, 13], although its nature is still controversial. Interestingly, RHAMM lacks the typical hydrophobic sequence found in transmembrane proteins for canonical extracellular export. It is thought that a GPI binding domain or an adaptor protein would be responsible for its attachment to the plasma membrane. In this way, it has been reported that RHAMM can interact with transmembrane receptors such as CD44, EGFR, PDGFR, TGFβR-1, bFGFR and RON [14–18]. Through these interactions, RHAMM can modulate pathways associated with these receptors, affecting the expression of genes involved in the cell cycle, and impacting on cell proliferation, cell survival and cell migration, among others [19–21].

Strikingly, although RHAMM was described as an HA receptor, several invertebrates that do not synthesise HA, express RHAMM orthologues that exhibit C-terminus conservation but not in the N-terminus regions. These predictions suggest that the ancient RHAMM presents signalling functions and heparin-binding, while the interaction with microtubules appeared later, with the emergence of vertebrates [2]. Conversely, N-terminal homology was found between RHAMM and Miranda, a determinant of asymmetric cell division in Drosophila [1]. Overall, these findings suggest that the original role of RHAMM was not to function as a hyaluronan receptor, highlighting the importance of RHAMM intracellular functions.

The role of RHAMM at the centrosome and mitotic-spindle pole

In the cytosol, RHAMM participates in mitotic-spindle assembly. Indeed, RHAMM and XRHAMM, its orthologue in Xenopus, were considered a spindle assembly factor (SAF) dependent on Ran [22, 23]. In this way, the ubiquitin ligase anaphase-promoting complex (APC/C) degrades RHAMM together with other substrates such as Bard1, HURP and NuSAP, after being released from their inhibitor importin-beta by Ran (GTP). This process is tightly regulated to guarantee the correct formation of the mitotic spindle [23]. Moreover, it was shown that RHAMM forms a complex and acts as an adaptor for CHICA/FAM83D to microtubules [24]. The RHAMM-CHICA complex interacts with dynein light chain 1 (DYNLL1) and CK1alpha, which constitute a regulatory system for the correct mitotic-spindle orientation [24, 25]. In the mechanisms that act for the correction of spindle misorientation, RHAMM acts through its centrosome binding domain, in a PDL1-dependent pathway that involves the active Ran, the direct interaction with ERK and the cortical location of the NUMA-Dynein complex [26–29]. Recently, it has been demonstrated that RHAMM, together with ASPM, and NUMA1 are directly translated at the spindle poles during mitosis, and its localisation at the centrosome is temporally regulated [30, 31].

At the molecular level, it was demonstrated that the N-terminal domain of RHAMM interacts with microtubules, while the C-terminal leucine zipper is required for centrosome targeting. Interestingly, the RHAMM C-terminal exhibits high homology with the dynein interaction domain of Xklp2 and the kinesin Kif15 [32, 33]. In this way, it was shown that this domain of RHAMM is necessary to generate interkinetochore tension and to promote anaphase entry and centrosome separation [32, 34]. These processes involve the balance of kinesin Eg5-mediated forces through localising the targeting protein for Xklp2 (TPX2) and promoting the formation of inhibitory TPX2-Eg5 complexes [32, 34]. In addition, it was described that the tumour-suppressor complex BRCA1/BARD downregulates RHAMM functions during mitosis, facilitating the binding of TPX2 to spindle poles, which contributes to proper spindle assembly [22, 35]. Furthermore, it was shown that BRCA1 facilitates microtubule reorganisation whereas Aurora kinase A (AURKA) impairs it. The latter is regulated through RHAMM and TPX2 [36], which also produce the activation of microtubule nucleation by RanGTP [37].

Interestingly, a study on the interactome has shown high co-expression of RHAMM with BRCA1, indicating that RHAMM is a high risk factor to breast cancer [38]. This finding was supported by another study showing that the perturbation of apicobasal polarity, which is regulated by BRCA1 and RHAMM, increases the risk of breast cancer [36]. Similarly, it was suggested that the loss of RHAMM and the consequent spindle misorientation and aberrant division of male germ cells could promote hypofertility and testicular germ cell tumours [39].

Interestingly, the loss of RHAMM expression is also associated to peripheral nerve sheath tumours by a mechanism involving TPX2 release and activation of AURKA [40]. This absence of RHAMM could explain that these tumours exhibit slow growth and are rarely malignant. Therefore, the correct generation of mitotic-spindle bipolarity requires optimal levels of RHAMM, which if deregulated, would lead to genomic instability, favouring cancer initiation. Due to the increasing evidence about the main role of RHAMM in mitotic-spindle assembly and genomic stability, some authors are currently debating whether it should be considered more as a microtubule-associated SAF than a putative hyaluronan receptor [1]. Nevertheless, both roles of RHAMM become relevant in the tumour context.

Role of RHAMM in cancer

Considering that RHAMM is a cell-cycle-regulated gene product [30, 31], it is not surprising that it is poorly expressed in most homoeostatic adult tissues [41, 42], but it is overexpressed in several tumours, such as breast, endometrial, ovarian, bladder, pancreas, colorectal, head, neck and stomach cancers, choriocarcinoma, hepatocellular carcinoma, myeloma and leukaemia and prostate, among others [19, 43–49]. In all cases, the deregulation of this protein has been associated with poor prognosis and tumour progression.

The role of RHAMM in cancer has been studied at the molecular level through the modulation of several signalling pathways and biological processes, mainly associated with its role as HA receptor. In this way, we demonstrated that HA-RHAMM binding activates PI3K/Akt signalling, which favours proliferation and chemoresistance of human leukaemic cell lines [50]. Likewise, we demonstrated that HA-RHAMM interaction increases human choriocarcinoma cell migration through PI3K/Akt and MEK/ERK activation [46]. In concordance, several authors reported that HA enhances cell proliferation and migration in different cancer models through its interaction with RHAMM and the activation of other receptors such as CD44, PDGFR, EGFR which modulate PI3K/AKT and ERK [43, 51–54]. Moreover, it has been recently suggested that the HA-RHAMM interaction would regulate RHAMM expression in a cell-specific feedback loop in the signalling cascade [55].

As we described above, RHAMM not only acts as a receptor with the ability to transduce signals but also plays an important role in the regulation of homoeostasis, mitosis and meiosis [20]. Indeed, RHAMM expression is cell-cycle-regulated, and both its overexpression and its deficiency lead to genomic instability, which also contributes to tumour progression [1, 20, 56]. In this point, it is important to highlight that the tumour suppressor P53, as well as BRCA1, downregulate the expression of RHAMM, which is expected due to their anti-oncogenic roles [35, 36, 38, 39, 56].

The fact that RHAMM is overexpressed in pathological conditions and plays an important role in tumour progression, makes this protein an interesting molecular target for cancer therapies. Along this line, many efforts have been done to develop

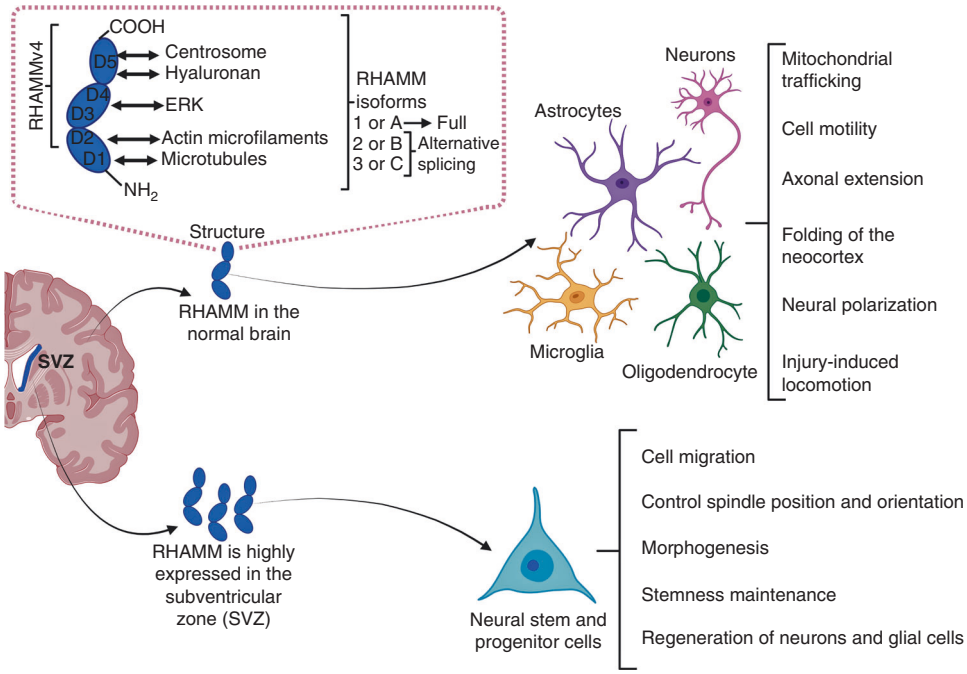

Fig. 1 RHAMM in the central nervous system. In the brain, RHAMM is expressed in all cell lineages participating in cell motility, axonal extension, folding of the neocortex, mitochondrial trafficking, neural polarisation and injury-induced locomotion. As mentioned in the main text, RHAMM mainly presents four splice variants with differences in the domains expressed. In this way, the C-terminus domains are involved in the interaction with HA, and centrosome while the N-terminus is responsible for binding actin microfilaments and microtubules. Interestingly, RHAMM is highly expressed in the subventricular zone participating in several processes of the neural stem cell (NSC). Created with BioRender.com.

several molecules, such as HA or RHAMM mimetics aiming to block RHAMM/HA interaction or recombinant RHAMM peptides to inhibit both its effects on tumour cell motility and its role as a mitotic regulator [57–59]. Moreover, RHAMM is considered a tumour-associated antigen [60, 61] and its overexpression can trigger both humoral and cellular immune responses. Indeed, its immunogenicity was considered for the development of cancer vaccines in gliomas and haematological malignancies [47, 62–64]. Although some of these studies showed promising results in phase I/II clinical trials, further analyses are necessary for their application as a therapeutic option in cancer [65, 66].

RHAMM in the central nervous system and its key role in neural stem cells

In the central nervous system (CNS) RHAMM is expressed by neurons, astrocytes, oligodendrocytes and microglial cells and was found to be associated with several processes such as injury-induced cell locomotion, axonal extension, mitochondria trafficking and brain morphogenesis during development [67–71] (Fig. 1). This expression of RHAMM in several cell types of the developing and adult brain, and the fact that HA is the main extracellular matrix (ECM) component, suggest a relevant role of RHAMM in this tissue.

It was demonstrated that the levels of HA are increased after brain ischaemic insult, accompanied by migrating astrocytes overexpressing RHAMM in these peri-infarct areas [72]. Therefore, it is tempting to speculate that the migration of these cells, at least partially, could be dependent on RHAMM-HA interaction. Likewise, inhibitory peptides used to block the HA-binding domains of RHAMM, reduced astrocytes and microglia motility in vitro [70]. Similarly, both neurite extension and neuroblast migration were inhibited [73]. Interestingly, it was suggested that HA-RHAMM interaction could occur in the cytoplasm of neurons, for regulating mitochondrial trafficking and localisation through calmodulin signalling [69].

It was demonstrated that RHAMM participates in the PLK1-dependent regulatory pathway, which orients progenitor cell division, regulates polarisation and supports brain morphogenesis during development [27, 74]. In accordance, the presence of the RHAMM gene in a small cluster together NUNDC2, with similar functions as adaptors for dynein motor proteins, has critical roles in the process of neural development [1]. In this way, the NUDC proteins form a complex with the cytoplasmic dynein partner protein, LIS1 (Lissencephaly 1), the loss of which can produce cortical malformation disorders [75]. Therefore, the presence of RHAMM and NUNDC2 in the same gene cluster could represent an evolutionary advantage.

Although RHAMM is found both in the adult and developing brain, its expression is remarkably heterogeneous among different cell populations [69]. In the adult tissue, RHAMM is strongly expressed in highly proliferative brain regions, such as the ventricular and subventricular zone (SVZ) of the brain and in migratory neuroblasts of the rostral migratory stream, which give rise to neurons for the olfactory bulb [26, 72, 76]. Although HA-RHAMM interaction is reported, it is tempting to think that RHAMM has a key role at the centrosome and mitotic-spindle pole during cell proliferation in the neural tissue.

Furthermore, in murine models, RHAMM controls spindle position and orientation, which determines neuroepithelial differentiation and directly impacts CNS development, brain morphogenesis as well as on neural stem and progenitor cells (NSC/NPC) maintenance [26, 27].

NSC/NPC are undifferentiated and multipotent cells of the CNS which can self-renew and also give rise to daughter cells committed to lineage-specific differentiation that ultimately generate neurons, astrocytes and oligodendrocytes [77–80]. Even though NSC/NPC are located lining ependymal cells of the ventricle walls of the brain, numerous progenitors, neuroblasts and other glial precursors coexist in this cellular structure of the brain that serves as a source for morphogenesis during

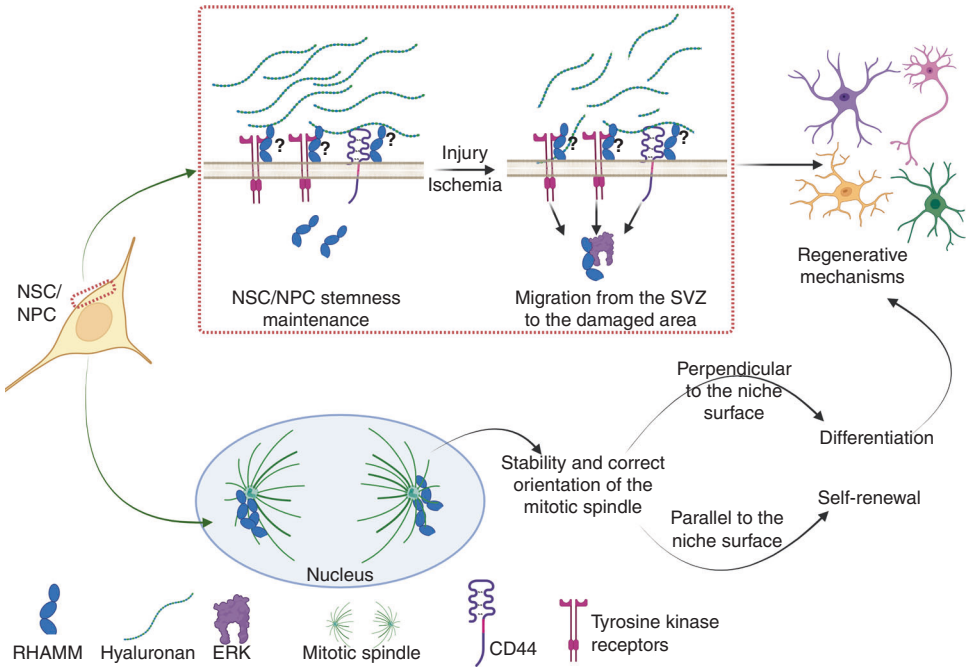

Fig. 2 Role of RHAMM in neural stem cells. The intracellular expression of RHAMM in neural stem cells (NSC) is required for the stability and correct orientation of the mitotic spindle. This is important for cell division orientation, the choice between stemness maintenance or differentiation pathway for the generation of neural progenitors implicated in the regenerative mechanism. As a putative receptor in the cell surface, it might control stemness maintenance and migration of progenitors after injury through its interaction with HA. Created with BioRender.com.

development or regeneration in the adult tissue. NSC/NPC are highly proliferative during morphogenesis, but they remain in a quiescent state in the adult brain, and can activate their proliferation or differentiation pathways depending on tissue requirements, which is relevant for regenerative mechanisms [79, 81].

Similarly to what was observed in other tissues, RHAMM seems to have different functions in neural tissue depending on its cellular localisation, as it can act as a cell surface receptor but it can also be localised in the cytoplasm or in the nucleus, to exert both hyaluronan-dependent and independent functions [1, 69].

It is noteworthy that HA plays essential roles in the control of NSC/NPC behaviour, stemness maintenance, long-term self-renewal and progenitor's migration, as well as neurons and glial cell regeneration from neurogenic niches [67, 82–84]. These neurogenic niches not only contain high levels of HA, but are enriched in RHAMM, persisting in the adult brain [26, 72, 76, 85]. Moreover, it has been suggested that HA-RHAMM interactions would be required for the proper migration of immature neurons in the rostral migratory stream [72]. Furthermore, the interaction of HA with RHAMM plays a key role in the regulation of the early folding of the human neocortex during embryogenesis, through the activation of ERK signalling [67]. Similarly, RHAMM is involved in the growth and regeneration of noradrenergic fibres from locus coeruleus by stimulating neuronal projections throughout the neuroaxis [86].

On the other hand, intracellular RHAMM is required for the stability and correct orientation of the mitotic spindle during NSC/NPC division and is thought to regulate the orientation of the cell division plane with respect to the lateral ventricle wall [26, 27]. If the mitotic spindle lies perpendicular to the niche surface, in an apicobasal orientation, the cell division plane aligns parallel to the niche edge, thus by asymmetrical division one daughter cell maintains its contact with the ventricle wall and persists in an undifferentiated state as an NSC, while the other daughter cell undergoes the differentiation programme as a progenitor that moves away from the SVZ to generate differentiated progeny. Moreover, if the mitotic spindle is oriented parallel to the niche surface, in a planar fashion, the cell division plane is set perpendicular to the niche edge and by symmetrical division both daughter cells maintain their contact with the niche, generating two NSCs that retain multipotency and self-renewal ability. Thus, intracellular RHAMM regulation on the orientation of NSC/NPC division and cell polarity ultimately might define the cell choice between self-renewal or differentiation pathways [26, 40, 87].

Overall, these studies support the key role of RHAMM in both the adult and developing brain, highlighting its functions on NSC/NPC features and maintenance (Fig. 2).

RHAMM in gliomas

As previously discussed, RHAMM is essential for NPC viability and the sustainment of cell potency. NSC/NPC in the SVZ niche and glioblastoma cells, which give rise to the most malignant primary brain tumour, share many cellular features and show similar gene expression patterns [88–90]. Growing evidence supports the hypothesis that NSCs of the SVZ are the most probable cells of origin of glioblastoma (GBM) [91–94].

Interestingly, RHAMM has been shown to promote self-renewal and multipotency of glioblastoma stem-like cells by the activation of stemness markers in NSC/NPC, such as CD133, Sox2, Sox4 and Olig2 [95]. Furthermore, the silencing of RHAMM diminishes both self-renewal and the expression of GSC markers, suppresses tumour growth and increases the survival time of mice with GSC xenografts [95]. These findings support the role of RHAMM at the centrosome and mitotic-spindle pole and highlight the similitude of this protein functions between GSC and NSC/NPC. In addition, it was demonstrated that RHAMM D was expressed both by astrocytoma cell lines and tissue samples, but not by their healthy counterparts. Moreover, RHAMM was associated with microtubules in astrocytoma cells but not in normal astrocytes, suggesting that RHAMM D could be involved in the interaction with

microtubules [96]. These observations are expected if considering that loss of the N-terminal domain in such variant increases the expression of RHAMM in the cell nucleus and enhances cancer initiation and/or metastasis [2, 6, 8, 9]. Additionally, it was shown that the overexpression of such variants in U87 and U374 glioma cells increases the invasion into an organotypic human brain slice model [97]. These results show remarkable coincidences with lung and breast cancer cells [14, 98] and suggest that the expression of this variant could be upregulated during malignant GBM transformation. It may be speculated that the function of RHAMM on microtubules could explain the exacerbated cell proliferation and migratory features of GBM cells.

As expected, RHAMM also plays a role as a putative cell surface receptor on GBM cells.

In 2001, Akiyama et al. have shown that several glioma cell lines expressed RHAMM in at least one of its variants. Moreover, the authors found that high-grade gliomas exhibited higher expression of RHAMM protein than low-grade gliomas. In addition, non-neoplastic surgical specimens with increased astrogliosis showed higher RHAMM expression in comparison to samples of non-gliotic human brains. Furthermore, they demonstrated that RHAMM secreted by GBM cell lines was able to bind HA. The addition of a RHAMM soluble peptide that contains the HA-binding domain to GBM cell culture diminished cell proliferation and migration [51]. Furthermore, the use of a siRNA targeting RHAMM diminished the migration and invasion of X01 GBM cells [99]. In agreement with these findings, we recently demonstrated that HA induces cell migration in the GL26 cell line, which expressed RHAMM but not CD44, suggesting that HA-induced migration was mediated by RHAMM [100]. Supporting that finding, we demonstrate the surface expression of RHAMM and showed that RHAMM-HA interaction induces migration in both LN229 and U251 cells through ERK signalling [13]. In other studies, RHAMM was evaluated as a marker for the stem-*like* phenotype in U87 GBM cells. The authors demonstrated that cells growing in an HA-3D model showed a stem-*like* phenotype compared to those cultured in a 3D model without HA. These findings suggest that RHAMM-HA interaction contributes with the stem phenotype in GBM cells [101]. These results highlight the importance of RHAMM-HA interactions in GBM malignancy and show marked similitudes with the RHAMM functions in NSC/NPC. Conversely, the silencing of RHAMM in U87 glioma cells neither modified HA-induced migration nor radiation-induced migration in these cells [102], suggesting the compensation of this signalling by another HA receptor in this cell model.

All in all, these reports reveal the key role of RHAMM, particularly of variant D, in GBM malignant features and identify this interesting protein as a target for GBM therapy.

In this respect, it was demonstrated that the vaccination of glioma-bearing mice with dendritic cells transfected with RHAMM mRNA increased survival time with respect to animals immunised with non-transfected dendritic cells [62]. Furthermore, while the mice of the second group died on day 50, 15% of the mice vaccinated with dendritic cells transfected with RHAMM mRNA were healthy and neurologically normal after 80 days [62]. In this way, it was suggested that the antitumour effect of these dendritic cells transfected with RHAMM mRNA was mediated by $CD4^+$ T cells [103]. Moreover, it was observed that the expression of RHAMM inversely correlates with the survival time of patients with brain tumours [99]. In addition to the relevance of RHAMM as a potential target for GBM antitumour treatment, the mechanisms of regulation of RHAMM expression are also considered interesting therapeutic targets. An example of this is the RHAMM antisense long noncoding RNA 1 (HMMR-AS1), which stabilises the mRNA of RHAMM. It was demonstrated that the knockdown of HMMR-AS1 reduced the expression of RHAMM, leading to the inhibition of cell migration and invasion, as well as the suppression of GBM cell growth both in vitro and in vivo. Furthermore, the silencing of HMMR-AS1 sensitised GBM cells to radiation by downregulation of DNA repair proteins such as ATM, RAD and BMI1, postulating HMMR-AS1 as a novel target in GBM [104]. Likewise, similar evidence were found in other tumour pathologies, such as lung adenocarcinoma, and ovarian and breast cancer [105–107].

A few years ago, it was demonstrated that the inhibition of COX-2 on U251 and U87 glioma cells markedly diminished the levels of RHAMM protein, decreases proliferation and generates G1 phase cell-cycle arrest in vitro, while suppressing tumour growth and angiogenesis in vivo [108]. In addition, we demonstrated that 4-methylumbelliferone, which inhibits HA synthesis, decreases cell proliferation and induces senescence while diminishes membrane RHAMM expression in U251 and LN229 cells [13]. These data reinforce the idea of using the modulation of RHAMM expression as a therapeutic strategy in GBM.

In a similar way, the protein profile of U87 glioma cells after treatment with TGF-β, which induces the epithelial-to-mesenchymal transition (EMT) in several types of carcinomas, showed that although the expression of CD44 remained unchanged, the levels of RHAMM were increased, suggesting that this receptor could be involved in the EMT process [109]. According to the role of RHAMM in migration and invasion, Kim et al. (2011) showed that the expression of this receptor, as well as MMP-2 and MMP-9, were higher in the invasive edge of the tumour rather than in the core. In agreement, we demonstrated that 4-methylumbelliferone decreased GBM cell migration and reduced MMP-2 activity, as well as cell surface RHAMM expression [13]. Furthermore, RHAMM and MMP-2 showed the greatest expression in the margin of the most aggressive glioma group, which presented tumour recurrence [110]. Similarly, Virga et al. (2017) showed that RHAMM, together with MMP-2 and integrin α1, were useful proteins to distinguish between low and high-grade gliomas, as their increment was associated with tumour severity [111]. Two years later, the same group found that RHAMM protein was increased in patients with poor prognosis with respect to patients with better prognosis, suggesting the possibility of using this receptor as a prognostic marker, emphasising its relevance in GBM malignancy [112].

All in all, these results reveal the implication of RHAMM in several malignant features of GBM such as proliferation, migration, invasion and GSC self-renewal both in vitro and in vivo and even in GBM patient samples, thus highlighting its potential use as a therapeutic target in GBM (Fig. 3).

CONCLUSION

As we described in this review, RHAMM has multiple functions depending on its cellular location and isoform variants. Here we revised the role of RHAMM as a putative cell surface (HA) receptor, and its involvement in the centrosome and mitotic-spindle pole formation. Through the analysis of these roles, we attempted to clarify the function of RHAMM in the CNS with special attention to its requirement for NSC/NPC proliferation, migration and differentiation programmes both during development as well as for brain regeneration after injury.

It is noteworthy that many physiological functions of RHAMM in the neural tissue seem to be conserved in the GBM context (Fig. 4). However, as RHAMM expression is upregulated in GBM cells, these normal functions become uncontrolled and lead to undesirable upregulation of cell invasion, tumour progression, chemoresistance and genomic instability. Interestingly, strong similarities exist in the RHAMM roles between NSC/NPC and GSC. Finally, we described the strategies for targeting RHAMM as a potential GBM therapy that could improve the prognosis and outcome of patients.

Future investigations would pave the way towards a better understanding of the functional complexity of RHAMM in health

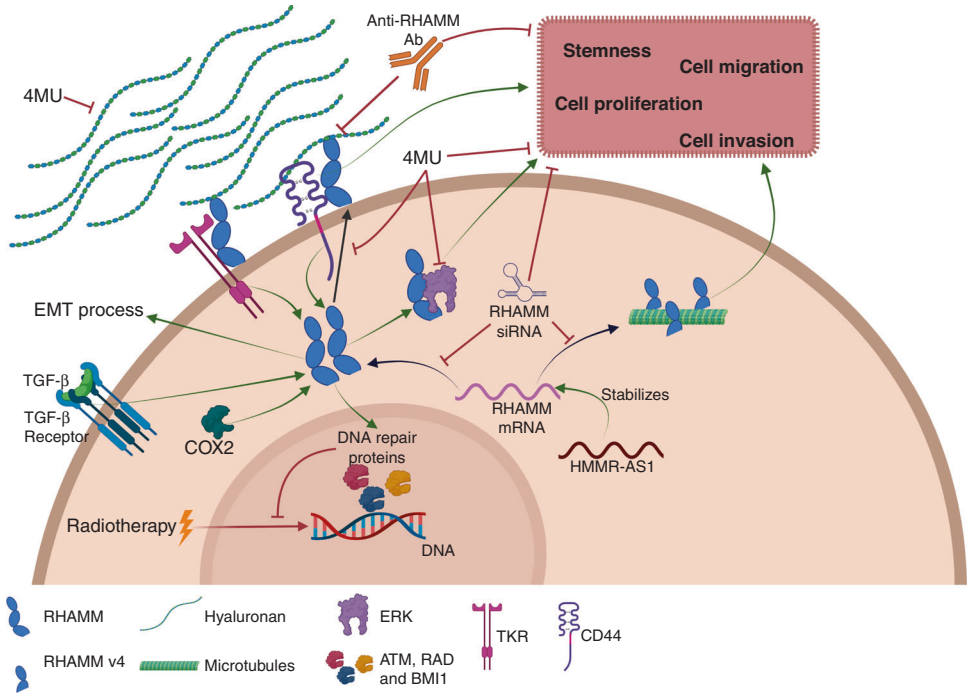

Fig. 3 The implication of RHAMM in GBM progression. RHAMM has multiple functions in GBM progression. The increased levels of RHAMM in GBM cells lead to overexpression of DNA repair proteins, which impair the effect of radiation therapy. Moreover, after RHAMM-HA interaction (both molecules are upregulated in GBM), the activation of signalling pathways such as MEK-ERK promotes cell migration and proliferation along with stemness maintenance. Interestingly, the antisense HMMR-AS1 plays a key role in RHAMM mRNA stabilisation, enhancing all RHAMM functions, including cell invasion mediated by RHAMM–microtubules interaction. Interestingly, targeting RHAMM at protein level (using antibodies or drugs) or at mRNA level (using RHAMM siRNAs) was shown to reduce malignant features of GBM cells. Created with BioRender.com.

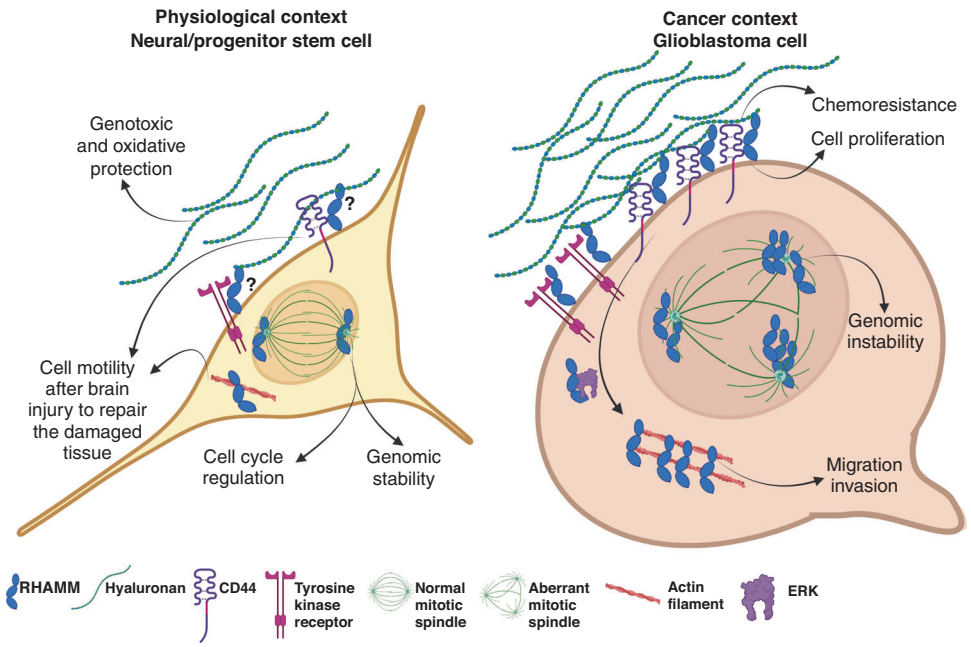

Fig. 4 Similarities between the roles of RHAMM in neural stem/progenitor cells and GBM cells. RHAMM roles exhibit strong similarities in neural stem/progenitor cells and GBM cells. In a physiological context, RHAMM might protect stem cells from DNA damage and oxidative stress by its interaction with HA. Moreover, RHAMM controls cell division through its interaction with the mitotic spindle. Interestingly, after brain injury, neural stem cells migrate to the damaged region by using RHAMM-HA and RHAMM-actin filament interactions. In a tumoral context, RHAMM is overexpressed by GBM cells and promotes tumour proliferation and invasion by RHAMM-HA and RHAMM–microtubule interactions. Regarding DNA damage, RHAMM protection favours radio and chemoresistance. Finally, the overexpression of RHAMM in tumour cells produces genomic instability and aberrant division, which promotes the generation of mutations, resistance and aggressiveness of GBM. Created with BioRender.com.

and disease in order to develop new therapeutic strategies and alternative biomarkers for GBM.

DATA AVAILABILITY

The datasets used and/or analysed during this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

MAP searched the bibliography, created the figures, analysed the data and wrote the manuscript. DP and YAM performed the edition of figures and analysed the bibliography. MD, AB and SA contributed to the design of the study and edition of the manuscript. SH and SL collaborated in the edition of the manuscript and contributed to the design of the study. PF supervised the work. All authors contributed to the work and have read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study did not require ethical approval.

CONSENT TO PUBLISH

Not applicable.

ADDITIONAL INFORMATION

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