Review

Research Progress of EMR2 Receptor Function in Glioma and its Potential Application as Therapeutic Target

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ABSTRACT: The most frequent primary brain malignancy is glioma. Alterations in several adhesion G-protein-coupled receptors (aGPCRs) are present in cancer as they regulate adhesion, migration, and guidance. Epidermal growth factor (EGF) module-containing mucin-like receptor 2 (EMR2) is included in group II GPCRs and functionally in a family of brain angiogenesis inhibitor molecules (BAIs). Recent studies have shown that BAIs regulate phagocytosis and synaptogenesis, and their extracellular domain inhibits angiogenesis and tumor growth. In neoplastic processes, EMR2 appears to play a role in disease aggressiveness, patient survival rates, and tumor grade. This review summarizes the EMR2 involvement in cellular mechanisms and pathologies, particularly in cancer. We searched the Pubmed Central, Google Scholar and Scopus databases for terms “EMR2” and “glioma”. The initial search yielded a total of 92 results. After excluding studies not written in English, based on design, and excluding duplicates and non-relevant studies, we included 38 studies in the review. EMR2 was shown to be expressed in various histologic grades of gliomas and to be linked to the PI3K pathway, as both are upregulated in glioblastoma after bevacizumab therapy. The PI3K-Akt pathway is involved in tumorigenesis, and upregulation of EMR2 may in turn upregulate PI3K, leading to increased tumor invasiveness. Indeed, overexpression of EMR2 was associated with the mesenchymal glioblastoma subtype, tumor invasiveness, and poor survival. EMR2 also regulates neutrophil function by producing reactive oxygen species (ROS) and degranulation. Possible therapeutic approaches have been studied, such as the stimulation of microglia and monocytes to inhibit tumor-initiating cells by down-regulating the EMR2 gene or through an antibody against EMR2. The current review summarizes the knowledge about the EMR2 receptor that can serve as motivation for future studies on its role in the clinical evolution and tumor biology of gliomas in order to find new modulator therapeutic approaches.

KEYWORDS: *EMR2 receptor, glioblastoma, inflammation.*

Introduction

The most frequent primary brain malignancy is glioma. Because gliomas evade radiotherapy, are resistant to conventional and anti-angiogenic therapy and immunotherapy, and are universally lethal, there is an urgent need to identify new drug targets. Glioblastoma is a malignant tumor originating from glial cells in the brain or spinal cord. It is characterized by its highly aggressive nature, rapid progression, and severe prognosis, with a median survival of approximately 15 months [1].

The average age at diagnosis of patients with glioblastoma is 58.6 years, with a male/female ratio of 1.34 [1].

In recent decades, driver mutations and transcriptional programs have been identified.

Tyrosine kinase receptors (TKRs) are major proteins involved in cancer development [2].

One route to activate TKRs is through G-protein-coupled receptors (GPCRs). Alterations in several adhesion GPCRs (aGPCRs) are present in cancer as they regulate adhesion, migration, and guidance, all of which are of major importance in tumor biology. aGPCRs regulate angiogenesis by cleaving their extracellular domain (ECD) at certain sites [3,4], as the conserved GPCR-proteolytic site (GPS) releases soluble fragments [3,5,6].

Epidermal growth factor (EGF) module-containing mucin-like receptor 2 (EMR2), also known as ADGRE2 or CD312 (cluster of differentiation 312), is included in group II of GPCRs and functionally in a family of brain angiogenesis inhibitor molecules (BAIs). Recent studies have shown that BAIs regulate phagocytosis and synaptogenesis, and the mean of their extracellular domain inhibits angiogenesis and tumor growth [7,8].

EMR2 is found in isoforms with variable EGF domains owing to alternative splicing [9].

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Initially identified because of its similarity with CD97 [10], EMR2 is involved in cellular adhesion, migration, and signaling [11,12].

In cancer, EMR2 appears to play a role in aggressiveness, patient survival rates, and tumor grade [13].

Similar to gliomas, EMR2 is associated with cellular migration, which can in turn increase cancer invasiveness [12,14,15].

More studies are necessary to determine whether the blockade/activation of EMR2 plays a role in the clinical progression, treatment resistance, and increasingly invasive recurrence of gliomas.

This review summarizes the EMR2 involvement in cellular mechanisms and pathologies, particularly in gliomas, which can be translated into targeted drug therapies.

Material and Method

This systematic review was performed in accordance with guidelines from Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

We searched the scientific journal databases Pubmed Central, Scopus and Wiley Web of Science for the terms "EMR2", "mucin-like receptor 2", "ADGRE2" and "glioma". The exact search strings are presented in Table 1.

Table 1. Search strings used to search for articles.

Search string used
EMR2 (Title) or EMR2 (Abstract) or ADGRE2 (Title) or ADGRE2 (Abstract) or mucin-like receptor 2 (Title) or mucin-like receptor 2 (Abstract) and glioma (Title)
EMR2 (Title) or EMR2 (Abstract) or ADGRE2 (Title) or ADGRE2 (Abstract) or mucin-like receptor 2 (Title) or mucin-like receptor 2 (Abstract) and glioma (Abstract)
EMR2 (Title) or EMR2 (Abstract) or ADGRE2 (Title) or ADGRE2 (Abstract) or mucin-like receptor 2 (Title) or mucin-like receptor 2 (Abstract) and glioblastoma (Abstract)
EMR2 (Title) or EMR2 (Abstract) or ADGRE2 (Title) or ADGRE2 (Abstract) or mucin-like receptor 2 (Title) or mucin-like receptor 2 (Abstract) and glioblastoma (Abstract)

The initial search yielded a total of 92 results. After excluding 3 studies not written in English, we further excluded 13 more studies as they were surveys, comments, letters, conference abstracts, or posters, or they were not written in English. This led us to 76 studies, of which two were duplicates; therefore, we retained 74 studies for abstract retrieval. After reading the abstracts, we eliminated 36 studies as they were not related to subject, for example they were not referring to human diseases, or were describing other molecules and the search terms were found in bibliography or described closely related molecules and the term "EMR2" appeared in description of the members of Adenosine Purinergic G Protein-Coupled Receptors (ADPCR) family. Ultimately, 38 studies were included in the review (Figure 1, Table 2).

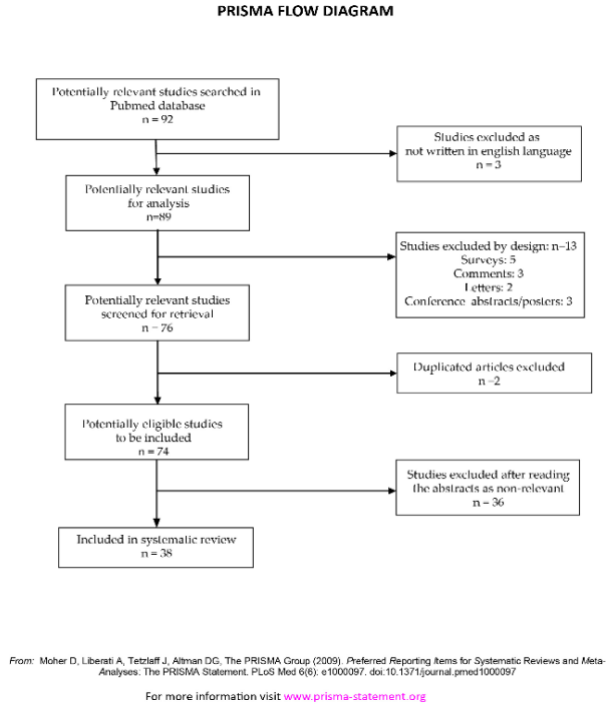

Figure 1. PRISMA flow diagram of the study selection process.

Table 2. Studies included in the review.

Authors	Year	PMID	Main findings
Abbott et al. (2004) [16]	2004	15103144	This study reports the crystallization and preliminary X-ray diffraction analysis of three EGF domains (1, 2, and 5) of EMR2, which binds weakly to the complement regulator CD55. The presence of calcium (Ca^{2+}), barium (Ba^{2+}), and strontium (Sr^{2+}) ions in the crystallization setup demonstrates their potential role in stabilizing the structure of EMR2's EGF domains. Since EMR2's EGF domains closely resemble those in CD97, these structural insights may explain why EMR2 binds CD55 with a lower affinity compared to CD97, despite their high sequence similarity.
Abbott et al. (2007) [17]	2007	17449467	This study characterizes the interaction between CD97, an adhesion GPCR, and CD55, a complement regulatory protein, revealing their role as a T cell receptor co-regulatory complex. CD97-CD55 interactions, mediated by EGF and SCR domains, enhance T cell proliferation and IFN-γ secretion upon activation, showing that CD97-CD55 engagement modulates T cell responses. Structural analyses using crystallography and NMR indicate that the binding interface between CD97 and CD55 is on the opposite side of CD55's complement regulatory site, allowing simultaneous complement regulation and T cell modulation.

Aust et al. (2022) [18]	2022	9101421	aGPCRs control cellular processes closely associated with cancer cell biology, including adhesion and detachment, migration, polarity and guidance. In one of the most severe tumours, dedifferentiated anaplastic thyroid carcinoma, CD97/ADGRE5 was found to be induced. In many tumour entities, including glioblastoma, CD97 appears to be induced or altered.
Beliu et al. (2021) [19]	2021	33497605	This study investigates the structural flexibility of the GAIN domain in adhesion GPCRs and its role in exposing the tethered agonist (TA) without receptor dissociation. Using molecular dynamics (MD) simulations, the researchers demonstrate that specific conformational changes in the GAIN domain unmask the TA, enabling receptor activation while maintaining structural integrity. Bioorthogonal labeling techniques further reveal that TA accessibility varies among adhesion GPCRs, suggesting a common activation mechanism.
Bhudia et al. (2020) [20]	2020	31969668	Using yeast and mammalian cell assays, the authors show that truncated EMR2 and CD97 (lacking the N-terminal fragment) activate G protein signaling, with EMR2 coupling broadly across G protein families, while CD97 shows selective coupling. Additionally, EMR2's inhibition of cAMP and stimulation of IP1 and NFAT-Luciferase signaling in HEK 293 cells further demonstrate G protein activation
Bjarnadóttir et al. (2004) [21]	2004	15203201	This study provides a comprehensive analysis of the adhesion G-protein-coupled receptors (GPCRs) family in humans and mice. The authors identified two new human receptors, GPR133 and GPR144, along with 17 mouse orthologues, expanding the adhesion-GPCR family to 33 human members. Phylogenetic analysis revealed eight subfamilies, with one-to-one orthologue relationships except for EMR2 and EMR3, which lack mouse counterparts. Adhesion-GPCRs are shown to be widely expressed across tissues, including central and peripheral organs, indicating their roles in diverse physiological processes.
Bjarnadóttir et al.(2007) [22]	2006	17056209	This study examines alternative splicing in the adhesion G-protein-coupled receptor (GPCR) family, identifying 53 splice variants across 33 receptors. Of these, 29 variants were classified as functional, maintaining the seven-transmembrane (7TM) domain essential for GPCR activity, while 24 lacked critical domains and were deemed non-functional. Some variants exhibit altered N-terminal domains, impacting ligand binding and receptor interaction. Notably, variants of GPR56 and GPR124 lack the GPS (GPCR proteolytic site) domain, potentially hindering cell surface expression.
Chalise et al. (2022) [23]	2022	35991754	This study investigates a novel combination therapy using cancer-specific anti-podoplanin (PDPN) CAR-T cells (Lp2-CAR-T) and the oncolytic herpes virus G47Δ for glioblastoma. These CAR-T cells demonstrated effective, specific cytotoxicity against PDPN-positive GBM cells and patient-derived glioma stem cells in vitro. When combined with G47Δ, which also initiates an anti-tumor immune response, the therapy showed enhanced tumor inhibition and prolonged survival in a GBM mouse model.
Chang et al. (2003) [24]	2003	12860403	This study investigates the proteolytic cleavage of the EMR2 receptor, focusing on the GPS (GPCR proteolysis site) motif and the extracellular stalk. EMR2 undergoes cleavage at Leu517-Ser518, a process that does not require the transmembrane domain but depends on the GPS motif and an intact stalk. Truncated versions of the stalk or mutations in the GPS motif prevent cleavage, suggesting that the complete stalk provides essential structural support for this process. The cleavage produces a heterodimeric receptor composed of extracellular and transmembrane subunits, enabling functional diversity in EMR2 expression and regulation through alternative splicing.
Chen et al. (2009) [25]	2009	N/A	This study investigates the signaling pathways activated by EMR2, an EGF-TM7 receptor on neutrophils. Upon ligation by the 2A1 monoclonal antibody, EMR2 promotes neutrophil functions such as adhesion, migration, reactive oxygen species release, and degranulation. The authors found that EMR2 activation leads to rapid phosphorylation of MAPKs-p38, ERK, and JNK-indicating that these kinases mediate EMR2's effects. Additionally, EMR2 ligation counters LPS-induced inhibition of spontaneous neutrophil apoptosis, suggesting a role in prolonging neutrophil survival during immune responses.
Davies et al. (2007) [26]	2007	17620333	This study explores how receptor oligomerization affects the expression and function of leukocyte adhesion G protein-coupled receptors (GPCRs), focusing on EMR2. The authors show that EMR2 can form homodimers and heterodimers with related receptors like CD97, mediated solely by its TM7 domain. A unique EMR2 splice variant, EMR2-ΔS, acts as a dominant-negative modulator, reducing the surface expression of full-length EMR2 by dimerizing and promoting degradation. Additionally, heterodimerization between EGF-TM7 family members alters receptor expression and ligand-binding properties, suggesting that receptor oligomerization modulates immune cell receptor function and could impact immune responses
Davies et al. (2011) [13]	2011	21174063	This study investigates EMR2 expression in breast carcinoma, showing that while absent in normal breast tissue, EMR2 is significantly upregulated in ductal carcinoma in situ (DCIS) and invasive breast cancer. EMR2 is detected in both the cytoplasm and nucleus of cancer cells, with cytoplasmic expression correlating with higher tumor grade. Interestingly, nuclear EMR2 expression is associated with improved relapse-free and overall survival, suggesting a protective role.
Feliciano et al. (2017) [27]	2017	29072692	This study identifies EMR2 and E2F2 as novel targets of miR-99a, a microRNA with tumor-suppressive properties in lung cancer. miR-99a downregulation is observed in lung cancer, where its expression suppresses cancer cell proliferation, migration, and invasion, while enhancing cell adhesion. EMR2 and E2F2, which are oncogenically expressed in lung adenocarcinomas, are repressed by miR-99a, leading to apoptosis and cell cycle arrest. Additionally, miR-99a limits cancer stem cell (CSC) features and reduces epithelial-to-mesenchymal transition (EMT) in lung tumors, linking miR-99a to CSC inhibition and EMT suppression.

Hamann et al. (2015) [28]	2015	25713288	This comprehensive review discusses the nomenclature, structure, and functions of adhesion G protein-coupled receptors (aGPCRs), with a focus on their roles in human health and disease. aGPCRs, which include the ADGRE subfamily (e.g., EMR1-4, CD97), are expressed mainly in immune cells, with specific family members serving as markers for different leukocyte subsets. They exhibit diverse functions, such as promoting immune tolerance, aiding in cell migration, and modulating cytoskeletal dynamics. The authors emphasize the therapeutic potential of aGPCRs in inflammatory diseases, cancer, and neuropsychiatric disorders due to their unique structure and role in cell adhesion and migration.
Hamann et al. (2016) [29]	2018	27832495	This review discusses the expression and function of adhesion G protein-coupled receptors (aGPCRs) in immune cells, focusing on the ADGRE and ADGR subfamilies. These receptors, including EMR1, EMR2, CD97, and GPR56, show lineage-specific expression across leukocyte subsets, such as monocytes, macrophages, and dendritic cells, making them useful as immune cell markers. Recent research highlights diverse functions of aGPCRs, such as EMR1's role in tolerance induction, CD97's impact on granulopoiesis, BAI1's involvement in apoptotic cell clearance, and GPR56's regulation of hematopoiesis and cytotoxicity. The review explores the potential for these receptors as therapeutic targets in immune modulation and stem cell biology.
Huang et al. (2018) [30]	2018	29540735	This study investigates how the membrane association of the N-terminal fragment (NTF) of EMR2 is regulated by site-specific N-glycosylation. A small portion of EMR2-NTF independently associates with the membrane due to a unique glycosylation pattern that occurs after the ER, suggesting that N-glycosylation modulates the interaction of an amphipathic α-helix in the GAIN domain with the membrane. The study identifies specific glycosylation sites that impact membrane binding, providing insight into EMR2's complex activation mechanisms, potentially adding diversity to adhesion GPCR signaling.
Ivan et al. (2015) [14]	2015	25200831	There were described EMR2 expression patterns in various histologic grades of gliomas. Genomic data suggested that overexpression of EMR2 is associated with the mesenchymal GBM subtype. In GBM EMR2 displayed diverse isoforms, the highest expressed was of the EGF1–5 isoform. An increase in the expression of EMR2 was observed after treatment with bevacizumab in glioma.
Ivan et al. (2014) [15]	2014	2599223	Describes EMR2 expression patterns in various histologic types of gliomas. Show an association of high EMR2 expression and poor survival.
Komarow et al. (2020) [31]	2020	N/A	This study explores the role of ADGRE2 in mechanosensing, particularly in the context of familial vibratory urticaria (VU), a condition where skin friction causes mast cell (MC) degranulation. The researchers used human mast cells with either wild-type or p.C492Y-mutated ADGRE2, linked to VU, to investigate signaling pathways triggered by mechanical stimulation. Cells with p.C492Y-ADGRE2 showed heightened degranulation in response to vibration, especially when interacting with dermatan sulfate, a natural ligand for ADGRE2. Enhanced calcium influx and PLC activation led to downstream PI3K and MEK/ERK1/2 signaling. While PLC and calcium were crucial for MC degranulation, MEK/ERK1/2 was involved in prostaglandin D2 (PGD2) production, a novel mediator in VU.
Kuan-Yu et al. (2017) [32]	2017	28421075	EMR2 activation promotes the differentiation of the human monocyte cell line THP-1 and the expression of pro-inflammatory mediators, including IL-8, TNF-alpha and MMP-9.
Kwakkenbos et al. (2002) [33]	2002	11994511	This study examines EMR2, highlighting its structural similarity to CD97, differing by only six amino acids within the EGF domain. Despite this similarity, EMR2 shows distinct ligand specificity, as it does not bind CD97's ligand, CD55. Using the 2A1 monoclonal antibody, the authors reveal that EMR2, like CD97, exists as a heterodimeric receptor with separate extracellular and transmembrane components. Expression analysis of EMR2 shows a myeloid-restricted profile, predominantly on mature CD16(+) monocytes, macrophages, and BDCA-3(+) myeloid dendritic cells, with minimal or no expression on granulocytes and lymphocytes.
Kwakkenbos et al. (2004)[34]	2004	14647991	This review discusses the EGF-TM7 family, and highlights the functional roles of these receptors in leukocyte migration, ligand interactions (e.g., CD55 and chondroitin sulfate for CD97 and EMR2), and tissue-specific expression. Additionally, evolutionary insights reveal gene duplication events in the EGF-TM7 family, with specific genes like EMR4 being inactivated in humans.
Kwakkenbos et al. (2005) [35]	2005	15498814	This study investigates the binding of the largest isoforms of CD97 and EMR2 to chondroitin sulfate (CS) on B cells, highlighting a unique ligand specificity for CS-B. Both CD97 and EMR2, members of the adhesion GPCR family, show selective interaction with CS on B cells through their fourth EGF domain, while CD97 can also bind CD55 via other EGF domains.
Kwakkenbos et al. (2006) [36]	2006	17068111	EMR2 shares a chimeric structure, having high similarity with CD97 in its EGF domain and with EMR3 in its transmembrane region. The fourth EGF domain, responsible for chondroitin sulfate (CS) binding, is highly conserved, suggesting evolutionary pressure to maintain this function. Although similar to CD97, EMR2 does not bind CD55 due to species-specific mutations in humans, while chimpanzee EMR2 can still bind CD55.
Lin et al. (2000) [10]	2000	10903844	A new member, EMR2, closely resembles CD97 in structure and gene location on chromosome 19p13.1 but is specifically expressed in monocytes and granulocytes, likely interacting with a unique cellular ligand different from CD55, suggesting a distinct role in immune function.
Lin et al. (2001) [37]	2001	11297558	This study analyzes the protein-protein interactions mediated by the EGF-like domains of CD97 and its binding partner, CD55, both cell surface proteins involved in immune cell interactions. The authors demonstrate that CD97 binds CD55 with low affinity but high avidity, a feature enabled by the calcium-binding EGF domains. CD97's binding to CD55 is shown to depend solely on its EGF domains, without involvement of glycosylation or additional domains, though specific amino acid variations between CD97 and its homolog EMR2 significantly alter binding affinity.
Lin et al. (2004) [38]	2004	15150276	This study elucidates the autoproteolytic cleavage mechanism of the EMR2 receptor at a conserved GPCR proteolytic site (GPS) motif. The cleavage occurs at a specific tripeptide (His-Leu-Ser518) within the endoplasmic reticulum, resulting in two subunits that associate as a heterodimer on the cell surface. The study demonstrates that Ser, Thr, or Cys residues at the cleavage site are essential, while His516 promotes cleavage by facilitating the formation of an ester intermediate.

Mustafa et al. (2005) [39]	2005	15668483	This study examines the expression of CD97 and its ligand CD55 in oral squamous cell carcinoma (OSCC), comparing it to normal oral mucosa. Using UV-laser microdissection and immunohistochemistry, the authors found that CD97 expression is low in normal mucosa but significantly elevated in advanced (pT3/T4, G3/G4) OSCC stages, where it correlates with dedifferentiation. CD55 expression is consistently high in all OSCC stages, potentially enhancing cell adhesion. Treatments with sodium butyrate and retinoic acid reduced CD97 expression while increasing CD55 expression in OSCC cell lines. This study suggests that CD97 is a novel marker for aggressive OSCC, and its interaction with CD55 may promote metastasis and poor prognosis.
Rutkowski et al. (2011) [40]	2011	21503828	EMR2 expression is shown to be associated with poor overall survival in glioblastoma patients. EMR2 levels correlate with increased cell migration, although they do not impact cell proliferation. EMR2 knockdown significantly reduced invasion in glioblastoma cell lines, suggesting that EMR2 promotes an invasive tumor phenotype.
Safaee et al. (2014) [41]	2014	25992231	EMR2 is expressed on immune cells like monocytes and macrophages and binds dermatan sulfate, a glycosaminoglycan, suggesting a role in immune modulation and cell adhesion. Recent studies link EMR2 expression to tumor aggressiveness in glioblastoma and breast cancer, where it correlates with invasion and survival.
Schiöth et al. (2010) [42]	2010	21618822	This study provides an evolutionary overview of the Adhesion GPCR family, unique for its long N-termini with multiple domains. Comparative genomic analysis reveals that most human Adhesion GPCRs have one-to-one orthologues in rodents, dogs, and chickens, with exceptions like EMR2 and EMR3, which lack orthologues in rats and mice. Dogs have a similar Adhesion GPCR repertoire to humans, but with five additional genes, while chickens retain 21 of the 33 human orthologues. Primitive species, such as Branchiostoma and Nematostella, possess a diverse array of Adhesion GPCRs, with Branchiostoma showing novel N-terminal domains like Somatomedin B and TNFR. These findings suggest that the Adhesion GPCR family predates and may have given rise to the Secretin family of GPCRs, indicating a fundamental role in GPCR evolution across vertebrates and invertebrates.
Stacey et al. (2003) [43]	2003	12829604	Chondroitin sulfate is a specific ligand for EMR2, which, mediates cell attachment in a calcium-dependent manner through interaction with sulphated CS glycosaminoglycans (GAGs). This interaction, localized to the fourth EGF-like domain of EMR2, is conserved across species and observed in connective tissues.
Tjong et al. (2019) [12]	2019	31594642	CD97, which contains an RGD motif, promotes angiogenesis and cell invasion by upregulating MMP-9 and N-cadherin expression. In contrast, EMR2 lacks the RGD motif, limiting its angiogenic potential. However, modifying EMR2 to include RGD enhances MMP-9 expression and angiogenic activity. MMP-9 drives endothelial cell proliferation, migration, and invasion, partly by increasing pro-angiogenic factors like VEGF and bFGF.
Wandel et al. (2012) [44]	2012	22210915	This study identifies Thy-1 (CD90) as a novel interaction partner for the adhesion GPCR CD97 on activated endothelial cells (EC), highlighting its role in immune cell adhesion. In psoriatic skin lesions, CD97 on polymorphonuclear cells (PMNC) binds to Thy-1 on activated EC, facilitating leukocyte recruitment. Adhesion assays show that PMNC expressing high CD97 levels exhibit stronger adherence to Thy-1+ EC, an effect partially blocked by antibodies targeting CD97 or Thy-1. The CD97-Thy-1 interaction is mediated through the CD97 stalk, with binding unaffected by calcium, suggesting a distinct binding mechanism.
Warnecke-Eberz et al. (2016) [45]	2016	26631031	This study identifies a diagnostic gene signature for esophageal cancer, focusing on esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). Using transcriptome analysis, the authors identified 4844 genes with differential expression between tumor and normal tissues. From these, 23 genes were selected based on overexpression, including immune-related markers like EMR2, PRAME, and MMPs. Verification in a larger patient cohort confirmed the overexpression of these genes in both ESCC and EAC, including early-stage cancers. A diagnostic panel of 19 markers was proposed for potential clinical application, with many markers detectable via non-invasive blood tests.
Yona et al. (2008) [11]	2008	17928360	EMR2 ligation enhances neutrophil adhesion, migration, superoxide production, and degranulation in response to pro-inflammatory mediators. Notably, EMR2 expression is significantly elevated in neutrophils from patients with systemic inflammatory response syndrome (SIRS), indicating its potential role in inflammatory diseases. The study demonstrates that EMR2 activation at its stalk region augments neutrophil responses by engaging pleiotropic signaling pathways, suggesting that EMR2 may be a key player in inflammatory processes and a potential therapeutic target in conditions like sepsis.

Results

Quality assessment

This review is based on observational and experimental studies, clinical or preclinical studies, and assumes a risk of bias. The comparability between studies, which is linked to the transferability of study results, can be impaired by several issues.

The first studies included human individuals as well as cell lines, which weakened comparability. Second, the populations studied differed in sample size, observation periods, study methods, and treatments.

Furthermore, we excluded non-English studies that could have included important information.

Additionally, we searched only a few databases for eligible studies, but other databases could include other studies that were not retrieved. For these reasons, this systematic review cannot be free of bias; thus, interpretations of the results of the current review are limited.

Studies included in the review

The 38 studies that remained after the selection process are summarized in Table 2.

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Molecular structure

The EMR2 protein structure was elucidated using X-ray crystallography and in silico simulations [16,24].

EMR2, like its family members, has an extracellular region containing N-terminal EGF-like domains linked with a 7-span transmembrane (TM7) domain closely related to EMR3, connected by a stalk [16] (Figure 2).

The EGF domain region of EMR2 differed slightly from that of CD97, altering its ligand specificity.

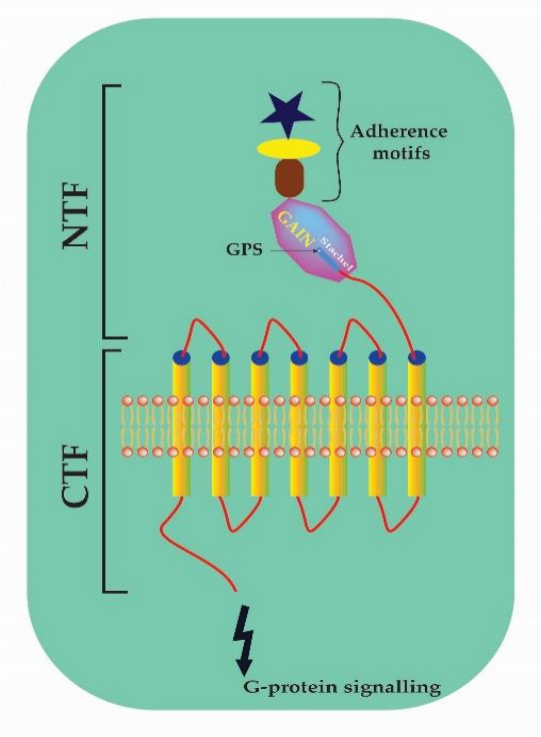

Figure 2. Structure of EMR-2 receptor. It is composed from a N-terminal fragment (NTF) and C-terminal fragment (CTF). Autoproteolysis at GPS site cleaves the receptor into CTF and NTF. CTF will have after proteolysis a new N-terminal sequence designated as Stachel peptide. NTF contains adherence motifs linked to a GAIN domain that contains the GPS autoproteolysis situs. After ligand binding a conformational change occurs which trigger downstream G protein signaling.

The N-terminal EGF-like domains contain tandem repeats and are subjected to variations owing to alternative splicing [17].

EGF-like domains mediate cell-cell interactions [10].

The stalk region contains multiple glycosylation sites, among which are many serine and threonine residues. Consequently, the stalk region is highly glycosylated and performs similarly to the mucin-like domain with a rigid structure [17].

The terminal part has a G protein-coupled receptor proteolysis site (GPS), also called the GAIN domain (GPCR Autoproteolysis Inducing).

The GAIN domain undergoes autoproteolytic cleavage. This process results in the division of receptors into two distinct non-covalently associated subunits referred to as protomers.

Recent scientific investigations have shown that the signaling activity of aGPCRs is predominantly governed by alterations in the interplay between these protomers [5,17,18].

The proteolytic cleavage of EMR2 at its highly conserved GPS motif in the membrane-proximal region is crucial for its function.

Cleavage occurs independently of the transmembrane segments, and a minimum of eight amino acids in the β-subunit are necessary for non-covalent binding between the resulting extracellular α-subunit and transmembrane β-subunit.

Alternative splicing can regulate this cleavage, resulting in receptors with different structures [19,20].

Truncated EMR2 and CD97 (lacking the N-terminal fragment) activate G protein signaling, with EMR2 coupling broadly across G protein families [20,21].

Expression pattern

EMR2 was shown to be expressed in lung adenocarcinomas, in correlation with β-catenin [22], in oral squamous cell carcinoma (OSCC), and esophageal cancer [23].

Ivan *et al.* [15] described patterns of EMR2 expression in glioma with various histologic grades and showed a correlation between EMR2 and the PI3K pathway, as both are upregulated in glioblastoma after therapy with bevacizumab (an anti-VEGF monoclonal antibody). The PI3K-Akt pathway is critical for cell survival, and its activation presumably leads to tumorigenesis [24].

In various cancers, upregulation of PI3K, an upstream regulator of Akt, and conversely, negative regulators of this pathway, such as PTEN, have tumor suppressor activity. Upregulation of EMR2 may in turn upregulate PI3K, leading to an invasive potential of tumor cells through selective advantage compared with cells without EMR2 upregulation [14].

Genomic data suggests that overexpression of EMR2 is associated with the mesenchymal GBM subtype [25].

In GBM, EMR2 displays diverse isoforms, with the highest expression of the EGF1-5 isoforms [14,15,26].

EMR2 is also expressed on dendritic cells, macrophages, granulocytes, and monocytes [27], is linked with the migration and activation of neutrophils, and increases the production of pro-inflammatory cytokines such as IL-8, TNF-α, and MMP-9.

Regulation

EMR2 is downregulated by miR-99a [22].

In lung cancer, the receptor EMR2 is activated by interaction with ATP-dependent RNA helicase DDX5 and modulates the transcription factor Forkhead box protein L1, which is essential for appropriate proliferation and differentiation, and its function is influenced by histone deacetylase 9.

This deacetylase plays a crucial role in removing acetyl groups from lysine residues in the N-terminal region of core histones, which is vital for the regulation of transcription, cell cycle progression, and developmental processes.

It exerts a positive regulatory effect on NF1, which is involved in cell proliferation and mobility. This regulation occurs through the mediation of CHD3 and AGR3 proteins in their respective signaling pathways [28] (Figure 3).

Activation of EMR2 induces inflammatory responses and macrophage differentiation via the Gα16/Akt/MAPK/NF-κB signaling pathway [27].

EMR2 is a binding partner of CD97 (ADGRE5), which is widely expressed by stromal cells [27] and is coupled with Gαs, Gαq, Gαi/o, or Ga12/13 proteins. The single known ligand is chondroitin sulfate, and its binding is mediated by the fourth EGF domain [12].

Biological functions

EMR2 has been shown to regulate neutrophil function, including adhesion, migration, production of reactive oxygen species (ROS), and degranulation. Targeting EMR2 with antibodies targeting its N-terminus leads to the enhancement of neutrophil function, which can be used in severe infections. EMR2 mutations are also involved in vibratory urticaria and vibration/stretching/friction [29,30].

Closely related EMR3/ADGRL3 are involved in enhancing the antibacterial activity of granulocytes and have a priming effect on polymorphonuclears that prepare them for antibacterial functions [31].

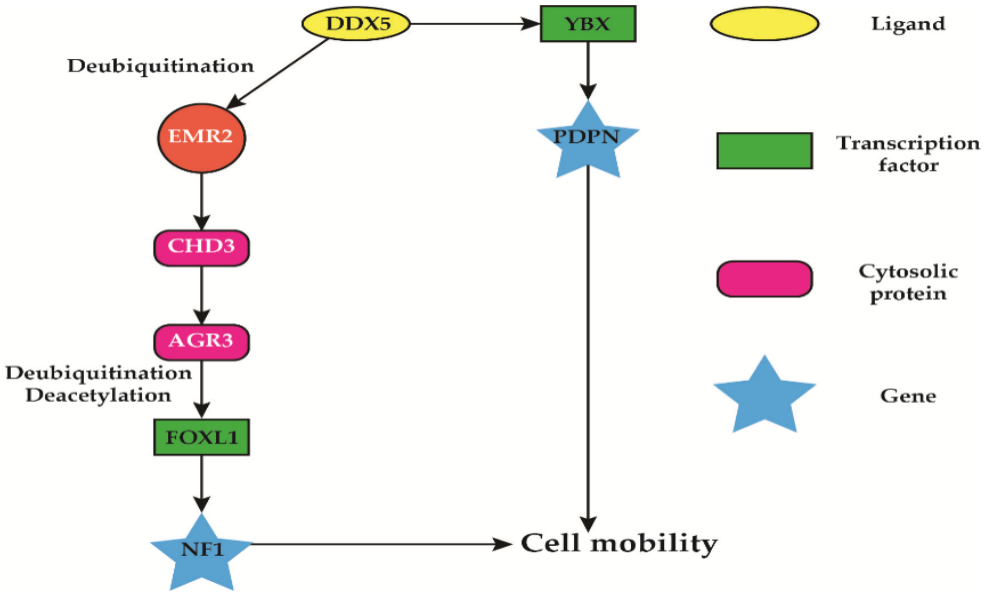

Figure 3. Involvement of EMR2 in Wnt/β-catenin signaling pathway. EMR2: Epidermal growth factor module-containing mucin like receptor 2. DDX5: DEAD box protein 5. CHD3: Chromodomain-helicase-DNA-binding protein 3. AGR3: Anterior gradient protein 3. FOXL1: Forkhead box protein L1. NF1: neurofibromatosis type 1. YBX: Y-box protein. PDPN: podoplanin gene.

Functions in cancer

In cancer, there are many reports of alterations in the homeostasis of adhesion GPCRs involved in tumor cell migration and invasion.

Higher levels of EMR2 expression were correlated with reduced survival rates among patients with glioma [14,15,32] (Figure 4).

Closely related family members, such as CD97, have been shown to promote the invasion and metastasis of tumor cells and are associated with the invasive phenotype of GBM [33,34].

EMR-3 was shown to potentiate invasion in GBM [35].

Studies have shown that an antibody targeting the extracellular domain of EMR2 promotes neutrophil adhesion and migration, guided by CXCL12 *in vitro* [36].

CD97, a closely related adhesion receptor, has been demonstrated to interact with endothelial cell integrins through an Arginine-Glycine-Aspartic acid (RGD) motif, resulting in the promotion of angiogenesis [37].

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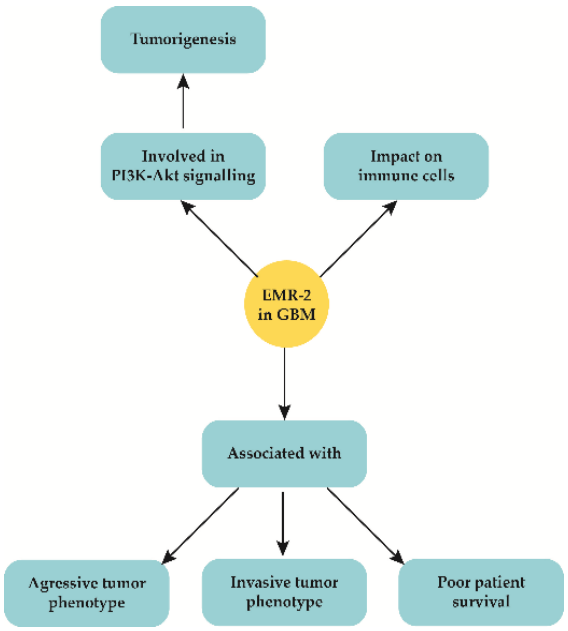

Figure 4. Implications of EMR2 in glioblastoma. EMR2: Epidermal growth factor module-containing mucin like receptor. PI3: Phosphoinositide 3-kinases. Akt: Alpha serine/threonine kinases. GBM: Glioblastoma.

Sarkar *et al.* showed that compromised microglia, macrophages and monocytes from the malignant gliomas can be reactivated by amphotericin-B and impair the growth of brain tumors, and also demonstrated that meclocycline increase the activity of microglia in culture and stimulates monocytes to inhibit tumor initiating cells through down-regulation of EMR2 gene, among others [38].

Antibodies against EMR2 can be linked to cytotoxic drugs, thereby delivering them to EMR2 expressing cells and inhibiting angiogenesis [39].

Novel combination therapy using cancer-specific anti-podoplanin (PDPN) CAR-T cells (Lp2-CAR-T) and the oncolytic herpes virus G47Δ for glioblastoma. *In vitro* experiments showed that these chimeric antigen receptor T cells exhibited potent and targeted cytotoxic effects against glioblastoma multiforme cells expressing podoplanin [40].

A recent study identified Thy-1 (CD90) as a novel interaction partner for the adhesion of GPCR CD97 and possibly EMR2. In psoriatic skin lesions, CD97 on polymorphonuclear cells (PMNC) binds to Thy-1, facilitating leukocyte recruitment.

CD97-Thy-1 interaction is mediated through the CD97 stalk, with binding unaffected by calcium, suggesting a distinct binding mechanism.

Conclusions

The evidence presented in this review supports the notion that tumors expressing EMR2, especially glioblastomas, exhibit an enhanced ability to spread invasively. This is corroborated by studies showing increased EMR2 expression in higher-grade gliomas, with EMR2 overexpression linked to poor survival rates across all glioma grades.

As classic targets for anti-cancer drugs, such as the p53 and retinoblastoma pathways and epidermal growth factor receptor gene alterations, have faced challenges due to complex regulatory networks, this review highlights a novel target for treating gliomas, especially IDH-wild type glioblastoma, because of their high expression in multiple solid tumors, including GBM.

The findings summarized in this review can motivate future research to explore whether EMR2 regulation influences the progression, treatment resistance, and increasingly aggressive recurrences of gliomas, and could provide valuable insights into the clinical course of these tumors. The receptor can be both blocked and activated using targeted monoclonal antibodies [25], leading to numerous possibilities for its modulation in cancer therapy [39].

Conflict of interest

None to declare.

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