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Review

Matrix Remodeling Associated Genes (MXRAs): structural diversity, functional significance, and therapeutic potential in tumor microenvironments

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Received: 22 January 2025 / Accepted: 16 May 2025
Published online: 20 May 2025

Abstract
The Matrix Remodeling Associated Genes (MXRAs) family, comprising eight distinct members (MXRA1-8), plays a crucial role in the development and maintenance of higher vertebrate cells. These proteins are primarily involved in the regulation of intercellular adhesion and the remodeling of the extracellular matrix (ECM). Recent investigations have highlighted the significant roles of MXRAs in the modulation of tumor growth and progression, establishing them as vital components in the oncogenic landscape. Notably, each MXRA member exhibits unique structural characteristics and functional properties, contributing to a diverse array of regulatory effects within the tumor context. This review seeks to provide a comprehensive analysis of the structural attributes, functional contributions, and activities of MXRAs within the tumor microenvironment. By elucidating the underlying mechanisms of action, this paper aims to offer novel insights and strategic approaches for the identification of early diagnostic biomarkers, as well as potential therapeutic targets that may facilitate molecular interventions aimed at inhibiting tumor development.

Keywords MXRAs · Tumor · Matrix remodeling · Cell adhesion

1 Introduction

Cell-to-cell adhesion and extracellular matrix (ECM) remodeling are critical processes that define the complex landscape of tumor biology. In normal tissue, cells establish robust intercellular connections with neighboring cells and absorb mechanical and biochemical signals from the stroma, facilitated by the expression of various adhesion proteins. However, in the transition from normal to malignant states, tumor cells often exhibit a marked departure from these conventions. This deviation is characterized by a loss of reliance on intercellular connections, which enables tumor cells to detach from the parental tissue and enter a state of exfoliation [1, 2]. This non-adhesive property is a double-edged sword; On the one hand, reduced adhesion enables escape from the primary tumor mass and facilitates dissemination through the circulatory system (blood or lymph) to seed distant sites; on the other hand, this reduced adhesion also renders

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these circulating tumor cells (CTCs) vulnerable. Without proper anchorage, they face increased susceptibility to anoikis (detachment-induced apoptosis) or destruction by immune cells, significantly limiting their ability to successfully colonize and form metastases. [3]. Therefore, the intricate relationship between cell adhesion mechanisms and the maintenance of tissue integrity becomes crucial in understanding tumor dissemination and progression.

In parallel, tumor cells exhibit a remarkable capacity to modify the composition and architecture of the ECM—a complex network of proteins, glycoproteins, and polysaccharides that encapsulate the cellular microenvironment. The process of ECM remodeling enables tumor cells to sculpt the tumor microenvironment (TME) to their advantage, creating a niche that supports their growth, survival, and capability to metastasize [4, 5]. Within this context, the TME is not merely a passive backdrop, but rather an active participant in tumor development, influencing features such as cellular proliferation, migration, and immune evasion. The interplay between tumor cells, the ECM, and various stromal constituents, including immune cells and fibroblasts, orchestrates a complex signaling ecosystem that ultimately dictates tumor progression and therapeutic outcomes.

Recent research has unveiled pivotal insights regarding a group of genes that play a crucial role in mediating cell adhesion and ECM dynamics. Specifically, Walker and Volkmuth's groundbreaking work in 2002 identified a family of genes termed Matrix Remodeling Associated Genes (MXRAs), encompassing members MXRA1 through MXRA8 [6]. These genes emerged from an analysis of transcriptome data co-expression across human cDNA libraries, highlighting their significance in coordinating essential biological processes linked to cell adhesion, matrix remodeling, inflammation, immune infiltration, angiogenesis, and the cyclical phenomena of matrix formation and degradation [7–12]. The MXRAs function as molecular architects in the TME, influencing not only the structural integrity of the matrix but also the signaling pathways that govern the behavior of adjacent cells.

The identification and characterization of MXRAs offer an avenue for understanding how cellular adhesion and ECM remodeling dynamically interact during tumor development. With a focus on their structural attributes, biological functions, and cutting-edge research findings, this paper significantly expands on the interwoven roles of MXRAs, cell adhesion, ECM remodeling, and the TME. A comprehensive analysis of these interconnected dimensions promises to elucidate the molecular mechanisms that drive tumor progression and metastasis, offering critical insights that could pave the way for novel therapeutic strategies targeting these interactions. Ultimately, understanding the synergy between MXRAs and other components of the TME will enhance our grasp of tumor biology and could inform innovative interventions to disrupt the cancerous trajectory.

2 Molecular properties of the MXRAs family

There is no homology between the gene and protein sequences of MXRAs family members (Fig. 1, Table 1). Consequently, this lack of homology leads to distinct structural and functional characteristics for each member of the family (Fig. 2).

2.1 MXRA1

MXRA1, also known as ATP2B4 or PMCA4, is a gene located on chromosome 1 at 1q32.1, spanning approximately 11.7 kb. The gene comprises 22 exons and 21 introns and encodes a protein predominantly localized to the cell membrane of eukaryotic cells. This protein functions as a crucial plasma membrane calcium ATPase with a molecular weight of approximately 138 kDa. Notably, the C-terminal region of MXRA1 contains a PDZ-binding motif (PBM) and a calmodulin-binding domain (CBD) [13].

The PBM within MXRA1 acts as a ligand for PDZ domains, facilitating interactions with various proteins, including neuronal nitric oxide synthase (nNOS), calmodulin-dependent membrane-associated kinase (CASK), Homer 1, PMCA-interacting single PDZ domain protein (PISP), and PDZ and LIM domain protein 1 (PDLIM1). These interactions allow MXRA1 to modulate calcium signaling pathways in vivo [14–16]. Conversely, the CBD of MXRA1 is its primary functional domain, enabling interactions with calmodulin and playing a critical role in regulating calcium ion activity [17]. These functional domains highlight the significance of MXRA1 in maintaining both intracellular and extracellular calcium homeostasis, particularly in the context of calcium-dependent cell signaling and the regulation of calcium equilibrium in hematopoietic cells [18–20].

Furthermore, studies have demonstrated that MXRA1 inhibits the Calcineurin (CaN)/nuclear factor of activated T cells (NFAT) pathway, leading to a downregulation in the expression of vascular endothelial growth factor (VEGF)-related

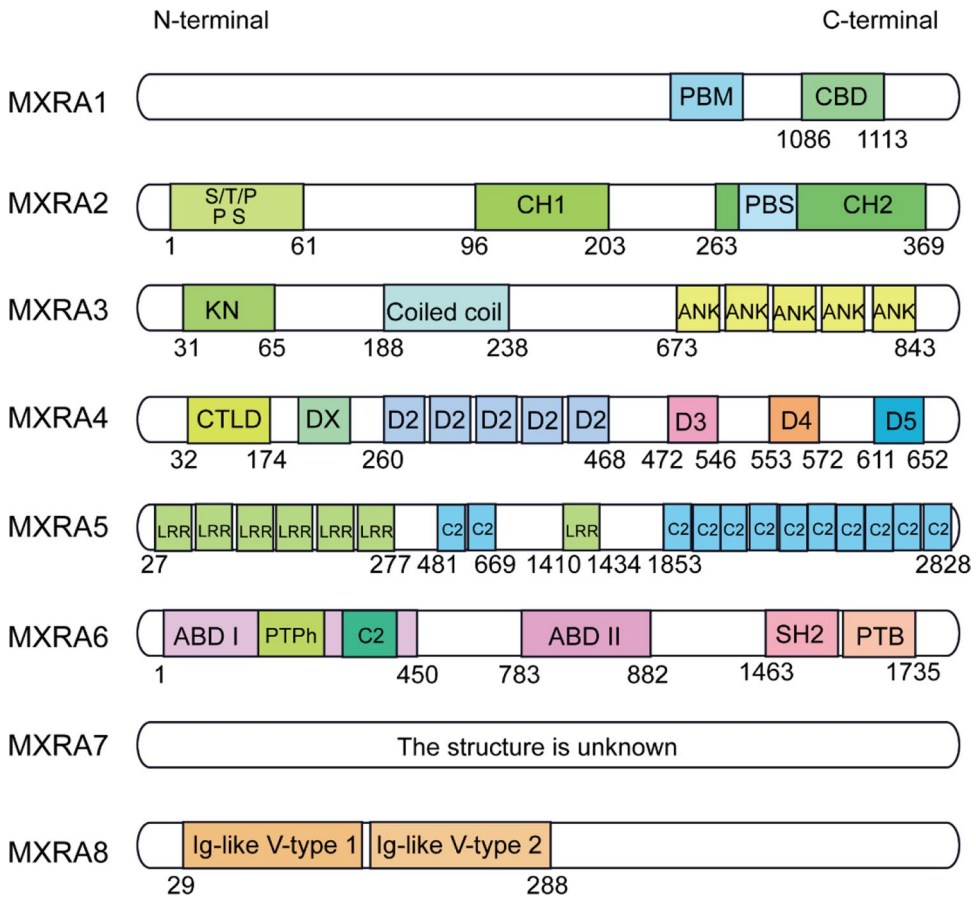

Fig. 1 The domain diagram of MXRAs. MXRA1 features a C-terminal PDZ-binding motif (PBM) and calmodulin-binding domain (CBD); MXRA2 possesses C-terminal tandem atypical calmodulin-homologous domains (CH1/CH2) and an N-terminal region with cyclin B1/Cdc2 phosphorylation sites, a tyrosine phosphorylation site, and PKC/CK2 phosphorylation sequences; MXRA3 contains a unique N-terminal KN motif and KANK, with a C-terminal region including ANKs and a coiled-coil domain; MXRA4 is structurally organized from N- to C-terminus with CTLD (D1), EGF-like domains (D2), a mucin-like domain (D3), a transmembrane domain (D4), a cytoplasmic domain (D5), and a domain DX; MXRA5 contains leucine-rich repeats (LRRs) and immunoglobulin-like C2-type domains for protein interactions and recognition; MXRA6 is composed of an N-terminal ABD I region (protein tyrosine phosphatase/C2), a central ABD II region, and a C-terminal region (SH2/PTB domains); MXRA7 is an ECM component with incompletely understood structure and function; and MXRA8 features an extracellular domain of double N-terminal V-type Ig-like domains, a transmembrane domain, and a short cytoplasmic domain

proteins RCAN1.4 and COX-2. This inhibitory effect on the pathway consequently impairs angiogenesis in vivo [21]. The multifaceted roles of MXRA1 in calcium homeostasis and cellular signaling underscore its importance in both cellular physiology and pathophysiology.

2.2 MXRA2

MXRA2, also known as Actopaxin or PARVA (alpha-parvin), is a gene located on chromosome 11 at 11p15.3, spanning approximately 15.9 kb and comprising 13 exons and 12 introns. The MXRA2 gene encodes a protein belonging to the focal adhesion (FA) protein family, with a molecular weight of approximately 42 kDa. It exhibits ubiquitous expression in various cell types and tissues. Notably, the C-terminal region of MXRA2 contains two atypical calmodulin-homologous domains, CH1 and CH2, arranged in tandem [22].

The CH2 domain within the C-terminal region of MXRA2 plays a critical role in binding to integrin-linked kinase (ILK), forming a complex that activates integrin signaling. This activation initiates actin cytoskeleton remodeling, thereby modulating cell adhesion, migration, and actin-dependent cell morphological changes [23–26]. Furthermore, the CH2 domain contains a conserved paxillin-binding subdomain (PBS) and binding sites for key target molecules [24]. Through binding to the LD motif in paxillin, the PBS subdomain facilitates the connection between integrins and the ECM, promoting actin cytoskeleton formation, cell adhesion, and cell motility [27, 28]. Conversely, the absence of the C-terminal

Table 1 Brief summary of information of MXRAs

Gene ID	Aliases	Gene length	Location	molecular weight	Domains	Biological functions	References
MXRA1	ATP2B4, PMCA4	11.7 kb	1q32.1	138 kDa	PBM, CBD	Calcium signaling, calcium homeostasis, angiogenesis	[13]
MXRA2	Actopaxin, PARVA, α-parvin	15.9 kb	11p15.3	42 kDa	CH1, CH2, N-terminus	Reconstruction of actin cytoskeleton, cell adhesion and diffusion, cell migration, formation of pseudopods	[22, 30]
MXRA3	KANK2	3.4 kb	19p13.2	91 kDa	KANK, ANKs, Coiled coil	Cell adhesion, cell migration, angiogenesis, anti inflammation	[37]
MXRA4	CD93	7.0 kb	20p11.21	69 kDa	D1, D2, D3, D4, D5, DX	C1q receptor, reconstruction of actin cytoskeleton, cell adhesion, angiogenesis, promotes inflammation	[44]
MXRA5	Adlican	38.1 kb	Xp22.33	312 kDa	LRR, C2	Cell proliferation, cell invasion, anti inflammation, anti fibrosis	[10]
MXRA6	TNS1	234.4 kb	2q35	197 kDa	ABD I, ABD II, SH2, PTB	Cell growth, polarization, and migration, cell proliferation	[60]
MXRA7	/	38.4 kb	17q25.1	22 kDa	/	Matrix remodeling, osteoinduction, angiogenesis, wound healing, promotes inflammation	[67]
MXRA8	DICAM	10.9 kb	1p36.33	49 kDa	V-type Ig like domain, Transmembrane domain, Short cytoplasmic domain	Cell adhesion, differentiation of osteoclasts, angiogenesis, anti inflammation	[72]

The table shows gene aliases, gene length, chromosome location, size of protein products, domain, and function of specific MXRAs

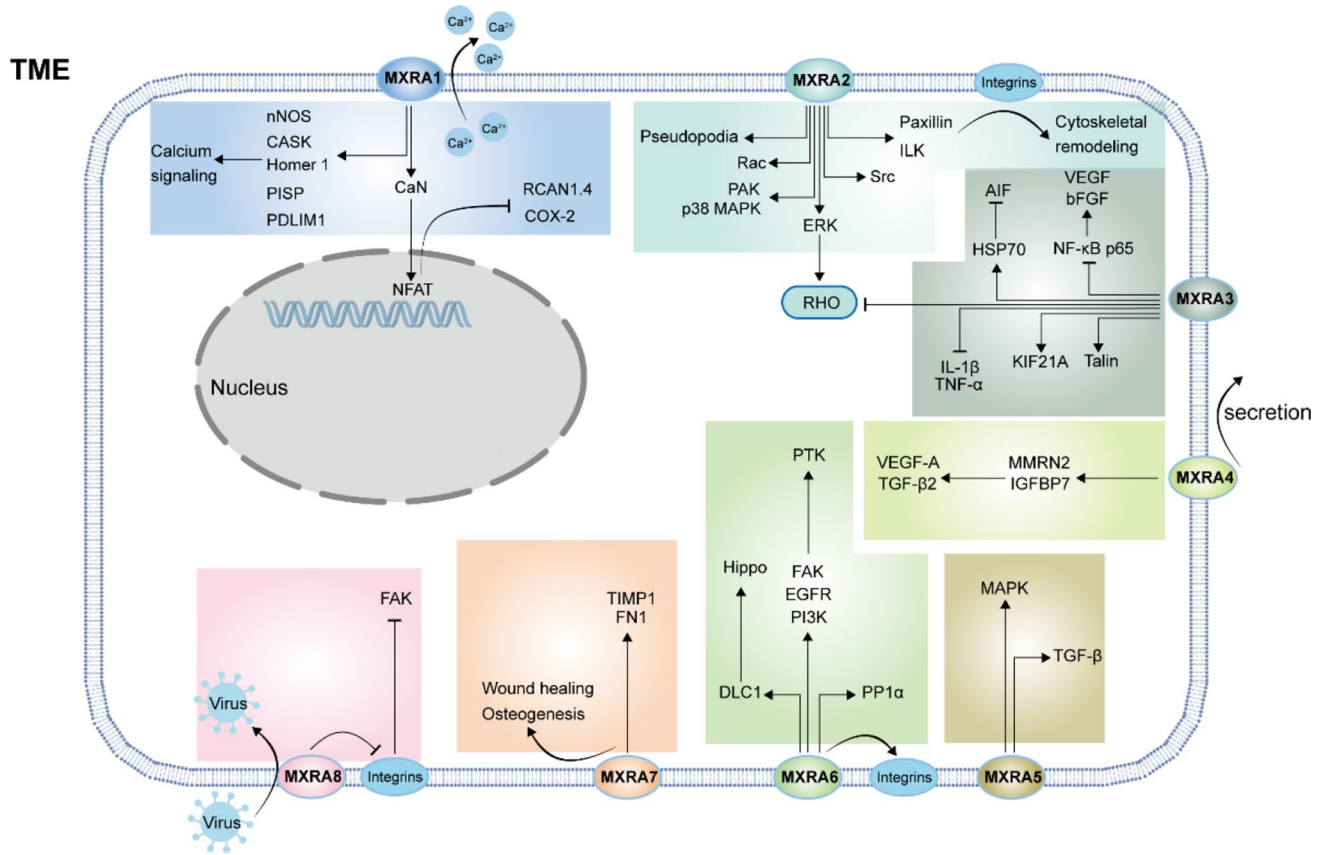

Fig. 2 Biological function of MXRAs. MXRA1, through its C-terminal PDZ-binding motif (PBM) that interacts with proteins like nNOS, CASK, Homer 1, PISP, and PDLIM1 to modulate calcium signaling, and its calmodulin-binding domain (CBD) that regulates calcium ion activity via calmodulin interaction, maintains intracellular and extracellular calcium homeostasis, inhibits the Calcineurin (CaN)/nuclear factor of activated T cells (NFAT) pathway (downregulating RCAN1.4 and COX-2 to impair angiogenesis); MXRA2, through its C-terminal CH2 domain that binds integrin-linked kinase (ILK) to activate integrin signaling, remodel the actin cytoskeleton, and modulate cell adhesion/migration (via a conserved paxillin-binding subdomain (PBS) interacting with paxillin's LD motif to connect integrins and ECM, an absence of the C-terminal fragment impairs MXRA2 function); and its N-terminal region containing cyclin B1/Cdc2 phosphorylation sites, a tyrosine phosphorylation site, and PKC/casein kinase II phosphorylation sequences activated by the ERK pathway to regulate Rho family signaling and cell spreading/movement/migration (inhibited by MEK1 inhibition via UO126), directly interacts with Rac (deficiency augmenting Rac activation and lamellipodia formation) and activates Src or promotes phosphorylation of p21-activated kinase (PAK) and p38 MAPK to degrade ECM and initiate metastasis; MXRA3 modulates cell migration by forming an MXRA3-talin complex (KN motif-mediated interaction with talin's R7 domain) that is recruited to adhesion plaques (β-integrins) to induce structural modifications and competitively inhibit integrin-actomyosin interactions (reducing adhesion strength/traction), recognizes KIF21A (ANK domains) to inhibit microtubule growth and influence cell transport/cytoskeleton maintenance/cellular development, regulates Rho GTPase activity (reducing podocyte migration by increasing GTP-bound RhoA), inhibits NF-κB p65 while enhancing VEGF/bFGF expression to benefit myocardial infarction, suppresses inflammation in a Parkinson's disease astrocyte model (reducing TNF-α/IL-1β secretion, decreasing oxidative stress, and enhancing antioxidant enzyme activity), and attenuates apoptosis in sepsis-related acute lung injury by interacting with HSP70 to inhibit AIF release. MXRA4, existing in soluble form (secreted by HUVECs as a serum complement C1q receptor) and membrane-bound form, exhibits pro-angiogenic capabilities by forming complexes with MMRN2 or IGFBP7 to activate VEGF-A/TGF-β2 signaling pathways and enhance tumor angiogenesis; MXRA5, activating the MAPK signaling pathway to promote cell proliferation and invasion in osteoarthritis cartilage/synovial fluid, appears to protect against kidney tissue injury by promoting an anti-inflammatory/anti-fibrotic response (linked to the TGF-β pathway by inhibiting chemokine/fibronectin expression to alleviate inflammation/fibrosis); MXRA6, with key functional SH2/PTB domains that bind tyrosine-phosphorylated proteins (PI3K, EGFR, FAK) to initiate PTK-mediated signaling for cell growth/polarization/migration and interact with integrin β subunits to modulate cell adhesion/migration/proliferation, regulates Rho GTPase activity by interacting with DLC1 to activate the Hippo signaling pathway (impacting cell proliferation/EMT/tumor progression), interacts with PP1α via the ABD I region to govern cell polarization/migration/invasion, and potentially influences cytoskeletal organization/membrane dynamics/intracellular signaling; MXRA7 modulates inflammatory responses (exacerbating liver injury by enhancing matrix remodeling genes FN1/TIMP1), and regulates other physiological processes (inhibiting corneal neovascularization/promoting skin wound healing); MXRA8, with its extracellular domain facilitating intercellular adhesion by interacting with integrin αvβ3 (directly impeding integrin αv/β3 heterodimerization, with genetic deletion upregulating osteoclast-related Ig-like receptors/integrin αvβ3 and negatively modulating osteoclast differentiation), suppresses integrin αvβ3/FAK signaling and inhibits angiogenesis upon overexpression in HUVECs, and functions as a key receptor for arthritis-causing alphaviruses by interacting with viral E2-E1 heterodimers to promote viral entry

fragment impairs the binding of MXRA2 to downstream targets, ultimately impeding its function [29]. The N-terminal region of MXRA2 contains six cyclin B1/cell division cycle 2 (cdc2) phosphorylation sites (serine/threonine/proline), a tyrosine phosphorylation site, and multiple binding sequences for protein kinase C and casein kinase II phosphorylation [22]. Activation of the N-terminal region is typically mediated through the extracellular signal-regulated kinase (ERK) pathway, leading to the subsequent activation of Rho family signaling and the regulation of cellular processes like cell spreading, movement, and migration [9, 31].

Interestingly, inhibition of mitogen-activated protein kinase kinase 1 (MEK1), a key regulator of the ERK signaling cascade, using the specific inhibitor UO126 has been shown to significantly suppress MXRA2 activity and impair cell migration [31]. Notably, cell migration relies on the critical processes of pseudopod protrusion and extension [32], and MXRA2 influences migration by modulating the length and density of pseudopods [33–35].

Additionally, MXRA2 directly interacts with Rac, and its deficiency augments Rac activation, leading to increased formation of lamellipodia [36]. Furthermore, MXRA2 plays a role in ECM degradation by activating the Src signal or promoting the phosphorylation of p21-activated kinase (PAK) and p38 MAPK, which are downstream effectors of Rac1. These regulatory mechanisms are implicated in initiating tumor metastasis [9]. The multifaceted functions of MXRA2 highlight its importance in various cellular processes, particularly in cell adhesion, migration, and metastasis.

2.3 MXRA3

MXRA3, a gene located on chromosome 19 at 19p13.2, spans 3.4 kb and comprises 13 exons and 12 introns. This gene encodes a protein belonging to the integrin-adhesion complex (IAC) family, with a molecular weight of approximately 91 kDa. MXRA3 is predominantly expressed in podocytes and is characterized by a unique N-terminal region containing a conserved KN motif and ankyrin repeat domains (KANK). The C-terminal region includes five ankyrin repeat sequences (ANKs) and a central coiled-coil domain [37].

In the context of cell migration, MXRA3 plays a critical role in the formation of the MXRA3-talin complex through an interaction with the R7 domain of talin, specifically mediated by the KN motif. This complex is subsequently recruited to adhesion plaques by β-integrins, inducing structural modifications within the adhesion plaque and reducing cell migration rates [38]. Furthermore, the MXRA3-talin complex competitively inhibits the interaction between integrins and actomyosin, diminishing adhesion strength and traction, which consequently reduces the speed of cell migration [38]. Additionally, MXRA3 can recognize KIF21A through its ANK domains, facilitating the recruitment of KIF21A to the cellular cortex. This inhibits microtubule growth and influences various cellular processes such as cell transport, cytoskeleton maintenance, and cellular development [39]. Moreover, MXRA3 has been identified as a regulator of Rho GTPase activity. Reduction of MXRA3 in podocytes leads to an increase in the GTP-bound form of RhoA, resulting in decreased migratory behavior of podocytes [40].

Studies by Li et al. demonstrated that MXRA3 may inhibit the activation of NF-κB p65 while enhancing the expression of VEGF and bFGF in the infarct area and its vicinity in a rat model of myocardial infarction. This increase in capillary density, a process also relevant to tumor angiogenesis, has been shown to be beneficial in treating myocardial infarction [41].

Furthermore, in an astrocyte model of Parkinson's disease, MXRA3 was shown to function as a suppressor of inflammation by reducing the secretion of inflammatory cytokines such as TNF-α and IL-1β, decreasing oxidative stress, and enhancing the activity of antioxidant enzymes [42]. Given the well-established link between chronic inflammation and cancer development, these findings suggest a potential role for MXRA3 in modulating the tumor microenvironment. Similarly, in cases of sepsis-related acute lung injury, downregulation of MXRA3 exacerbates apoptosis and tissue damage. Conversely, the interaction of MXRA3 with heat shock protein 70 (HSP70) attenuates the release of apoptosis-inducing factor (AIF), thereby inhibiting apoptosis [43]. The regulation of apoptosis is a critical factor in both tumor development and response to therapy, highlighting the potential relevance of MXRA3's anti-apoptotic function in cancer.

2.4 MXRA4

MXRA4, a gene spanning 7.0 kb, is located on chromosome 20 at 20p11.21. It comprises two exons and one intron. MXRA4 encodes a type I single transmembrane glycoprotein, also known as the cell membrane surface molecule CD93, with a molecular weight of approximately 69 kDa. Structurally, MXRA4 features several distinct domains from the N-terminus to the C-terminus, including one C-type lectin-like domain (CTLD) D1, five EGF-like domains D2, one mucin-like domain D3, one transmembrane domain D4, one cytoplasmic domain D5, and a domain DX located between D1 and D2 [44].

In vivo, MXRA4 exists in two discernible forms: soluble MXRA4 and membrane-bound MXRA4. The soluble form is predominantly secreted by human umbilical vein endothelial cells (HUVECs) into the plasma, functioning as a receptor for serum complement C1q [45]. Conversely, the membrane-bound MXRA4 is prominently expressed in endothelial cells and plays a critical role in the tumor ECM, facilitating cell adhesion within tumors and the clearance of apoptotic cells. Moreover, while MXRA4 directly influences the pathophysiology of various inflammatory conditions, making it a valuable biomarker [46–48], these inflammatory processes are also often dysregulated in the tumor microenvironment, highlighting the potential for MXRA4 to contribute to cancer-related inflammation. Studies have evidenced increased MXRA4 expression in the synovial fluid of patients with rheumatoid arthritis and in the skin of individuals with psoriasis [49, 50]. However, it's important to note that similar inflammatory signaling pathways are often activated in cancer, suggesting that these findings may have implications for understanding MXRA4's role in tumor progression. Deletion of the MXRA4 gene in murine models of cerebral ischemia and encephalomyelitis has been associated with escalated neuroinflammatory responses and the upregulation of inflammatory mediators [51, 52]. Given the growing appreciation for the role of neuroinflammation in cancer metastasis and the establishment of pre-metastatic niches, further investigation into the link between MXRA4 and neuroinflammation in the context of cancer is warranted. Furthermore, MXRA4 exhibits significant pro-angiogenic capabilities [53] By forming complexes with multimerin-2 (MMRN2) or insulin-like growth factor binding protein 7 (IGFBP7), MXRA4 activates both the VEGF-A and TGF-β2 signaling pathways, ultimately enhancing tumor angiogenesis [54, 55]. Targeting the MXRA4 pathway holds promise for normalizing tumor vasculature, thereby enhancing drug delivery and amplifying the effectiveness of immunotherapy.

2.5 MXRA5

MXRA5, also referred to as Adlican, spans a genomic region of 38.1 kb and is located on chromosome X at Xp22.33. The gene comprises 7 exons and 6 introns and encodes a secreted glycoprotein with a molecular weight of approximately 312 kDa, predominantly found in primates. The protein contains seven leucine-rich repeats (LRRs) and 12 immunoglobulin-like C2-type domains, known for their roles in facilitating protein–protein interactions and molecular recognition, respectively. These structural features suggest a potential role for MXRA5 in mediating protein interactions critical for various biological processes, including signaling cascades and cell adhesion.

Studies have demonstrated that MXRA5 can activate the MAPK signaling pathway, thereby promoting the proliferation and invasion of both prostatic cells and placental trophoblast cells [56, 57]. These findings suggest that MXRA5 may contribute to the progression and metastasis of certain cancers. Furthermore, increased MXRA5 expression has been observed in both cartilage and synovial fluid of individuals with osteoarthritis [58], indicating a potential role in the pathogenesis of this disease. However, the underlying mechanisms and functional consequences of this upregulation remain incompletely understood.

In the context of kidney tissue injury, MXRA5 appears to play a protective role by promoting an anti-inflammatory and anti-fibrotic response linked to the TGF-β pathway. By inhibiting the expression of various chemokines and fibronectin, MXRA5 contributes to alleviating inflammation and fibrosis in kidney tissue [10, 59]. This dual role of MXRA5 in promoting tumorigenesis while exerting protective effects in certain pathological conditions highlights its complexity and potential as a therapeutic target for diverse diseases.

2.6 MXRA6

MXRA6, also known as Tensin 1 (TNS1), is a critical adhesion protein that bridges the actin cytoskeleton to integrins, with a molecular weight of approximately 197 kDa. Located on chromosome 2 at 2q35, the coding gene for MXRA6 spans 234.4 kb and comprises 37 exons and 36 introns. Structurally, MXRA6 consists of distinct regions, including the N-terminal ABD I region containing the protein tyrosine phosphatase and C2 domain, the central ABD II region, and the C-terminal region containing the Src homology 2 (SH2) and phosphotyrosine-binding (PTB) domains [60].

Among these regions, the SH2 and PTB domains serve as key functional regions within MXRA6. The SH2 domain facilitates binding to tyrosine-phosphorylated proteins, such as phosphatidylinositol 3-kinase (PI3K), epidermal growth factor receptor (EGFR), and focal adhesion kinase (FAK), thereby initiating a protein tyrosine kinase (PTK)-mediated signaling cascade crucial for cell growth, polarization, and migration [61–63]. Furthermore, through its PTB domains, MXRA6 interacts with integrin β subunits, modulating cell adhesion, migration, and proliferation dynamics [64].

Moreover, MXRA6 is implicated in regulating Rho GTPase activity by interacting with DLC1, an activator of Rho GTPase enzymes, via its SH2/PTB domain. This interaction triggers the activation of the Hippo signaling pathway, impacting cell

proliferation and epithelial-mesenchymal transition (EMT) processes, thereby influencing the progression of malignant tumors [65]. Additionally, MXRA6 interacts with protein phosphatase-1alpha (PP1α), facilitating the localization of PP1α through the ABD I region. This interaction is critical in governing cell polarization, migration, and invasion regulation [66].

Studies suggest potential implications of MXRA6 in other cellular processes such as cytoskeletal organization, membrane dynamics, and intracellular signaling pathways, highlighting its diverse roles in various physiological and pathological contexts. Further investigations into the precise molecular mechanisms orchestrated by MXRA6 may reveal novel insights into its multifaceted functions and therapeutic potential in regulating cellular processes and diseases.

2.7 MXRA7

MXRA7, a gene spanning 38.4 kb, is located on chromosome 17 at 17q25.1, comprising 4 exons and 3 introns. This gene encodes a protein with a molecular weight of approximately 22 kDa. MXRA7 has been identified as a component of the cellular matrix, although its precise structure and functional significance remain incompletely understood.

Studies have illuminated the role of MXRA7 in osteogenesis, with MXRA7-deficient mice exhibiting notable delays in bone formation. Comparative analyses between MXRA7-deficient and wild-type mice revealed shortened femurs and reduced bone mass in both trabecular and cortical bone regions in the former. Notably, bone marrow mesenchymal stem cells lacking MXRA7 displayed compromised osteogenic potential upon induction, which was effectively restored upon supplementation with recombinant MXRA7 protein [67]. While these findings relate primarily to bone development, the intricate relationship between bone remodeling and cancer metastasis to bone highlights the potential for MXRA7 to play a role in cancer-induced bone disease.

Furthermore, MXRA7 has been implicated in the modulation of inflammatory responses. Research has indicated that MXRA7 can enhance the expression of matrix remodeling-related genes, such as FN1 and TIMP1, thereby exacerbating liver injury [68]. However, similar ECM remodeling processes are often observed in the tumor microenvironment, suggesting a potential role for MXRA7 in modulating tumor-stroma interactions. Conversely, in the context of psoriasis, MXRA7 exerts a negative regulatory effect, as observed through the heightened severity of psoriasis-like features in MXRA7-deficient mice [69]. Given the complex and sometimes opposing roles of inflammatory signaling in cancer progression, these findings suggest that MXRA7's influence on inflammation may be context-dependent in tumorigenesis.

Moreover, MXRA7 demonstrates regulatory roles in other physiological processes, exhibiting inhibitory effects on corneal neovascularization and promoting skin wound healing. Despite these observations, the precise molecular mechanisms underlying these activities remain to be fully elucidated [70, 71]. Notably, both angiogenesis and wound healing share molecular pathways with tumor growth and metastasis, suggesting potential areas of overlap in MXRA7's function. Further investigations into the structural insights and functional intricacies of MXRA7 are warranted to comprehend its diverse roles in cellular processes and pathophysiological conditions, particularly in the context of cancer, paving the way for potential therapeutic implications.

2.8 MXRA8

MXRA8, characterized as a type I transmembrane protein and a dual Ig domain-containing cell adhesion molecule (DICAM), has a molecular weight of approximately 49 kDa. The MXRA8 gene, spanning 10.9 kb, is located on chromosome 1 at 1p36.33, comprising 11 exons and 10 introns. Structurally, MXRA8 features an extracellular domain comprising double N-terminal V-type Ig-like domains, a transmembrane domain, and a short cytoplasmic domain [72].

The adhesion function of MXRA8 is attributed to its extracellular domain, facilitating interactions with integrin αvβ3 and promoting intercellular adhesion [72]. Notably, MXRA8 directly interacts with integrin β3 to impede the heterodimerization of integrin αv and β3. Genetic deletion of MXRA8 in murine models leads to upregulated expression of osteoclast-related Ig-like receptors and integrin αvβ3, resulting in the negative modulation of osteoclast differentiation processes [73].

In autoimmune optic neuritis and colitis models, reduced MXRA8 expression levels have been observed compared to normal mice, with MXRA8-deficient mice displaying exacerbated inflammatory responses relative to wild-type counterparts [74, 75]. Given the complex interplay between the immune system and cancer, these findings suggest that MXRA8's influence on inflammation may have implications for understanding its role in the tumor microenvironment and response to immunotherapy. Conversely, overexpression of MXRA8 in human umbilical vein endothelial cells (HUVECs) has been associated with the suppression of integrin αvβ3/FAK signaling and the inhibition of angiogenesis [76]. As angiogenesis

is a critical process in tumor growth and metastasis, these findings suggest that MXRA8 may have tumor-suppressive properties by inhibiting angiogenesis.

Furthermore, MXRA8 functions as a key receptor for arthritis-causing alphaviruses, including Ross River virus, Chikungunya virus, Mayaro virus, and O'nyong-nyong virus, facilitating viral entry into host cells during infection. Specifically, the extracellular domain of MXRA8 interacts with E2-E1 heterodimers present on the viral surface, promoting efficient viral entry mechanisms [77]. While the direct relevance of MXRA8's role as a viral receptor to cancer is currently unclear, it's important to consider that some viruses are known to be oncolytic, and understanding MXRA8's interaction with these viruses could potentially have implications for developing novel cancer therapies. Elucidating the pivotal role of MXRA8 as a receptor for these alphaviruses is instrumental in advancing the understanding of viral pathogenesis and may hold promise for the development of novel antiviral therapeutics or preventive strategies in the future.

3 Expression, Function and mechanism of MXRAs family in tumorigenesis and development

Research has revealed that the MXRA family members significantly contribute to tumorigenesis and its progression, exhibiting distinct expression profiles across various types of malignancies (Fig. 3). While these findings highlight the potential of MXRA family members as biomarkers, their clinical utility for diagnostic, prognostic, or predictive purposes remains largely unvalidated and requires further investigation. The biological roles of the MXRA family in tumor development and progression have garnered significant attention and are currently under intense investigation. In recent years, researchers have endeavored to unravel the multifaceted functions of MXRA proteins across a spectrum of malignancies.

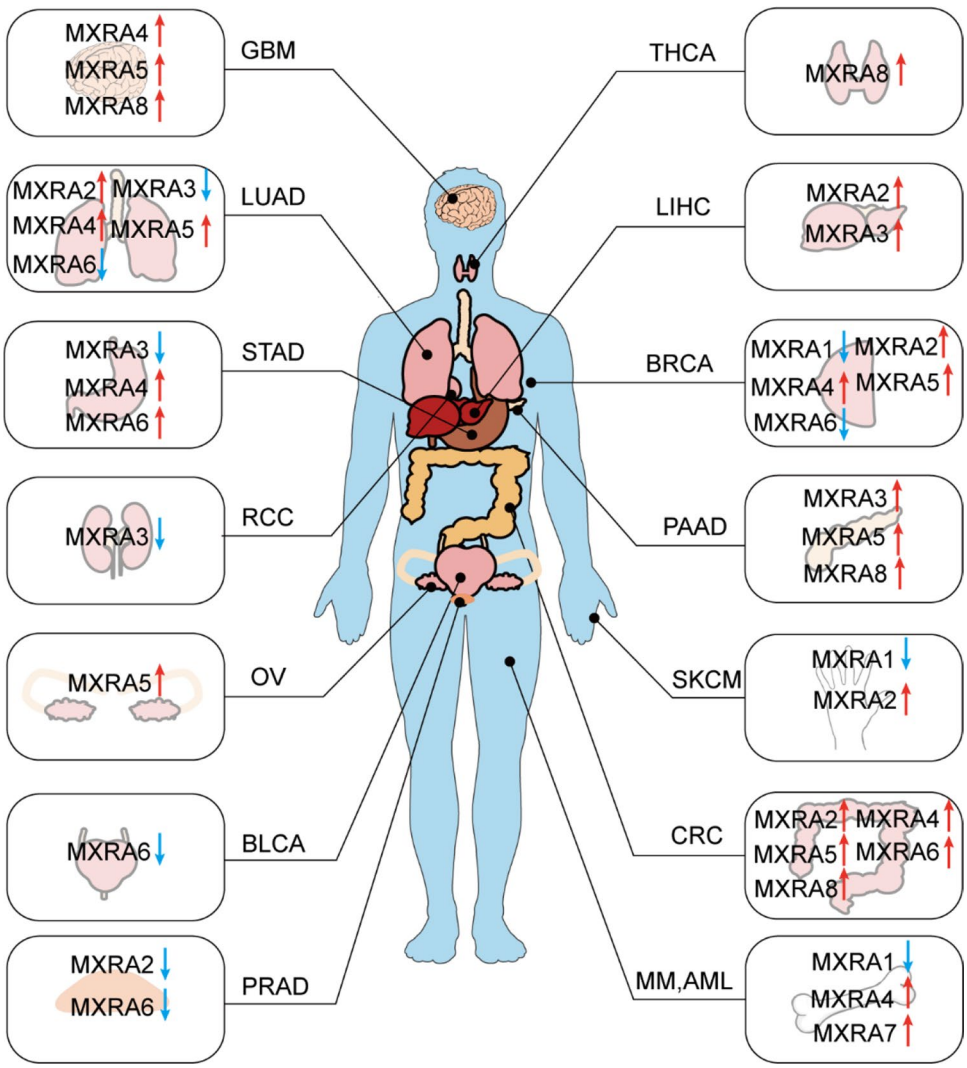

Fig. 3 Expression of MXRAs in tumors. The blue arrow indicates down-regulation in tumor tissues, and the red arrow indicates up-regulation in tumor tissues. Tumor abbreviation: *AML* Acute myeloid leukemia, *BLCA* Bladder urothelial carcinoma, *BRCA* Breast invasive carcinoma, *CRC* Colorectal cancer, *GBM* Glioblastoma multiformeGBM, *LIHC* Liver hepatocellular carcinoma, *LUAD* Lung adenocarcinoma, *MM* Multiple myeloma, *OV* Ovarian serous cystadenocarcinoma, *PAAD* Pancreatic adenocarcinoma, *PRAD* Prostate adenocarcinoma, *RCC* Renal cell carcinoma, *SKCM* Skin cutaneous melanoma, *STAD* Stomach adenocarcinoma, *THCA* Thyroid carcinoma

Various members of the MXRA family exhibit distinct and dynamic roles, ranging from promoting to suppressing cancer pathogenesis as tumors evolve. Elucidating the specific expression patterns and functional mechanisms of each MXRA family member in different cancer contexts is crucial for determining their potential as clinically relevant biomarkers.

MXRA1 expression is downregulated in invasive breast cancer, melanoma, and multiple myeloma [78–80]. MXRA1 exhibits tumor-suppressive activity in invasive breast cancer and multiple myeloma. This reduced expression disrupts calcium efflux from red blood cells, leading to intracellular calcium accumulation and increased reactive oxygen species (ROS) production, ultimately promoting cellular damage. Moreover, in B-RAF-mutated melanoma, diminished MXRA1 levels correlate with impaired cell migration, colony formation, and reduced metastatic potential, highlighting MXRA1's crucial role in regulating tumorigenic processes in this setting [81].

Overexpression of MXRA2 is a common feature in several cancers, including hepatocellular carcinoma, breast cancer, colorectal cancer, lung adenocarcinoma, and melanoma. In these cancers, elevated MXRA2 levels are associated with adverse clinicopathological features such as larger tumor size, advanced clinical stage, increased invasion, and metastasis, highlighting its potential as a novel biomarker for poor prognosis. [9, 24, 33, 82–85]. Notably, within primary tumors, MXRA2 expression is significantly elevated in tumor cell subpopulations exhibiting high metastatic potential compared to those with low metastatic potential [83, 85]. In the context of breast cancer and hepatocellular carcinoma progression and metastasis, MXRA2 participates in the regulation of Rho GTPase signaling pathways, thereby influencing ECM degradation and facilitating tumor cell invasion [9, 83]. Particularly in breast cancer cells, MXRA2 not only stimulates pseudopodia formation and enhances cell invasion capabilities but also plays a critical role in the induction of EMT, a key driver of metastatic competence in cancer cells [33, 34]. In human triple-negative breast cancer cells, MXRA2 interacts with Ras GTPase-activating protein SH3 domain-binding protein 2 (G3BP2). Experimental evidence demonstrates that reducing MXRA2 expression via gene knockdown attenuates its interaction with G3BP2, thereby promoting the binding of G3BP2 to TWIST1. This, in turn, leads to increased TWIST1 ubiquitination and subsequent degradation through the proteasome pathway, ultimately reducing intracellular TWIST1 protein levels and suppressing the activity of related downstream signaling pathways, effectively inhibiting the growth, migration, and invasion of breast cancer cells [84]. In contrast to the aforementioned tumor types, MXRA2 functions as an oncogene in lung adenocarcinoma, promoting tumor cell invasion, colony formation, and endothelial cell tubulogenesis through the activation of ILK phosphorylation [24]. Interestingly, an inverse expression pattern has been observed in prostate cancer. Compared to the adjacent TME, MXRA2 expression is often decreased in prostate tumor tissues [86]. Furthermore, MXRA2 acts as a negative regulator of the MAPK/ERK signaling pathway, downregulating Myosin Light Chain 2 (MLC2) expression via the ILK signaling pathway. Intriguingly, gene knockout experiments have revealed that MXRA2 depletion paradoxically enhances the migration and invasion abilities of prostate cancer cells, highlighting its complex and context-dependent role in prostate cancer biology [86]. These observations underscore the divergent functions of MXRA2 across distinct tumor types, emphasizing its tissue specificity and the complex molecular mechanisms governing its context-dependent actions in cancer biology. Exploring the nuanced regulatory roles of MXRA2 in a diverse range of malignancies is crucial for unveiling its therapeutic potential and enhancing our comprehension of tumor-specific responses to MXRA2 modulation.

MXRA3, an integrin adhesion-associated protein, exhibits a complex and seemingly contradictory role in tumorigenesis, with evidence suggesting both tumor-suppressive and, potentially, oncogenic functions depending on the cancer type. In renal cell carcinoma, MXRA3 expression is significantly reduced in tumor tissue compared to normal tissue [87], a finding supported by in vitro studies showing that MXRA3 inhibits RCC cell proliferation and growth by downregulating the expression of genes associated with cell cycle progression and proliferation [87]. Similarly, Miao et al. observed reduced MXRA3 expression in gastric cancer cell lines compared to normal cell lines [88]. Further supporting a tumor-suppressive role, a genome-wide analysis of non-small cell lung cancer (NSCLC) cells by Zhang et al. identified MXRA3 as a potential tumor suppressor in NSCLC, with its expression correlating with improved overall survival in NSCLC patients [89]. However, a recent pan-cancer analysis challenges this view, revealing elevated MXRA3 expression in clear cell renal cell carcinoma, hepatocellular carcinoma, and pancreatic cancer, suggesting a potential oncogenic function in these specific contexts [90]. Although evidence indicates MXRA3 involvement in cell proliferation, cell cycle regulation, and tumor prognosis, the precise mechanisms underlying its diverse and seemingly paradoxical roles in tumorigenesis remain to be fully elucidated.

MXRA4, also known as the cell surface molecule CD93, is a receptor predominantly expressed on endothelial cells [91]. By interacting with ligands such as MMRN2 and IGFBP7, MXRA4 mediates endothelial cell functions, including adhesion to other endothelial cells, migration, and interactions with the ECM [55, 92–94]. Studies have shown that MXRA4 is significantly upregulated in tumors of gastric, breast, lung squamous cell, nasopharyngeal, colorectal, multiple myeloma, and glioma origin. This overexpression is associated with pathological grade, distant metastasis, clinical stage, and poor

prognosis, suggesting MXRA4 as a potential novel prognostic and diagnostic biomarker [92, 95–100]. This multifaceted role positions MXRA4 as a key coordinator of tumor angiogenesis. Mechanistically, MXRA4 promotes tumor growth and angiogenesis by activating signaling pathways such as VEGF-A, PI3K/AKT, and TGF-β upon ligand binding. Furthermore, studies indicate that inhibiting MXRA4 can induce vascular remodeling within the TME, enhance T cell infiltration, and potentially augment the efficacy of immunotherapeutic interventions [101]. MXRA4 exhibits a notable association with the tumor microenvironment in colorectal cancer, showing a positive correlation with macrophage infiltration. High MXRA4 expression levels also appear to be linked to tumor vasculature normalization and improved patient survival. Therefore, assessing MXRA4 expression within colorectal tumor tissue may offer a means of identifying patients likely to benefit from therapies targeting angiogenesis or the tumor microenvironment and predict overall patient outcomes [96]. These findings underscore the critical role of MXRA4 in tumor angiogenesis and highlight its significant potential as a therapeutic target, particularly in the immunotherapy setting. A thorough elucidation of the complex interactions and signaling pathways modulated by MXRA4 could pave the way for novel therapeutic strategies aimed at disrupting the angiogenic process and improving the effectiveness of immunotherapeutic approaches in cancer treatment.

MXRA5 is widely acknowledged as an oncogene and is commonly overexpressed in NSCLC, colorectal cancer, breast cancer, glioma, ovarian cancer, pancreatic cancer and various other cancers. Its expression level was significantly correlated with key pathophysiological processes such as TNM stage, expression of immune checkpoint molecules, immune infiltration and angiogenesis highlighting its potential as a biomarker. [102–107]. For instance, in NSCLC, Xiong et al. demonstrated the critical role of the MXRA5 gene in driving ECM remodeling, a process crucial for tumor progression [107]. Correspondingly, Minafra et al. demonstrated MXRA5's contribution to promoting EMT and ECM remodeling in breast cancer, underscoring its multifaceted role in tumor aggressiveness [103]. Additionally, recent studies by Peng et al. unveiled MXRA5's involvement in advancing pancreatic cancer by orchestrating EMT processes through modulation of the PI3K/AKT/mTOR signaling pathway, implicating MXRA5 as a key driver of cancer progression [88]. Single-cell analysis by Deng et al. [108] identified upregulated MXRA5 expression in cancer-associated fibroblasts (CAFs) associated with lymph node metastasis, potentially representing a key molecular target within the CAF2 subgroup implicated in breast cancer metastasis. Given its significant impact on cancer development and progression, targeting MXRA5 may hold promise as a viable therapeutic strategy for combating tumor growth and metastasis. Further exploration of the intricate mechanisms through which MXRA5 influences tumorigenesis across different cancer types could provide valuable insights for developing targeted interventions to impede cancer progression and enhance treatment outcomes.

MXRA6, also identified as TNS1, serves as an adhesion protein with significantly lower expression levels in lung adenocarcinoma, bladder cancer, breast cancer and prostate cancer [109–112]. In colorectal cancer, research has revealed that MXRA6 triggers the activation of the MAPK signaling pathway, fostering enhanced proliferation, migration, and invasion of cancer cells [113–115]. Meanwhile, MXRA6 expression in gastric cancer is notably elevated in undifferentiated and metastatic tumor cells, contrasting with lower expression in less aggressive tumor cells, implicating MXRA6 in driving tumorigenesis and progression in gastric cancer. Substantiating this, a study by Jiang underscored that depletion of MXRA6 significantly curtails the proliferation of gastric cancer cells, affirming its active involvement in gastric cancer development [116]. Conversely, in lung adenocarcinoma, MXRA6 displays diminished expression levels. Its upregulation is capable of activating the p53 signaling pathway, exerting pro-apoptotic effects on tumor cells, thus suggesting a potential tumor-suppressing role [111]. The expression profiles and functions of MXRA6 in bladder and breast cancer mirror the observations in lung adenocarcinoma, showcasing a reduction in proliferative, migratory, and invasive capacities of tumor cells upon MXRA6 upregulation [109, 110]. Moreover, in prostate cancer, studies by Zhu et al. have associated elevated MXRA6 expression with extended disease-free survival compared to low MXRA6 expression levels, underscoring a potential prognostic value of MXRA6 in prostate cancer [112]. These findings emphasize the divergent expression patterns and functional roles of MXRA6 in various cancer contexts, highlighting its distinct impact and therapeutic potential across different tumor types. Unraveling the underlying mechanisms driving MXRA6-mediated effects in specific cancers could offer valuable insights for devising targeted therapeutic strategies, personalized treatment approaches, and prognostic markers tailored to the tumor tissue specificity of MXRA6. Further exploration and elucidation of MXRA6's intricate roles in cancer biology are crucial for advancing precision oncology and improving patient outcomes in the clinical setting.

MXRA7, identified as a burgeoning oncogene, demonstrates significant associations with hematological malignancies. Notably, in acute lymphoblastic leukemia, increased MXRA7 expression triggers the proliferation of REH cells, fostering resistance to cytarabine chemotherapy [117, 118]. Conversely, in acute myeloid leukemia, MXRA7 plays a distinct role by inhibiting methotrexate-induced apoptosis through the elevation of the apoptosis suppressor protein BCL-2 expression [119]. These findings suggest a comprehensive therapeutic approach encompassing conventional chemotherapy alongside targeted interventions directed at MXRA7, offering a promising treatment avenue for hematological malignancies.

MXRA8, a transmembrane protein, emerges as a critical player in shaping the tumor immune microenvironment. Studies have delineated the significant impact of MXRA8 on immune cell infiltration and its contribution to the establishment of an immunosuppressive tumor immune milieu [120, 121]. Investigations in glioma underscore the role of MXRA8 in ferroptosis induction within glioma cells, leading to the inhibition of cell proliferation and decreased infiltration of M2 macrophages, thereby influencing patient prognosis and therapeutic outcomes [12]. Recent research highlighting the association between MXRA8 and CAFs has elucidated the contributory role of MXRA8 + CAFs in the initiation and progression of pancreatic cancer [99]. Consequently, MXRA8 emerges as a promising novel prognostic biomarker and a potential target for innovative tumor immunotherapy strategies aimed at modulating the TME for improved patient outcomes and treatment efficacy.

In conclusion, the intricate involvement of MXRA family proteins in diverse aspects of tumorigenesis, including cell migration, invasion, proliferation, apoptosis, angiogenesis, immune modulation, and more, underscores their potential as promising targets for novel cancer intervention strategies. Understanding the complex roles and regulatory mechanisms of MXRA proteins may unlock new avenues for personalized cancer therapies, paving the way for innovative approaches in combating malignancies.

4 MXRAs family and post-translational modifications of proteins

The functional regulation of MXRAs is intricately linked to post-translational modifications (PTMs). These chemical alterations, occurring after protein synthesis, profoundly impact protein structure, function, localization, and intermolecular interactions, thereby fine-tuning cellular processes. Common PTMs include phosphorylation, lactylation, glycosylation, ubiquitination, and methylation. However, research on MXRA PTMs remains limited, with only a few modifications reported to date. For instance, studies demonstrate that MXRA2 is phosphorylated at Ser4/8, a site dependent on Erk activity in vivo [31]. This phosphorylation event promotes matrix degradation and cell invasion by modulating Rho GTPase signaling [9]. Further, Jiang et al. observed upregulated m6A peaks in MXRA5 within pterygium tissue, suggesting potential m6A methylation [122], while increased N-glycosylation of MXRA5 has been reported in Kashin-Beck disease and primary knee osteoarthritis [123, 124]. These findings collectively indicate that the PTM landscape of MXRAs is likely more complex than currently appreciated, necessitating further experimental validation.

5 MXRAs family and chemotherapy resistance

Chemotherapy failure, often stemming from tumor drug resistance, remains a significant challenge in cancer treatment, although the underlying mechanisms are not fully elucidated [125]. Emerging evidence suggests that aberrant expression of MXRA family proteins within tumor cells may play a critical role in driving resistance (Fig. 4). For instance, in breast cancer, MXRA2 is implicated in resistance to bosutinib. As previously mentioned, MXRA2 forms complexes with ILK and PINCH, linking cells to their surrounding environment through integrins and participating in processes such as cytoskeleton remodeling, angiogenesis, proliferation, survival and differentiation [126]. Conversely, downregulation of MXRA3 is associated with increased sensitivity to paclitaxel in melanoma cells. MXRA3 knockdown disrupts the functional link between talin2 and MXRA3, altering MT dynamics by increasing MT growth speed, thereby enhancing paclitaxel sensitivity and reducing migration [127]. Furthermore, MXRA4 inhibition has been shown to promote improved tumor vessel maturation and functionality, enhancing drug delivery within the primary TME and augmenting the anti-tumor response to drugs such as gemcitabine or fluorouracil [11]. In acute lymphoblastic leukemia, MXRA7 knockdown leads to increased expression of activated Caspase-3 and Caspase-9 proteins, suggesting that MXRA7 may influence cytarabine-induced apoptosis by modulating the Caspase pathway [128, 129]. Notably, inhibition of MXRA8 has been shown to suppress glioma cell viability and sensitize them to temozolomide treatment, although the precise mechanism remains unclear [12]. The significant association between MXRA family proteins and tumor drug resistance suggests that targeting MXRAs could potentially sensitize tumor cells to chemotherapy drugs, thereby improving therapeutic responses. Further exploration into the molecular mechanisms underlying these proteins and their functions may pave the way for the development of innovative strategies to overcome drug resistance and enhance the efficacy of cancer therapy.

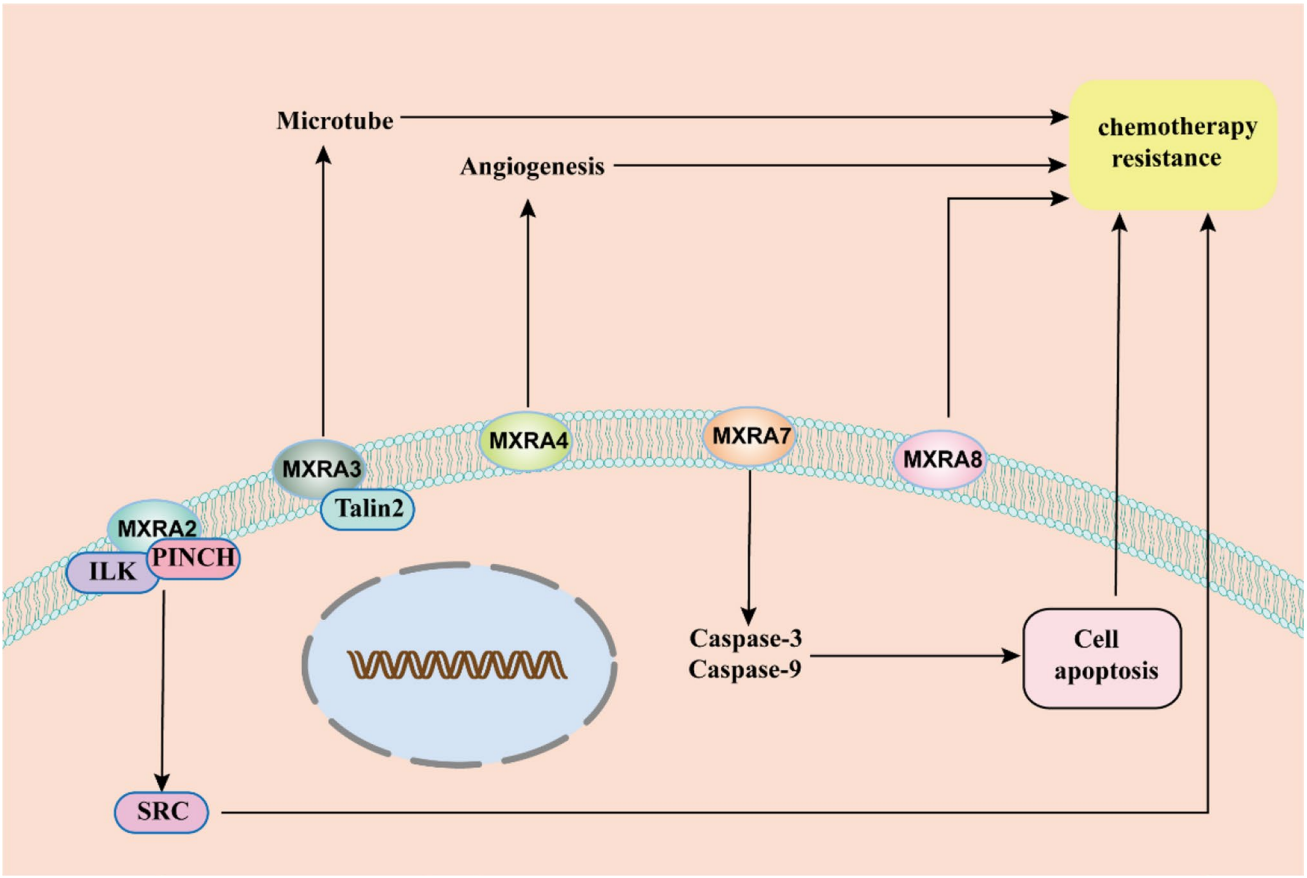

Fig. 4 MXRAs is involved in chemotherapy resistance. MXRA2, by disrupting adhesion signaling in tumors, leads to chemotherapy drug resistance; conversely, MXRA3 downregulation increases chemotherapy drug sensitivity through altered microtubule dynamics. Furthermore, MXRA4 inhibition enhances drug delivery by normalizing tumor vessels, improving the response to chemotherapy drugs. In tumors, MXRA7 influences chemotherapy drug-induced apoptosis via the caspase pathway, while MXRA8 inhibition sensitizes tumor cells to chemotherapy drug treatment

6 MXRAs family and immunotherapy

Emerging evidence highlights the potential of MXRAs as key players in immunotherapy, positioning them as promising therapeutic targets beyond conventional chemotherapy. Regarding immunotherapy, several MXRA family members exhibit the capacity to modulate the tumor immune microenvironment. For instance, pan-cancer analyses have revealed a significant positive correlation between MXRA3 expression and immune checkpoint molecules such as PD-1, PD-L1, and CTLA-4 [90], suggesting a potential role in promoting an immunosuppressive TME. Conversely, MXRA4 has been shown to drive osteosarcoma cell proliferation, angiogenesis, and immune evasion through activation of the PI3K/AKT signaling pathway [93]. Consequently, inhibiting MXRA4 may delay immune escape and enhance the efficacy of immunotherapy in osteosarcoma. Furthermore, pan-cancer assessments indicate that MXRA4 is expressed across a range of TME cell types, including CAFs, endothelial cells, myeloid dendritic cells, hematopoietic stem cells, mononuclear/macrophage subpopulations, and neutrophils [130], implying a multifaceted regulatory role within the TME. Notably, MXRA4 expression correlates positively with nearly all known immune-related genes that promote tumor growth, angiogenesis, and metastasis [130], further supporting the hypothesis that MXRA4 contributes to TME-mediated immunosuppression, and that targeting MXRA4 could enhance immunotherapy outcomes. In addition, bioinformatics analyses have identified MXRA5 as a novel immune-related biomarker for predicting poor prognosis in glioma patients [105]. Other MXRA members, such as MXRA8, have also been linked, through bioinformatics approaches, to immune responses in colorectal cancer [124], prostate cancer [131], glioma [12], and thyroid cancer [125], although these associations require further experimental validation.

Targeting MXRAs, particularly in light of their significant influence on the immune microenvironment, presents a potential therapeutic avenue for advanced or recurrent cancers. Currently, research on drugs targeting the MXRA family is sparse, with a predominant focus on MXRA4 and its immunomodulatory properties. This emphasis is reflected in the recent initiation of two Phase I clinical trials by DynamiCure Biotechnology (DCBY02 [NCT05496595] and DCSZ11 [NCT05785754]), designed to assess the impact of anti-MXRA4 antibodies on patients with advanced or metastatic solid tumors. These trials are actively enrolling participants, but efficacy and safety data remain unavailable.

7 MXRAs family and microRNA

MicroRNAs (miRNAs) are short non-coding RNA molecules, approximately 22 nucleotides in length, that regulate endogenous gene expression by interacting with distinct transcription factors [132]. Extensive research has consistently revealed a negative correlation between the expression levels of MXRA family proteins and certain miRNAs, which act as direct regulators of these proteins (Fig. 5). Notably, in multiple myeloma, miR-4261 has been identified to downregulate MXRA1 expression, leading to calcium overload in red blood cells and implicating a role in disease pathogenesis [78]. In whole blood, inhibition of miR-92a-3p has been shown to result in increased MXRA4 levels, highlighting the regulatory role of miRNAs in MXRA protein expression modulation [133]. In placental trophoblast cells, miR-30b promotes apoptosis through the MAPK pathway by targeting and suppressing MXRA5 expression [128]. Moreover, the expression of MXRA6 is negatively modulated by miR-942, miR-152, miR-31-5p, and miR-548j, leading to enhanced tumor cell proliferation and migration in various cancer types [109, 111, 129, 134, 135]. The dysregulation of these miRNAs, which target MXRA family proteins, plays a critical role in tumor progression by influencing cellular proliferation and migration. Investigating the intricate regulatory network involving miRNAs and MXRA family proteins may unveil deeper insights into the molecular mechanisms of tumor development, offering potential novel targets for anti-tumor therapeutics in clinical practice.

8 Conclusion

MXRAs, a protein group intricately involved in cell adhesion and ECM remodeling, have emerged as key players in diverse cellular processes. MXRA proteins, including MXRA1-8, are characterized as transmembrane or secreted molecules with functions spanning cell adhesion, migration, immune modulation, and angiogenesis. The review emphasizes the tissue-specific expression patterns of these proteins, which dictate their often-opposing roles as either oncogenes or tumor suppressors in different malignancies.

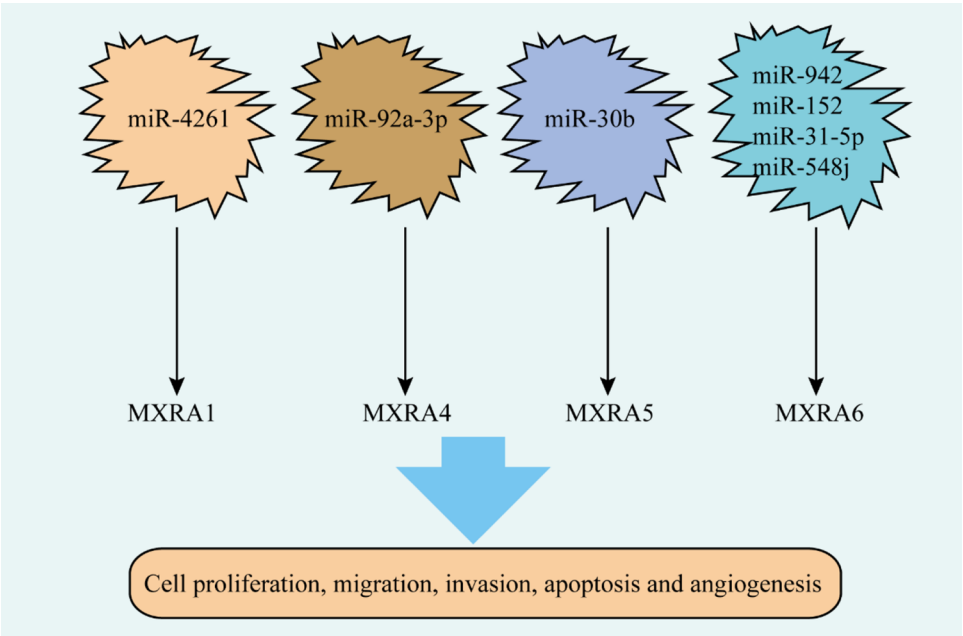

Fig. 5 MXRAs are regulated by miRNA. MXRA1, MXRA4, MXRA5, and MXRA6 are negatively regulated by miR-4261, miR-92a-3p, miR-30b, and a group of miRNAs including miR-942, miR-152, miR-31-5p, and miR-548j, respectively

Specifically, the review delineates the oncogenic roles of MXRA2 and MXRA5, noting their frequent overexpression in cancers such as breast, lung, and colorectal tumors, where they promote metastasis and drug resistance via pathways like EMT, ECM remodeling, and MAPK/PI3K signaling. Conversely, MXRA1, MXRA3, and MXRA6 are frequently downregulated in several tumor types, suggesting tumor-suppressive functions. MXRA4 is identified as a key regulator of tumor angiogenesis through the VEGF-A/TGF-β2 pathways. The review further examines the roles of MXRA7 in hematological malignancies and MXRA8 in modulating the tumor immune microenvironment.

Importantly, this review elucidates the involvement of MXRA proteins in drug resistance, noting that altered expression can impact chemotherapy effectiveness. It also highlights the regulatory role of specific microRNAs in modulating MXRA expression, underscoring their potential as therapeutic targets. This comprehensive review demonstrates that the MXRA family constitutes a valuable area for further research in cancer biology.

Several key avenues for future research merit particular attention. First, a deeper understanding of the structural mechanisms governing MXRA interactions with their ligands and downstream signaling partners is essential. High-resolution structural studies, coupled with advanced biophysical techniques, could reveal novel allosteric sites or cryptic pockets that can be targeted by rationally designed inhibitors. Second, given the limited data on the epigenetic regulation of MXRA genes, future studies should investigate the role of histone modifications and DNA methylation in modulating MXRA expression in different cancer contexts. Identifying epigenetic vulnerabilities could pave the way for novel epigenetic therapies to restore MXRA tumor-suppressive function or silence oncogenic MXRAs. Third, further exploration of the interplay between MXRAs and the tumor immune microenvironment is crucial. This includes investigating the potential of targeting MXRAs to enhance the efficacy of immune checkpoint inhibitors or to promote the infiltration of cytotoxic T cells into tumors. Fourth, given the emerging role of MXRA2 and MXRA5 in promoting EMT, future studies should investigate the precise mechanisms by which these MXRAs contribute to the acquisition of stem-like properties and enhanced plasticity in cancer cells. This includes examining their influence on key stemness-related transcription factors and their impact on the ability of cancer cells to adapt to diverse microenvironmental stresses. Finally, the ongoing Phase I clinical trials of anti-MXRA4 antibodies offer a promising glimpse into the therapeutic potential of targeting this family of proteins. Future clinical studies should focus on identifying predictive biomarkers to select patients most likely to benefit from MXRA-targeted therapies and on exploring combination strategies with other anticancer agents to overcome potential resistance mechanisms. Such endeavors will be critical to translating the exciting preclinical findings into tangible benefits for cancer patients.

Author contributions Chao Zeng, Xiao Lv, Yanxian Ren, Yaomin Huang, Feng Wang and Hengwei Zhang wrote the main manuscript text and Xiao Lv prepared Figs. 1, 2, 3, 4 and 5. All authors reviewed the manuscript.

Funding This work was supported by the Natural Science Foundation of China (82260464), the Youth Talent Project of Gansu Province (2023LQGR02), the Natural Science Foundation of Gansu Province (22JR11RA040), and the Medical Research Improvement Project of Lanzhou University (lzuyxcx-2022–185).

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate This study does not involve ethical issues.

Competing interests The authors declare no competing interests.

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