Research advances of MAL family members in tumorigenesis and tumor progression (Review)

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Abstract. The myelin and lymphocyte protein (MAL) family is a novel gene family first identified and characterized in 2002. This family is comprised of seven members, including MAL, MAL2, plasmolipin, MALL, myeloid differentiation-associated marker (MYADM), MYADML2 and CMTM8, which are located on different chromosomes. In addition to exhibiting extensive activity during transcytosis, the MAL family plays a vital role in the neurological, digestive, respiratory, genitourinary and other physiological systems. Furthermore, the intimate association between MAL and the pathogenesis, progression and metastasis of malignancies, attributable to several mechanisms such as DNA methylation has also been elucidated. In the present review, an overview of the structural and functional properties of the MAL family and the latest research findings regarding the relationship between several MAL members and various cancers is provided. Furthermore, the potential clinical and scientific significance of MAL is discussed and directions for future research are summarized.

Contents

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1. Introduction

The myelin and lymphocyte protein (MAL) family belongs to the MAL and related proteins for vesicle formation and membrane link (MARVEL) superfamily, first characterized in 2002 (Fig. 1A) (1,2). Alonso and Weissman (3) first identified the human MAL cDNA while searching for genes selectively expressed during T cell differentiation. MAL has been demonstrated as an element of the machinery that transports apical proteins through direct pathways in Madin-Darby canine kidney cells depleted of endogenous MAL (4-7). At a steady state, MAL predominantly localizes to the apical zone of polarized epithelia and continuously shuttles between the Golgi apparatus and plasma membrane, functioning as a key carrier in membrane signaling in the direct transcytosis pathway (8,9).

Transcytosis is a specialized transcellular transport process enabling targeted transport of cargo, such as soluble molecules, macromolecules and pathogens, across epithelial barriers via direct and indirect pathways (10). The indirect pathway is common in most polarized epithelia, while the direct pathway is exclusive to certain epithelial cell types. The direct pathway appears mediated by incorporation of cargo proteins into specialized membrane microdomains or lipid rafts that generate apical-destined vesicular carriers (11). In the direct pathway, cargo is endocytosed on one epithelial side, transported in vesicles formed through the Golgi and delivered subsequently to the opposite side of the epithelial barrier (10,11). Conversely, the indirect pathway first shuttles cargo to the basolateral or apical membrane (chiefly basolateral), where it is endocytosed into early endosomes before targeting the opposite membrane surface (11,12). Endocytosed proteins can be recycled to the original membrane, degraded in late endosomes and lysosomes, or transcytosed to the opposite surface (Fig. 2) (11,12).

The MARVEL superfamily consists of proteins containing the evolutionarily conserved MARVEL domain, present in 24 human proteins (2). Besides the MAL family, the MARVEL superfamily also comprises the chemokine-like factor MARVEL transmembrane domain containing (CMTM), physin and tight junction-associated MARVEL protein families (Fig. 1B) (1,13-17).

The MAL family is generally considered to consist of six members based on MAL proteins. MAL2, T-cell differentiation protein-like (MALL)/BENE and plasmolipin (PLLP)

exhibit a tetraspanin topology similar to MAL. The other two members, myeloid differentiation-associated marker (MYADM) and MYADM-like2 (MYADML2), contain an additional MARVEL domain and form a distinct branch within the family (15). Additionally, the chemokine-like factory (CKLF) superfamily was originally described in 2001, and CKLF-like MARVEL transmembrane domain-containing 8 (CMTM8) shares 39.3% of amino acid homology with PLLP, thus it is often classified as a MAL family member (18,19). Although MAL family members have different nomenclatures, they are considered proteolipid proteins due to the 20-40% overall amino acid identity and similar hydrophobicity profiles (Table I) (20).

Functionally, the MAL family plays an important biological role in membrane transport, impacting neurological, digestive, respiratory, genitourinary and other physiological systems through signaling pathways including Notch, ERK/MAPK and EGFR (21-27). Moreover, the MAL family is involved in the pathogenesis, progression and metastasis of various cancers, with each member exhibiting differential functions in malignancies to promote or inhibit disease advancement (28,29). Numerous digestive system and female reproductive system cancers have been linked to MAL family members through various mechanisms (30-34).

DNA methylation occurs at cytosine residues in the cytosine-guanine sequence (CpG). CpG islands, often located around the gene promoters, are genomic regions with high CpG density and G+C content >50% (35,36). Abnormal hypermethylation of CpG islands upstream of tumor suppressor genes is a main mechanism of gene inactivation in human tumorigenesis, playing an important role in pathogenesis (37). Except for MYADM and MYADML2, all MAL family genes contain a CpG island at their promoter region, making them susceptible to epigenetic regulation by DNA methylation (38).

As carriers in transcellular trafficking pathways, MAL proteins can function as either tumor suppressors or promoters, influencing cancer development (39). Methylated MAL combined with cell adhesion molecule 1 (CADM1) has been widely utilized as an early diagnostic biomarker for cervical cancer (40,41). Conversely, MAL2 participates in indirect apical transport and may modulate antitumor immunity when expressed at aberrant high or low levels in different tissues (42,43). Moreover, the homologs PLLP is expressed not only in the nervous system and kidney, but also in a number of other tissues such as thymus, testis, lung, and thyroid gland (44). MALL induces nuclear aberrations that can promote carcinogenesis in various tissues (45), while CMTM8 closely regulates EGFR signaling pathways and disease progression (27). MYADM and MYADML2 are associated with myeloid differentiation and endothelial inflammation, with upregulated expression in certain diseases (46).

Therefore, MAL family members have differential tumor-associated functions and mechanisms. Further elucidating their roles in tumor pathogenesis, progression and metastasis will significantly advance molecular detection and gene therapy, providing new hope to patients with cancer. The present review discusses the relationships between individual MAL proteins and cancers, aiming to elucidate patterns and offer alternative therapeutic strategies.

2. MAL/VIP17

MAL is encoded on chromosome 2q11 and produces a 17 kDa integral membrane protein found in lipid rafts (47-49). Lipid rafts are sphingolipid- and cholesterol-enriched microdomains important for segregating cell surface components and influencing membrane dynamics, trafficking, adhesion, signaling and apoptosis (50,51). In epithelial cells, MAL predominantly localizes to the trans-Golgi network (TGN), transporting vesicles to regulate protein sorting (6). MAL knockdown decreases apical vesicle transport, leading to accumulation of apical proteins in the Golgi (6). In T cells, MAL affects differentiation by modulating sorting but does not impact membrane localization of lymphocyte-specific kinase (Lck) or T cell receptor signaling (52,53). MAL interacts with the glycosylphosphatidylinositol-anchored protein CD59 and Lck, suggesting that it can bind lipids to function as a membrane adaptor (6). MAL is also a key factor in exosome secretion from human T cells (54).

Beyond T cells, MAL is expressed in polarized epithelia and myelinating cells including the kidney, stomach, colon and oligodendrocytes (55-59). In these cells, apical protein/lipid transport is essential for epithelial function, with loss of polarity associated with transformation (49). During oligodendrocytes maturation and Schwann cell myelination, MAL expression and lipid raft binding mediate polarization (59).

MAL is widely expressed in respiratory, neurological, genitourinary, gastrointestinal and endocrine/exocrine epithelial tissues (Table II) (24,60,61). It has dichotomous roles in carcinogenesis as either a tumor suppressor or progression factor (39). Evidence supporting its tumor suppressor activity includes ectopic MAL expression inhibiting growth and reducing viability of cancer cells in nude mouse models, blocking G1/S transition and increasing Fas-mediated apoptosis (32,62-67). However, MAL acts as an oncogenic factor in endometrial carcinoma and certain lymphomas, such as thymic large B cell lymphomas but not in nodal diffuse large B cell lymphomas (39,68-72).

Association between aberrant MAL gene methylation/protein expression and pathological features or clinical outcomes have been reported in multiple cancers such as colon, esophagus, breast and so on (73-75). Rescue expression experiments using 5-aza-2'-deoxycytidine (decitabine, DAC) with or without trichostatin A to inhibit DNA methylation and deacetylation have provided further evidence that hypermethylation is the predominant mechanism silencing MAL in particular malignancies (Table III) (32,41,62,63,73-115).

Several studies have demonstrated that aberrant MAL promoter methylation is associated with MAL silencing in breast, esophageal and colorectal carcinomas, and shows promise as an early biomarker alongside other markers (73-75). MAL hypermethylation is common in Barrett's-associated esophageal adenocarcinoma but not squamous cell carcinoma, suggesting utility as an adenocarcinoma-specific biomarker linked to high-risk features (74). Besides suppressing motility, aggressiveness, tumorigenicity and inducing apoptosis, MAL exerts tumor suppressive effects in esophageal cancer (32). Univariate and multivariate analyses have associated MAL methylation with poorer disease-free survival in patients with gastric cancer, highlighting its potential as an independent

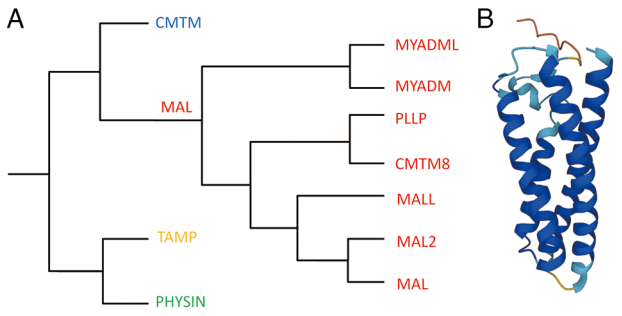

Figure 1. (A) Phylogenetic tree depicting the relationship of the MAL-family within human MARVEL domain-containing proteins. (B) Predicted structure of human MAL according to AlphaFold (https://alphafold.ebi.ac.uk/entry/P21145). The alignment of the indicated proteins, excluding their cytoplasmic amino- and carboxyl-terminal tails, was performed using the Muscle algorithm of the Jalview software, and the resulting alignment was analyzed using Mega 11 software. The protein accession numbers are as follows: MAL (NP_002362.1), MAL2 (NP_443118.1), MALL (NP_005425.1), PLLP (NP_057077.1), CMTM8 (NP_849199.2), MYADM (NP_612382.1), MYADML2 (NP_001138585.2). MAL, myelin and lymphocyte protein; MARVEL, MAL and associated proteins for vesicle formation and membrane link; PLLP, plasmolipin; CMTM8, CKLF-like MARVEL transmembrane domain-containing 8; MYADM, myeloid differentiation-associated marker; TAMP, tight junction-associated MARVEL protein.

marker (76). Moreover, the MAL protein can inhibit gastric cancer invasion and metastasis by interfering with STAT3 phosphorylation (77). Another study detected MAL hypermethylation in 80% (49/61) of colorectal cancers and 71% (45/63) of adenomas vs. only 4% (1/23) of normal mucosa samples using methylation-specific polymerase chain reaction, indicating MAL is downregulated early during progression (73).

In breast cancer cells and 69% of primary tumors, bisulfite sequencing revealed MAL promoter CpG island hypermethylation relative to normal breast epithelia (75,78). Restoring MAL expression reduces tumor cell migration and alters lipid raft organization (75,78). Among patients with breast cancer not receiving chemotherapy, low MAL expression is prognostic for worse disease-free survival, supporting its use as an adjuvant predictor (75).

CADM1/MAL methylation in high-risk human papillomavirus (HPV) positive Pap smears associates with extent and duration of underlying cervical pathology, increasing in invasive cervical cancer (79,80). Combined detection plays an important diagnostic role in identifying precancerous cervical intraepithelial neoplasia (81-83). MAL also serves as an indicator distinguishing long-term and short-term ovarian cancer prognoses, with silencing conferring treatment resistance (84,85). Lee *et al* (86) found that MAL methylation status marks platinum sensitivity in ovarian cancer, suggesting MAL represents a therapeutic target. Furthermore, low CADM1/high MAL levels associate with improved prognosis in Merkel cell carcinoma (87), whereas low MAL predicts poor Wilms' tumor outlook by altering the microenvironment (88). Finally, MAL demonstrates consistently reduced expression in head/neck and oral squamous cell carcinomas, with overexpression inhibiting proliferation, invasion and tumorigenesis (63,89-91,115).

Non-coding mRNAs (ncRNAs) modulate the expression of protein-coding genes and are classified as short, such as micro RNAs (miRNAs), or long ncRNA (lncRNA). LncRNA-AC103563.8 promotes oral carcinoma development by suppressing MAL expression or interacting with other tumor-related proteins, such as RPS3A, hnRNPK, HSPA9, RPS3, NCL and RPL12 (105).

3. MAL2

MAL2, encoded on chromosome 8q24, was first identified by Wilson *et al* (116) in 2001. MAL2 protein is a 19 kDa, four-transmembrane integral protein sharing 35.8% homology with the MAL proteolipid required for apical transport, considered to be the closest family member to the MAL protein (116). In hepatoma HepG2, MAL2 selectively localizes to cholesterol-rich lipid raft membrane microdomains and is crucial for indirect route of raft-dependent apical membrane transport (42). MAL2 interacts with the constitutively active, Golgi-associated serine/threonine kinase 16 to sort soluble secretory cargo through the constitutive secretory pathway at the TGN in polarized hepatocytes (117). Unlike the Golgi-predominant distribution of MAL, immunohistochemistry (IHC) of thyroid follicles indicated that MAL2 localizes to the apical membrane within lipid rafts, implicating MAL2 in transcytotic cargo transport from perinuclear endosomes to the apical surface via a raft-dependent pathway (118). However, studies in PC-3 prostate and breast cancer cells demonstrated additional MAL2 distribution in non-lipid raft components, suggesting its distinct functions inside and outside the lipid raft (119,120). In HepG2 cells, after CD59 endocytosis, some MAL2 redistributed into vesicular clusters concentrating CD59 and leaving CD59 accessible to the basolateral recycling transferrin receptor. The receptor then segregates before the clusters fuse into $MAL2^+$ structures that move apically to deliver CD59 (21). MAL2 loss blocks apical transport of polymeric immunoglobulin A receptor (pIgA-R) and CD59, leading to perinuclear endosomal accumulation reachable by transferrin (42). MAL2 also regulates pIgA-R Golgi-to-membrane transfer, whereby pIgA-R remains in the Golgi when expressed alone in hepatic WIF-B cells, but reaches the cell surface, undergoes endocytosis and localizes to $MAL2^+$ regions when co-expressed with MAL2 (121).

IHC shows MAL2 expression in the respiratory, digestive, genitourinary, endocrine and exocrine epithelia (often apically) as well as in specialized secretory cell clusters such as pancreatic endocrine cells. Peripheral neurons, mast cells, dendritic cells and hepatocytes also express MAL2 (Table II) (22). Chromosome 8q24 gains, encompassing the MAL2 locus, associate with several epithelial cancer types and may explain upregulated MAL2 transcription in subsets of these malignancies (122,123).

Overexpression of MAL2 in breast cancer can interact with β-catenin in breast cells, inducing c-Myc to promote proliferation and invasion by regulating epithelial-mesenchymal transition (124,125). MAL2 also associates with decreased immune infiltration and eosinophil/dendritic cell expression, conferring worse prognosis (126). Multi-omics analysis and cytology experiments by Yuan *et al* (127) showed high MAL2 levels in invasive breast, pancreatic, bladder, ovarian, cervical and other carcinomas, and high MAL2 expression associated with unfavorable prognosis in certain tumors. Yeast two-hybridization, pull-down and coimmunoprecipitation

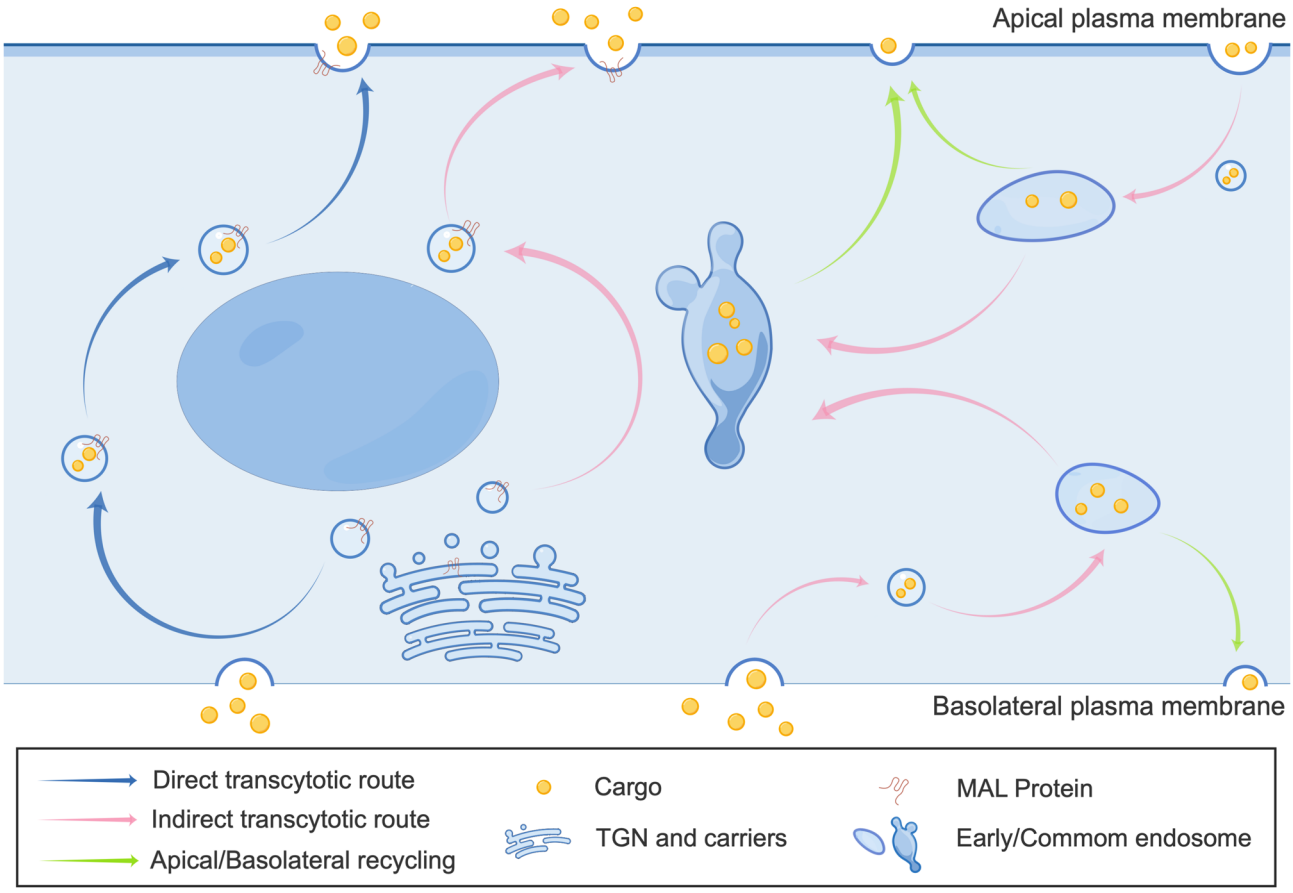

Figure 2. Schematic representation of transcytosis. Transcytosis involves two fundamental pathways. In the direct route, proteins are sorted in the TGN and transported directly to the apical or basolateral surface. In the indirect route, proteins are initially sent to one surface, then endocytosed and subsequently delivered to early endosomes. Endocytosed proteins may either recycle to the surface, undergo degradation by late endosomes and lysosomes (not shown) or undergo transcytosis to the opposite surface. MAL protein primarily localizes to the TGN, facilitating the transport of vesicles to regulate protein sorting. TGN, trans-Golgi network; MAL, myelin and lymphocyte protein.

experiments showed that the N-terminus of MAL2 interacts with tumor protein D52 (TPD52) in breast cancer cells per (116). Jeong *et al* (128) demonstrated that MAL2 plays key roles in breast cancer lipid raft formation, HER2 signaling and membrane stability. As a chaperone protein for tumor-associated protein mucin 1 (MUC1), MAL2 binds MUC1 in non-raft fractions, potentially promoting breast tumorigenesis by modulating MUC1 expression and localization (120). In addition, MAL2 can prompt breast cancer immune evasion through MHC-I endocytosis and degradation, hindering antigen presentation and $CD8^+$ T cell response. MAL2 inhibition conversely enhances cytotoxicity and recognition to suppress tumor growth (43,129). Zhu *et al* (130) found that the MAL2/MUC1-C/PI3K/AKT/mTOR signaling elicits triple-negative breast cancer (TNBC) aggressiveness, mitigated by targeted small molecules.

In non-small cell lung cancer cells, MAL2 overexpression hyperactivates MAPK/mTOR signaling, thus, targeting this pathway may improve therapeutic efficacy in these patients (29,131). MAL2 also interacts with IQGAP1 in pancreatic cancer, heightening ERK1/2 phosphorylation to drive progression and associate with increased metastasis (25,131,132). Chronic pancreatitis maintains MAL2 expression, providing utility as a diagnostic marker (133). The ST8SIA6-AS1/miR-145-5P/MAL2 axis promotes the progression of cholangiocarcinoma and may help improve clinical outcomes (134). MAL2 is expressed in prostate cancer and may regulate disease progression through the Notch signaling pathway (26). Gao *et al* (134) found that miR-129 negatively regulates expression of MAL2 in papillary thyroid carcinoma and may be a potential therapeutic target. The high expression of MAL2 exhibits TPD52-associated expression in ovarian/colorectal tumors, although the survival of patients with ovarian cancer shows no clear association (30,135,136). Various other malignancies overexpress MAL2, including gastric, cervical, bladder, oral and head/neck squamous cell carcinoma (31,34,137-139).

Circular (circ) RNAs, which are a subclass of lncRNA structured in a loop with the 3' and 5' RNA ends joined covalently, can inhibit miRNA activity, whereas other lncRNAs promote miRNA functions (140,141). For instance, miR-129 suppresses MAL2 in papillary thyroid cancer, representing a potential therapeutic target (140). The ST8SIA6-AS1/miR-145-5P/MAL2 axis promotes the progression of cholangiocarcinoma and may help improve clinical outcomes (142). Additional examples include co-regulation of MAL2 by miR-802 and the circRNA, circ_0084904 in cervical cancer (31), by miRNA320a alongside the lncRNA, metastasis-associated lung adenocarcinoma

Table I. Overview of MAL family members.

Gene names	Protein names	Length
MAL	Myelin and lymphocyte protein (T-lymphocyte maturation-associated protein)	153
MAL2	Protein MAL2	176
PLLP PMLP TM4SF11	Plasmolipin; plasma membrane proteolipid	182
MALL BENE	MAL-like protein; protein BENE	153
MYADM UNQ553/PRO1110	Myeloid-associated differentiation marker; protein SB135	322
MYADML2	Myeloid-associated differentiation marker-like protein 2	307
CMTM8 CKLFSF8	CKLF-like MARVEL transmembrane domain-containing protein 8; chemokine-like factor superfamily member 8	173

Table II. Distribution of MAL and MAL2 in different human tissues.

Tissue/organ	MAL^+ and $MAL2^+$ expression	MAL^+ and $MAL2^-$ expression	$MAL2^+$ and MAL^- expression
Esophagus	Stratified squamous epithelium	-	-
Stomach	Parietal cells, chief cells and surface mucous cells	-	-
Small intestine	Crypt cells, Paneth cells and enterocytes with microvilli	Lymphocytes (Peyer's patches)	-
Large intestine	Mucous cells	-	-
Liver	Hepatocytes and intrahepatic ductal epithelium	-	Biliary canaliculi
Pancreas	Acinar cells, ductal cells and endocrine cells	-	-
Kidney	Distal convoluted tubules, collecting tubules and loop of Henle	-	Glomerulus
Bladder/ureter	-	Superficial cells from transitional epithelium	Ductal and acinar cells
Prostate	-	Ductal and acinar cells	-
Bronchi/trachea	Respiratory epithelium and goblet cells	-	-
Lung	Type 2 pneumocytes and mucous cells	-	Alveolar lining cells
Lymph node	High endothelial venules endothelium	T cells	Dendritic cells
Thymus	Hassall's corpuscles	Cortical thymocytes and medullary thymocytes	Epithelial cells
Thyroid gland		Thyrocytes	-
Adrenal gland	Medullary cells, zona reticularis, zona glomerulosa and zona fasciculata	-	-
Testis	Leydig and Sertoli cells	-	-
Uterine	Cervix	Uterine corpus endometrium	-
Skin	-	Ductal eccrine cells	Apical keratinizing epithelium and sebaceous glands

MAL, myelin and lymphocyte protein.

Table III. Regulation of MAL gene hypermethylation and expression in cancer.

Cancer	MAL gene hypermethylation	Silenced MAL mRNA expression	MAL mRNA expression rescue by DAC treatment	(Refs.)
Esophagus	Yes	Yes	Yes	(32,74,92-94)
Stomach	Yes	Yes	-	(76,77,95,96)
Colon	Yes	Yes	Yes	(73,97-101)
Breast	Yes	Yes	Yes	(75,78,102)
Cervix	Yes	Yes	Yes	(41,62,79,81,82,103-106)
Ovary	No	No	-	(84-86,107,108)
Skin	No	No	-	(87)
Prostate	Yes	Yes	-	(109,110)
Head and neck	Yes	Yes	Yes	(63,90,111-114)
Oral cavity	Yes	Yes	-	(89,115)

MAL, myelin and lymphocyte protein; DAC, decitabine.

transcript 1 in bladder cancer (34) and by LINC00460 and miRNA320a to enable breast cancer cell proliferation and ferroptosis evasion (143).

Notably, the research of López-Coral *et al* (122) showed lower MAL2 protein levels in hepatocellular carcinoma, cholangiocarcinoma and renal cell carcinoma relative to normal tissue. This implies MAL2 protein may have tumor-suppressive roles, potentially by inducing actin-remodeling filopodia to reduce migration, invasion and proliferation-effects reversed upon MAL2 loss (Table IV) (122).

4. PLLP/TM4SF11

PLLP protein is a transmembrane protein encoded by the PLLP gene, also known as transmembrane 4 superfamily member 11 (TM4SF11), which plays a role in epithelial development, differentiation and migration (144-147). PLLP is chemically similar to MAL and proteolipid protein (PLP), a type of myelin protein, sharing 29% homology and 49% similarity with MAL. This conserved sequence facilitates the classification PLLP as a MAL family member (2,148,149). In polarized cells, PLLP predominantly localizes to the apical membrane with some basolateral distribution. PLLP, like its homologue MAL, is isolated in the lipid raft in the trans-Golgi apparatus network and before its transport to the apical and basolateral cell surfaces (147,150-152). PLLP is delivered to the plasma membrane via microtubules as a component of vesicles (147,150). Endocytosed PLLP then forms marginal vesicles transported back to the Golgi and other regions, completing an intracellular cycle (144,153,154). Interaction with ganglioside GM1 restructures the extracellular loops of PLLP, propagating a conformational signal through the plasma membrane to the intracellular domain, consistent with the role of PLLP in signal transduction (155).

Western blotting experiments demonstrate PLLP expression in nervous, digestive (stomach, esophagus and colon), renal, cardiac, pulmonary, musculoskeletal, immune (thymus) and reproductive (ovarian and testicular) tissues, as well as endocrine glands such as the adrenal, parotid, submandibular, Cowper's and prostate (44,156-158). Abundant apical localization manifests in kidney tubular epithelia and diverse gastric glandular regions (44,158). Nervous system expression includes spinal leucoplast, peripheral Schwann cells and central oligodendrocytes (44,156,157,159). While PLLP resides apically in epithelia, phosphorylated PLLP in neural cells contributes to myelination by inducing myelin precursor domains in the Golgi (44,158). PLLP plays an important role by activating the Notch signaling pathway, which is essential for cell differentiation and processes such as epidermal regeneration and diabetic wound healing (145,160). Reduced PLLP levels in patients with idiopathic pulmonary fibrosis implies protective roles in promoting endothelial development, membranes and cell junctions (161). However, no clear evidence elucidates PLLP-mediated tumorigenesis via Notch or other pathways.

5. MALL/BENE

The MALL protein, also called BENE, was originally identified proximal to immunoglobulin light chain κ locus. MALL comprises a protein-lipid with a four-transmembrane topology resembling PLP, PLLP and MAL that circulates between cell membranes, endosomes and Golgi to mediate apical transport (162,163). Electron microscopy and immunofluorescence analyses in endothelial-like ECV304 cells revealed predominant MALL localization to intracellular tubulovesicular structures with partial caveolin-1 colocalization (163). Co-immunoprecipitations confirmed MALL-caveolin-1 interactions, reflecting roles in cholesterol regulation (163). Beyond this membrane form, MALL also resides within promyelocytic leukemia nuclear body condensates (164). During mitosis, MALL accumulates in solid-like condensates around the spindle but, when in excess, the condensates mis-localized, altered the distribution of nuclear proteins emerin LAP2β and BAF, and caused nuclear aberrations, which are a hallmark of cancer cells (164).

MALL is expressed in prostate, intestinal, cardiac and other tissues, but not brain, thymus, hepatic or splenic tissue (15). Oncogenesis appears to induce MALL expression in some cancers such as pancreatic and kidney while it is reduced in other malignancies such as colorectal, breast and lung (164).

Table IV. Relative mechanism with the expression of MAL2 in different cancers.

Cancer	MAL2+	MAL2-	(Refs.)
Breast	MAL2/β-catenin/c-Myc axis, epithelial-mesenchymal transition, low immune infiltration, TPD52, HER2signaling pathway, MAL2/MUC1-C/PI3K/AKT/mTOR pathway, MUC1, MHC-I complex, miR-320a/MAL2 axis, LINC00460/miR-320a/MAL2 axis	-	(43,116,120,125, 128-130,143)
Lung	MAL2/MAPK/mTOR pathway	-	(29)
Colon/rectum	TPD52	-	(134,135)
Liver	-	Myc protein expression	(122)
Pancreas	ERK1/2 phosphorylation	-	(25,131,133)
Bile duct	ST8SIA6-AS1/miR-145-5P/MAL2 axis	Myc protein expression	(122,142)
Kidney	-	Myc protein expression	(122)
Prostate	Notch signaling pathway	-	(26)
Bladder	MALAT/miR-384/MAL2 axis	-	(34)
Ovary	TPD52	-	(30)
Cervix	miR-802/MAL2 axis	-	(31)
Thyroid gland	miR-129/MAL2 axis	-	(141)
Oral cavity	miR-383-5p/MAL2 axis	-	(136)

MAL, myelin and lymphocyte protein; TPD52, tumor protein D52; MUC1, mucin 1; MALAT, metastasis-associated lung adenocarcinoma transcript.

In colorectal cancer, significantly decreased MALL impacts caveolin-1 signal transduction and Akt-1 activity (165-167). MALL suppresses colorectal growth and metastasis by inhibiting the metastasis/angiogenesis-associated ERK/MAPK pathway (167). Conversely, in pancreatic cancer there is overexpression of MALL and nuclear abnormalities conferring poorer prognosis (164). MALL also associates with unfavorable kidney cancer outcomes (168).

6. MYADM and MYADML2

MYADM is an eight-transmembrane protein with two MARVEL domains residing in nuclear and cytoplasmic membranes. It regulates plasma membrane-cytoskeleton connections, thereby controlling endothelial inflammation (46,159,169). Previous studies demonstrate selective MYADM expression in myeloid lineage and hematopoietic cells, implicating roles in myeloid differentiation (170-172). MYADM also shows abundant expression in various tissue epithelia and neural/pulmonary tissues (46,173). In pulmonary arterial hypertension, MYADM elicits smooth muscle proliferation through microRNA-182-3p induction and vascular remodeling (174).

Several cancers exhibit upregulated MYADM protein, including metastatic melanoma and hepatocellular carcinoma, where it constitutes an independent survival/prognostic factor (175-178). During prostate cancer metastasis, MYADM upregulation in tumor-osteoclast/endothelial co-cultures also support roles in facilitating spread (179). Furthermore, increased MYADM mRNA marks myeloid leukemia differentiation, providing utility as a disease monitoring marker (170). In biomarker studies of prostate cancer recurring within five years in African Americans, MYADM associates with this aggressive disease course (180).

MYADML2, a protein structurally similar to MYADM, exhibits elevated mRNA expression levels in hepatocellular carcinoma (181). Pathological results show cell population formed highly metastatic tumors in lung after being mutagenized with CRISPR activation. In vitro validation indicated overexpression of MYADML2 promoted proliferation and invasion of cells, and the inhibition suppressed cancer progress (181). Its role in reducing sensitivity to chemotherapeutic drugs has also been documented (181).

7. CMTM8

CMTM8, a novel chemokine comprising 173 amino acids, shares up to 39.3% amino acid sequence homology with the MAL family molecule PLLP, thus classifying it within the MAL family (18). Research has demonstrated that CMTM8 expedites the internalization of transferrin receptor and EGFR, hastening the clearance of EGFR from the cell surface upon ligand induction (182). Furthermore, CMTM8 modulates EGFR-mediated signaling pathways by reducing ERK phosphorylation levels (183). Subsequent investigations have revealed that CMTM8 induces apoptosis in cells through both caspase-dependent and caspase-independent pathways (184). Li *et al* (182) reported CMTM8-V2 as a selective splicing isoform of CMTM8, maintaining the ability to induce apoptosis. However, the second exon encoding the MARVEL

Table V. Strategies to test MAL family members in clinical oncology research.

Strategies	Methods	Samples	Advantages	Disadvantages	Prospect
Gene expression analyses	Hybridization of cDNA microarrays, RT-PCR/quantitative RT-PCR, RNA-seq and western blotting	Biopsy/surgical specimens and biofluids such as blood, urine and feces	Accurate and quantitative	Not sensitive and rare in clinical practice	Cancer research
DNA methylation	Sequencing of bisulfite-treated DNA, MSP, quantitative MSP and pyrosequencing	Biofluids such as blood, urine and feces	Predictive value	Complex data analysis and rare in clinical practice	Cancer prevention and treatment
IHC	-	Biopsy/surgical specimens	Direct, high sensitivity and gold standard for cancer cell characterization	Cannot be quantitative, only qualitative	Cancer diagnosis and treatment

MAL, myelin and lymphocyte protein; MSP, methylation-specific PCR; IHC, immunohistochemistry.

domain and cytoplasmic YXX motif is absent in this isoform, thereby not impacting EGFR internalization.

While CMTM8 is widely expressed in numerous healthy human tissues, its downregulation or deletion has been observed in several solid tumors, including gastric cancer, lung squamous cell carcinoma, cervical cancer and renal clear cell carcinoma (182,185-187). Overexpression of CMTM8 induces apoptosis in hepatocellular carcinoma cells by influencing caspase expression through mitochondria, thereby mediating related signaling pathways (184). Conversely, downregulation of CMTM8 activates the c-Met signaling pathway, leading to the epithelial-mesenchymal transition of hepatocellular carcinoma cells, facilitating tumor migration and invasion (188). In TNBC, miR-582-5p selectively inhibits CMTM8, resulting in decreased CMTM8 expression and attenuating its inhibitory effect on TNBC cell migration and invasion (189). Moreover, CMTM8 has been shown to inhibit the EGFR signaling pathway activity in osteosarcoma, suggesting its potential role as an osteosarcoma suppressor gene (190). Additionally, upregulation of CMTM8 inhibits the proliferation and invasion of bladder cancer T24 cells and enhances their sensitivity to chemotherapeutic drugs (191).

However, Gao *et al* (192) reported that overexpression of CMTM8 in bladder cancer promoted tumor growth and metastasis. High expression of CMTM8 has also been confirmed in colon and ovarian cancer (193,194). Lastly, Shi *et al* (195) identified CMTM8 as a critical mediator of lysophosphatidic acid (LPA)-induced pancreatic cancer invasion. CMTM8 interacts with LPA1 to activate the carcinogenic β-catenin signaling transduction, thereby enhancing tumor migration and invasion.

8. Conclusion

The MAL family encompasses members that are widely distributed across various bodily systems, with their involvement in the digestive, respiratory, urinary and circulatory systems being successively uncovered. These proteins play crucial roles in tumorigenesis signaling pathways and cell cycle regulation, thereby influencing tumor development and patient prognosis (38,39,42,68,136,164). However, the current understanding of their specific molecular mechanisms remains limited. Notably, high expression of MAL family members in normal tissues and their decreased expression in tumor tissues provide a reliable basis for tumor diagnosis. Furthermore, the expression of MAL in certain tumor tissues associates with the malignancy of tumors, offering prognostic value for patients with cancer (38,85,101, 127,155,164,184). Overexpression of MAL has been shown to induce apoptosis in tumor cells, while its inhibition leads to epithelial-to-mesenchymal transition, suggesting its potential as a suppressor of tumor cell proliferation and a candidate for tumor immunotherapy (1,38).

Non-invasive molecular detection techniques for cancer screening are rapidly advancing, with MAL family members serving as important cancer biomarkers in clinical testing (Table V). These members have been extensively utilized in non-invasive tests, such as MAL methylation assays in blood, urine and feces-derived samples from patients with various tumors (82,196-199), as well as the analysis of MAL2 transcript levels in blood from patients with gynecological and metastatic breast cancer (200,201). Integration of antibodies targeting MAL family members into existing antibody panels used in standard clinical practice for identifying cancer biomarkers in biopsies and surgical specimens, along with their application in liquid biopsies, may offer valuable avenues for enhanced prognostic and diagnostic insights in cancer cases.

While gene methylation or expression analyses are not commonly performed in medical pathology departments, IHC analysis of protein expression stands as the gold standard for

characterizing cancer cells and has been used in research. Additionally, RT-qPCR and western blotting techniques have been employed to investigate the expression of MAL family genes.

Moreover, MAL family members can serve as predictive biomarkers for specific treatment modalities. For instance, MAL has been identified as one of the most highly expressed genes in survivors of short-term serous ovarian cancer (84), with its transcripts significantly overexpressed in ovarian cancer cell lines resistant to conventional platinum-based and other chemotherapeutic agents (85). This suggests its potential use in predicting the response to platinum-based drugs and as a target for developing novel therapies to improve the sensitivity of ovarian cancer to these drugs. Similarly, MAL serves as a potential biomarker with clinical significance in predicting the response of patients with breast cancer to anthracycline and taxane, commonly used in adjuvant chemotherapy for early breast cancer (38,202,203). Additionally, the level of MAL2 transcripts in pancreatic cancer demonstrates an inverse correlation with resistance to various chemotherapeutic agents, making it a potential indicator of chemotherapy response (204). Furthermore, MYADM has been identified as a potential biomarker for predicting the response to the drug MS-275, and possibly other histone deacetylase inhibitors, in colon adenocarcinoma (205).

While progress has been made in understanding the function of certain MAL family proteins, further exploration of their expression, molecular mechanisms and related signaling pathways in tumors is expected to not only serve as molecular markers for detecting tumorigenesis, progression and metastasis, but also lead to new breakthroughs in prognostic prediction and treatment of patients with cancer. This necessitates continued research to fully comprehend the role of MAL family proteins in normal and tumor cells, with potential implications for the development of targeted therapeutic agents.

In conclusion, a deeper investigation into the expression, molecular mechanisms and associated signaling pathways of MAL family members in tumors is anticipated to serve not only as molecular markers for detecting tumorigenesis, progression and metastasis, but also to yield novel insights for prognostic prediction and treatment of patients with cancer.

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Availability of data and materials

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Authors' contributions

ML, YD and XZ substantially contributed to the conception and the design of the study, or in the acquisition, analysis and interpretation of the data; and ML, YD, XZ and WZ contributed to manuscript drafting or critical revisions on the intellectual content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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