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REVIEW ARTICLE

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The crucial role of CEMIP in cancer metastasis: Mechanistic insights and clinical implications

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Abstract

Cancer metastasis is the leading cause of cancer-related deaths, making early detection and the prevention of metastatic progression critical research priorities. Recent studies have expanded our understanding of CEMIP (KIAA1199, HYBID), revealing its involvement in cancer metastasis and its potential role in slowing cancer progression. CEMIP plays critical roles in several stages of cancer metastasis: First, CEMIP promotes cancer cell proliferation to maintain cell heterogeneity before the metastasis process. Second, it facilitates cancer cell detachment by promoting the epithelial-mesenchymal transition (EMT) through alterations in signaling pathways. Third, CEMIP contributes to cancer cell adherence and attachment by enabling cells to withstand cell death (anoikis and ferroptosis) and hypoxia. Fourth, during the invasion process, CEMIP induces hyaluronan depolymerization and further modulates signaling to promote EMT. Lastly, in the pre-metastatic niche, CEMIP influences the tumor microenvironment through hypoxia, angiogenesis, signaling pathway changes, and hyaluronan degradation. Recent studies have focused on leveraging CEMIP as a diagnostic tool or a predictor of metastasis and/or targeting CEMIP to overcome cancer resistance and progression. This review aims to explore the role of CEMIP at each stage of cancer metastasis and highlight recent advances in targeting CEMIP to inhibit cancer progression.

KEYWORDS

Anoikis, cancer metastasis, CEMIP, EMT, ferroptosis, hyaluronan, hyaluronidase, KIAA1199, premetastatic niche formation, tumor microenvironment

Abbreviations: CCA, cholangiocarcinoma; CRC, colorectal cancer; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; HA, hyaluronan, also known as hyaluronic acid; HMW-HA, high-molecular-weight hyaluronan; LMW-HA, low-molecular-weight hyaluronan; miRNA, microRNA; MSI, microsatellite instable; MSS, microsatellite stable; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; PKCα, protein kinase C α; RHAMM, receptor for hyaluronic acid-mediated motility; rHDL, reconstituted high-density lipoprotein; SCLC, small cell lung cancer; sHA, sulfated hyaluronan; shRNA, short hairpin RNA; siRNA, small interfering RNA; TME, tumor microenvironment; VLDL, very low-density lipoprotein.

1 | INTRODUCTION TO CEMIP

1.1 | CEMIP: A key player in cancer metastasis

Cancer metastasis is the leading cause of cancer-related deaths, making it crucial to identify its molecular drivers for the development of effective treatments. Therefore, early detection and slowing the progression of metastasis have become critical areas of study.[1]

CEMIP (cell migration-inducing hyaluronidase 1), also known as KIAA1199 or hyaluronan-binding protein (HYBID),[2,3] is one such protein that has garnered attention. CEMIP is most notable for its roles in cancer: It is found at high levels in various cancers, including colon,[4] lung,[5] pancreatic cancer,[6] prostate,[7] and gastric cancer.[8] High CEMIP levels are associated with cancer progression,[9,10] making it an important molecular marker for metastasis and a potential therapeutic target for treatments aimed at controlling metastasis.[6,11]

This review explores the multifaceted role of CEMIP in cancer metastasis, highlighting its involvement in key processes such as tumor cell proliferation,[12] detachment, adherence, invasion, and adaptation within the tumor microenvironment.[13] CEMIP influences critical metastatic events by modulating signaling pathways,[14–18] inducing epithelial-mesenchymal transition (EMT),[14,19,20] and degrading hyaluronan.[21,22] These interconnected processes contribute to cancer progression, positioning CEMIP as a promising target for new therapeutic strategies aimed at disrupting metastasis. Recent studies have increasingly focused on inhibiting CEMIP, reinforcing its potential as a key target for treating metastasis. This review will examine CEMIP's role in metastasis and its clinical implications, emphasizing its growing potential as a therapeutic target in cancer treatment.

1.2 | Structure of CEMIP

CEMIP was discovered in the early 2000s as part of a cDNA array analysis project.[2,3] Understanding the gene structure of CEMIP might suggest strategies to block its function. CEMIP, which is located on the human genome at 15q25.1, encodes a 1361-amino acid protein.[3,23] The genome structure of CEMIP consists of 29 exons and 28 introns, with the translational initiation site (AUG) starting at exon 2. The region essential for transcription in the CEMIP promoter is *pro*-1.4.[24,25] The CEMIP promoter contains binding sites for transcription factors, including one, two, and four sites for AP-1, NF-kB, and Twist, respectively. The CEMIP promoter is also regulated by methylation: There are two CpG islands; the first is rarely methylated, while the second often exhibits methylation. Promoter demethylation is associated with upregulation of CEMIP expression in breast cancer.[24] Colon adenocarcinomas of microsatellite instable (MSI) or microsatellite stable (MSS) status at stages 2 and 3 show less CpG island methylation in cells of the normal colon mucosa.[26] Shostak et al. found that the transcription factors, BCL-3 and p65, attach to the NF-kB site to induce CEMIP expression in human papillomavirus (HPV)-positive cervical cancer cells.[14] In breast cancer, the enzyme GALNT6 mediates the mucin-type O-glycosylation (O-GalNAc) of coiled-coil domain-containing 88C (CCDC88C), which increases CEMIP mRNA expression through c-JUN phosphorylation. This indicates that CCDC88C triggers CEMIP transcription, leading to breast cancer metastasis.[27]

CEMIP is a glycosylated protein; it is primarily located in the endoplasmic reticulum (ER) but is also found on the plasma membrane and secreted to the extracellular environment.[3,23,28] The CEMIP protein has one G8 domain, two GG domains, and four pbH1 domains. In rheumatoid arthritis fibroblast-like synoviocytes (RA FLS), the G8 domain in secreted CEMIP binds to ANXA1 (a CEMIP-interacting membrane protein) and promotes hyaluronic acid (also known as hyaluronan, HA) degrading activity. Therefore, deletion of the G8 domain or silencing expression of ANXA1 reduces HA-degrading activity.[29] The GG domain has been newly identified in CEMIP, and it is known to include glycine residues.[30] In CEMIP, the GG domain is also required for HA degradation and interaction with HA substrates.[31] The N-terminal 30 amino acids of CEMIP play roles in intracellular transport, HA-depolymerization activity, ER targeting, and vesicle transport through the Golgi apparatus. Therefore, CEMIP lacking the N-terminal exhibits folding defects, prevents passage through the ER, and accumulates in the cytoplasm.[32]

2 | CEMIP AND CANCER PROGRESSION: FROM PROLIFERATION TO METASTASIS

2.1 | CEMIP and cancer cell proliferation

Cancer proliferation is a fundamental process by which a single transformed cell undergoes rapid division, acquires genetic heterogeneity, and prepares for metastasis.[12] During this progression, CEMIP plays a critical role by modulating signaling pathways, regulating the cell cycle, and driving metabolic reprogramming, thereby supporting cancer cell growth and survival (Figure 1).

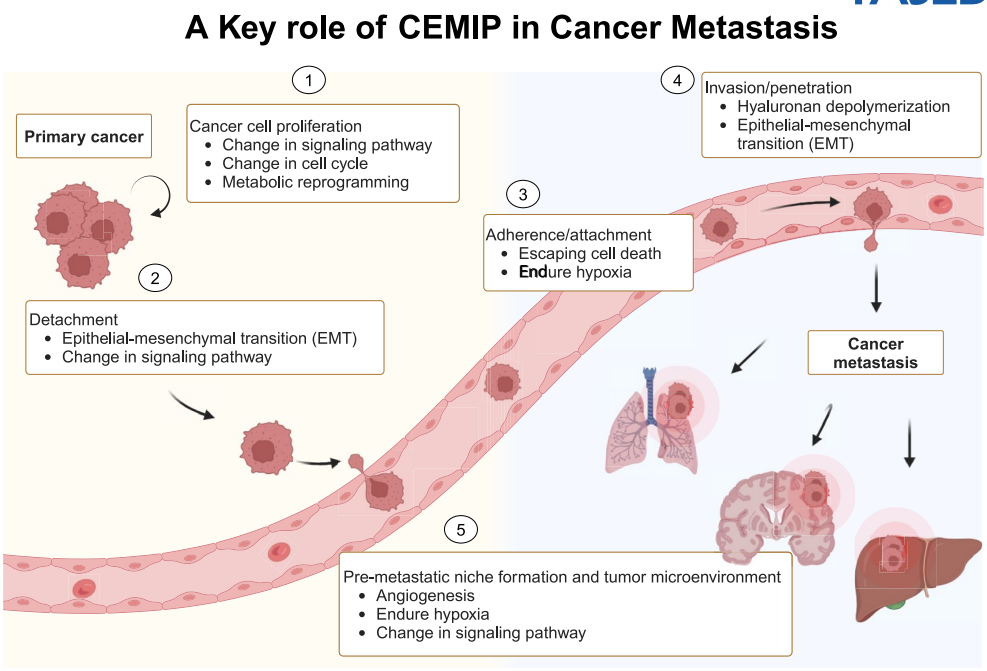

FIGURE 1 Cancer metastasis involves five main steps: (1) Cancer cell proliferation, (2) cancer cell detachment, (3) adherence/attachment, (4) invasion/penetration, and (5) pre-metastatic niche formation.[13,33] CEMIP influences each of these steps. In the cancer cell proliferation step, CEMIP alters signaling pathways,[14–17,20,26,34] changes the cell cycle,[35] and contributes to metabolic reprogramming in preparation for metastasis.[15,36–38] In the cancer cell detachment step, CEMIP promotes the epithelial-mesenchymal transition (EMT) by altering signaling pathways.[14,19–21] During the adherence/attachment step, CEMIP helps cancer cells evade cell death and withstand hypoxia.[39,40] In the invasion/penetration step, CEMIP degrades hyaluronan and alters signaling pathways.[41] Finally, in the pre-metastatic niche formation step, CEMIP contributes to the formation of the tumor microenvironment by addressing hypoxia, promoting angiogenesis through signaling pathway changes, and facilitating hyaluronan depolymerization.[35,42] This image was created with BioRender (https://biorender.com/).

2.1.1 | CEMIP-mediated signaling cascades and cell cycle regulation

CEMIP drives cancer cell proliferation by modulating key signaling pathways, including PI3K/AKT, EGFR, Wnt/β-catenin, MEK/ERK (Figure 2), and STAT3. These pathways collectively enhance cell cycle progression and tumor growth.

- EGFR pathway: In cervical cancer, CEMIP inhibits semaphorin 3A- and plexin A2-dependent apoptosis while maintaining high EGFR levels, contributing to sustained cell proliferation and survival (Figure 2).[14]
- MEK/ERK pathway: In BRAF-mutated colorectal cancer, CEMIP binds to MEK1 to enable cells to resist MEK1 inhibitors, such as selumetinib. This interaction increases phosphorylated MEK1/2, ERK1/2, and RSK1 levels, driving cancer cell proliferation and survival (Figure 2).[15]
- PI3K/AKT pathway: In ovarian cancer, silencing of CEMIP is associated with decreases in the levels of PI3K, AKT, ribosomal protein S6 kinase (P70S6K), BCL-2, phosphorylated PI3K, and phosphorylated AKT. CEMIP enhances PI3K activity, leading to the phosphorylation of Akt. This, in turn, activates P70S6K to increase cell growth, cell cycle progression, and protein synthesis. Additionally, BCL-2, which is a substrate of AKT, prevents cell apoptosis (Figure 2).[16,35]
- Wnt/β-catenin pathway: Wnt proteins interact with the cell surface receptor, Frizzled, and inhibit GSK-3β and casein kinase 1 (CK1) to stabilize β-catenin. Stabilized β-catenin moves into the nucleus, where it promotes the expression of c-myc, cyclin D1, ASCL2, and PPARδ by interacting with the TCF/LEF transcription factors (Figure 2).[18] In colorectal cancer (CRC) and gastric cancer cells in vitro, CEMIP knockdown downregulates members of the Wnt/β-catenin pathway, including β-catenin, cyclin D1, c-myc, and MMP family members.[20,26,34] Interestingly, another study demonstrated that increased nuclear β-catenin levels correlated with higher nuclear CEMIP levels in CRC cells.[26]
- STAT3 pathway: CEMIP upregulates glucose-regulated protein 78 (GRP78), a key ER chaperone, which in turn activates STAT3 signaling. This pathway promotes breast cancer cell proliferation and migration, further underscoring CEMIP's role in aggressive tumor behavior.[17,44]

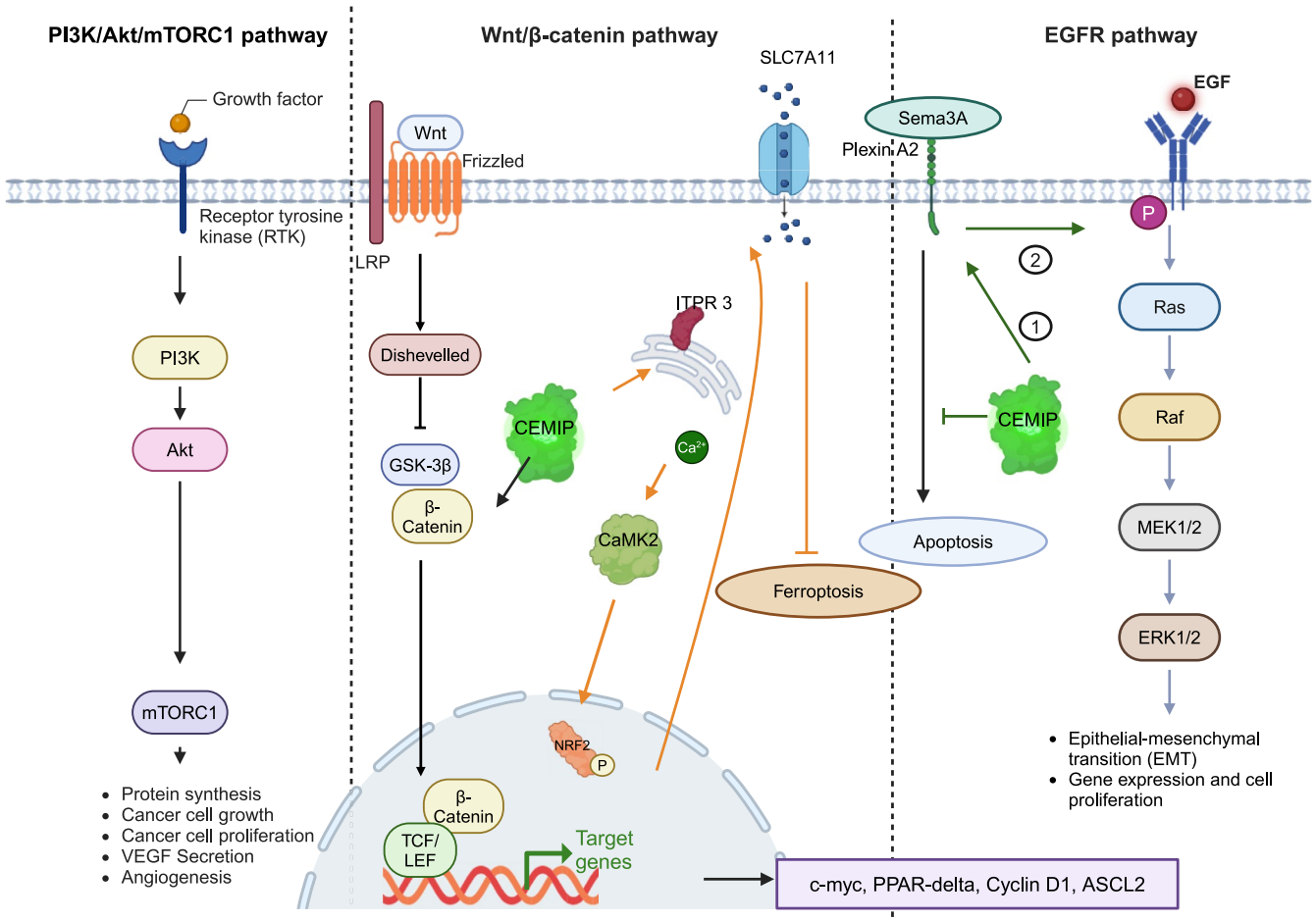

FIGURE 2 CEMIP affects the PI3K/AKT, EGFR, and Wnt/β-catenin signaling pathways, which contribute to cancer progression by promoting cancer cell growth, angiogenesis, and proliferation, while also inhibiting cell death.[18,43] CEMIP inhibits semaphorin 3A- and plexin A2-dependent apoptosis, activates the RAS/MEK1/ERK1/2 pathway, and promotes EMT.[14] CEMIP also activates the ITPR3/CaMK2/NRF2/SLC7A11 pathway, allowing cancer cells to escape ferroptosis.[40] CEMIP enhances PI3K activity, leading to Akt phosphorylation, which in turn promotes cell growth, enhances protein synthesis, and prevents cell apoptosis.[16,35] This image was created with BioRender (https://biorender.com/).

In addition to signaling cascades, CEMIP regulates the cell cycle, facilitating proliferation or arrest. In hepatocellular carcinoma, CEMIP knockdown reduces cyclin D1 levels, inducing G1 phase arrest.[45] In ovarian cancer, silencing CEMIP induces S phase arrest, accompanied by decreased expression of Cyclin A and CDK2 proteins.[35]

2.1.2 | CEMIP- mediated metabolic reprogramming

CEMIP enhances cancer cell proliferation through metabolic reprogramming, promoting key pathways like glycolysis, glutamine metabolism, and amino acid biosynthesis. These metabolic shifts are tightly linked to oncogenic signaling, helping cancer cells meet the increased energy and biosynthetic demands required for rapid growth.[46]

- Glycolysis: Under stress conditions, such as extracellular matrix (ECM) detachment, CEMIP activates AMPK, which reduces GSK3β, stabilizing β-catenin and leading to CEMIP overexpression. This drives PDK4-mediated glycolysis, a crucial step for cancer metabolism. Inhibition of PDK4 or glycolysis inhibitors like 2-DG can reduce VEGF expression, offering potential therapeutic strategies for prostate cancer.[36]
- Glutamine metabolism: CEMIP also alters glutamine metabolism by inducing O-GlcNAcylation of β-catenin, which translocates to the nucleus to promote the expression of CEMIP, GLS1 (glutaminase 1), and glutamine transporters (SLC1A5 and SLC38A2). This suggests a combinatory approach targeting both CEMIP and glutamine metabolism could inhibit CRC proliferation and metastasis.[37] Moreover, in small cell lung cancer (SCLC), CEMIP stabilizes nuclear c-Myc by inhibiting its degradation via F-box WD repeat domain-containing 7 (FBXW7).

Stabilized c-Myc increases the expression of the SLC1A5, driving glutamine-dependent tumor growth. Targeting FBXW7-mediated c-Myc degradation could therefore serve as a novel therapeutic approach for SCLC.[38]

- Amino acid biosynthesis: CEMIP upregulates Myc through the ERK pathway, enhancing amino acid biosynthesis, which fuels fatty acid, lipid, and protein production, all supporting cancer cell proliferation. Amino acids like leucine, tryptophan, and phenylalanine activate the mTOR pathway, further promoting cell growth and metabolism.[15]

2.2 | Cell detachment through CEMIP-induced EMT

EMT, which plays pivotal roles in metastatic cancer, is triggered by the TGF-β,[19] EGFR,[14] and Wnt/β-catenin[20] pathways (Figure 2), which are modulated by CEMIP. Most cancers originate from epithelial tissues, which are characterized by apico-basolateral polarization, robust cell–cell adhesion, restricted migration ability, and the expression of distinctive markers such as E-cadherin, cytokeratin, and occludin. In contrast, mesenchymal cells are more mobile and possess markers such as vimentin, N-cadherin, and fibronectin. EMT contributes to three main processes, namely embryonic growth, injury repair/tissue restoration, and cancer progression.[19,47] EMT plays critical roles in cancer progression by contributing to cancer stem cell detachment, cytoskeletal reorganization, tumor angiogenesis under hypoxia, immune escape, and chemoresistance.[21] CEMIP affects EMT in the following ways.

- TGF-β is a powerful EMT inducer.[21] In cholangiocarcinoma (CCA), CEMIP expression upregulates TGF-β-PI3K-AKT-mediated EMT and SMAD-independent manner-mediated EMT to facilitate the migration and invasion of CCA cells (Figure 2).[19]
- CEMIP interacts with EGFR to induce phosphorylation of the downstream signaling proteins, Src and MEK1. It also facilitates the interaction between Src and EGFR. These events activate RAS/MEK1/ERK1/2 signaling and induce EMT (Figure 2).[14]

In sum, CEMIP plays multiple roles in promoting EMT, altering cellular adhesion, and modulating various signaling pathways to significantly contribute to cancer cell detachment and metastasis. Understanding these mechanisms may provide valuable insights into the early stages of metastasis and potential therapeutic targets for intervention.

2.3 | CEMIP-induced resistance to cell death via anoikis and ferroptosis

Inhibition of cell death is essential for cancer metastasis, and CEMIP critically regulates cell death mechanisms such as anoikis and ferroptosis.[48] When cells detach from the ECM, they typically either undergo anoikis (a form of detachment-induced death) or survive by recycling energy from intracellular components.[7,39] Therefore, resistance to anoikis is crucial for cancer metastasis.[49] Yu et al. demonstrated that inhibition of ATF4/CEMIP/PKCα signaling may be a promising strategy to reduce anoikis resistance in prostate cancer. The ATF4 protein plays a crucial role in anoikis: It induces CEMIP transcription and facilitates the plasma membrane transposition of protein kinase C α (PKCα), causing Bcl-2 phosphorylation at serine 70. This phosphorylation disrupts the Bcl-2/Beclin1 complex to enhance protective autophagy and contribute to anoikis resistance in prostate cancer.[7] Moreover, in cervical cancer, CEMIP not only disrupts Semaphorin 3A-dependent cell death by promoting EGFR stability and signaling but also inhibits TNFα-mediated apoptosis.[14]

Ferroptosis is a form of non-apoptotic cell death that is iron-dependent and characterized by reactive oxygen species (ROS) accumulation. When prostate cancer cells detach from the ECM, CEMIP activates the ITPR3/CaMK2/NRF2/SLC7A11 pathway to enable the cells to escape ferroptosis (Figure 2).[40] In this process, CEMIP stimulates ITPR3 in ER, leading to the release of calcium ions into the cytoplasm and the activation of CaMK2. This triggers the nuclear localization of NRF2 and upregulates the cystine/glutamate multi-pass transmembrane antiporter, SLC7A11 (Figure 2), and thereby contributes to ferroptosis.[40,50,51] According to Badgley et al., SLC7A11 levels are increased in pancreatic ductal adenocarcinoma (PDAC) and other cancers, and SLC7A11 deficiency causes ferroptosis in vitro.[52] In addition to ferroptosis, increased calcium ion levels induce migration in MDA-MB-435 breast cancer cells. CEMIP binds to the chaperone, binding immunoglobulin protein, at the ER to trigger the release of calcium ions into the cytoplasm. These calcium ions activate PKCα to trigger the MAPK/PKC pathway, enhancing the motility and invasiveness of cancer cells.[53]

2.4 | CEMIP-induced hyaluronan depolymerization and effects on cancer progression

HA is a linear glycosaminoglycan; it comprises repeated units of glucuronic acid and N-acetylglucosamine and

has a molecular weight of 1000 ~ 10 000 kDa.[51] In normal tissues, HA predominantly exists in a high-molecular-weight hyaluronan (HMW-HA >1000 kDa). As a major component of the ECM, HA is synthesized by HA synthases (HAS1, HAS2, HAS3) on the cell surface and released into the extracellular space. Extracellular HA is absorbed by tissues, where hyaluronidases (HYAL1, HYAL2, CEMIP) depolymerize it into low- and intermediate-molecular-weight hyaluronan (LMW/IMW-HA <100 kDa) (Figure 3).[13,51,57]

LMW-HA plays crucial roles in cancer progression by promoting cell survival, growth, pro-cancer gene transcription, proliferation, migration, and invasion.[22,58] CD44 is a cell surface receptor that binds to various sizes of HA, thereby activating cell signaling pathways.[55] However, the interaction between HMW-HA and CD44 can be weakened when competing with LMW-HA, as they share the same binding site.[59] Another important receptor is a receptor for hyaluronic acid-mediated motility (RHAMM). RHAMM binds HA to regulate inflammation, fibrosis, and tumorigenesis. The LMW-HA/RHAMM interaction induces Wnt-dependent fibrosarcoma cell growth and increases β-catenin levels. Treating fibrosarcoma cells with LMW-HA increases the amounts of RHAMM and β-catenin complex in the membrane, cytoplasm, and nucleus.[56]

CEMIP-mediated HA depolymerization occurs quickly via vesicle endocytosis and recycling, instead of through accumulation within the cytoplasm or degradation in lysosomes. Studies in skin fibroblasts showed that HA depolymerization occurs primarily through the clathrin-coated pit pathway in an acidic environment, rather than the caveolar pathway involving CD44 and HYAL enzymes or through lysosomes.[51,54]

Related observations have been made in some non-cancer diseases. In mice with deep-tissue infection of *Staphylococcus aureus* (*S. aureus*), CEMIP mRNA levels increase, increasing HA digestion and decreasing HA size. Consequently, CEMIP−/− mice infected with *S. aureus* showed higher levels of IL-6 and neutrophil infiltration, indicating an enhanced inflammatory response. These experiments reveal that HA and CEMIP contribute to host antimicrobial defense.[60]

In sum, LMW-HA generated by CEMIP is vital for cancer progression, and understanding the mechanisms of HA degradation offers important insights for cancer research and treatment.

2.5 | CEMIP-induced changes in the formation of the pre-metastatic niche and the TME

CEMIP plays a pivotal role in both the formation of the pre-metastatic niche and the remodeling of the tumor microenvironment (TME). The primary tumor modifies

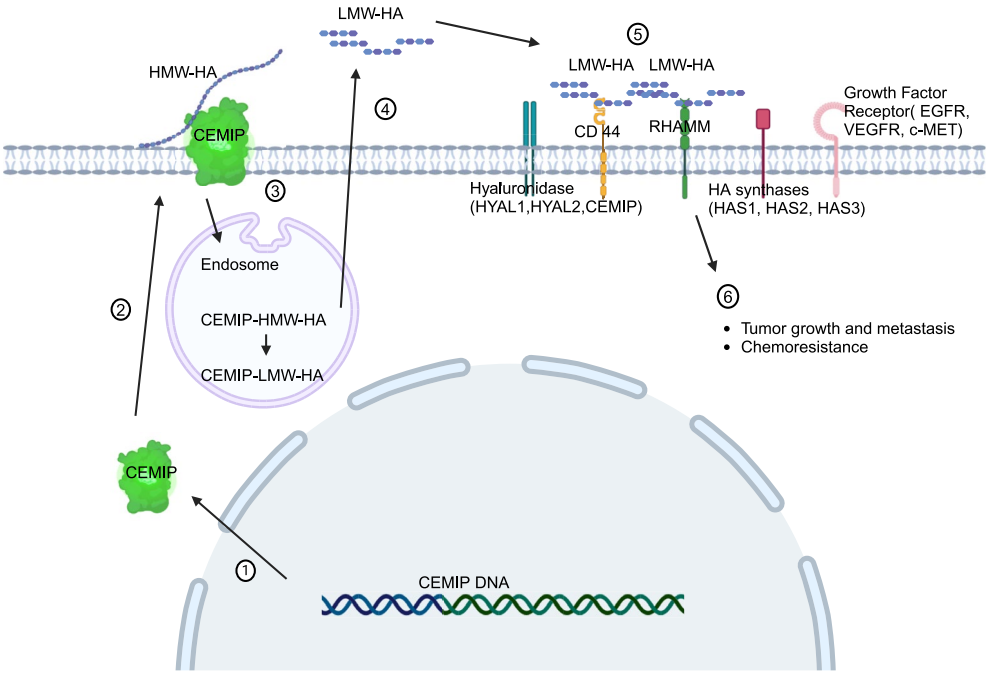

FIGURE 3 CEMIP-related hyaluronan (HA) degradation occurs through rapid vesicle endocytosis.[54] On the other hand, low-molecular-weight hyaluronan (LMW-HA) interacts with CD44 and receptor for hyaluronic acid-mediated motility (RHAMM), triggering various signal pathways that lead to cancer cell progression.[55,56] This image was created with BioRender (https://biorender.com/).

distant organs to create fertile soil for metastatic cancer, known as the pre-metastatic niche environment.[61] Once this niche is established, circulating cancer cells can enter this environment, which then transitions into a TME that supports metastatic growth.[62]

In the context of pre-metastatic niches in brain metastasis, exosomal CEMIP has been shown to upregulate pro-inflammatory cytokines in microglia (the macrophages of the central nervous system), compromising the integrity of the blood–brain barrier (BBB) and increasing vascular permeability. Exosomal CEMIP also modulates the WNT signaling pathway and triggers intracellular calcium release. Both of these functions contribute to the formation of pre-metastatic niches and ultimately aid in the colonization of brain metastases.[10] Moreover, microglia have been found to increase CEMIP expression in brain metastatic breast cancer cells by stimulating the JAK2/STAT3 signaling pathway. This leads to the release of CCL2, IL-6, TGF-β, and VEGF, which facilitates local immune suppression and angiogenesis. Therefore, both microglia and CEMIP may serve as future biomarkers in breast cancer with brain metastasis.[63]

The TME is a complex ecosystem that includes various cell types, including cancer cells, that collectively create a unique milieu characterized by hypoxia, altered pH, angiogenesis, and drug resistance.[33] This dynamic environment orchestrates ECM remodeling through the production of cytokines, such as TGF-β, IL-6, and TNFα, with cancer-associated fibroblasts (CAFs) playing a pivotal role in this process.[64] In lung adenocarcinoma, CEMIP has a positive connection with the infiltration of immune cells (Th2, Treg, Mem B, and Tcm_CD8 cells) and immunosuppressive cells (CAFs, M2 macrophages, Th2 cells, and Treg cells), and thereby modulates the ability of lung adenocarcinoma cells to invade the TME.[65]

These findings emphasize that CEMIP plays multifaceted roles in reshaping the TME and promoting metastasis in specific organs and under hypoxia, suggesting it as a potential target for innovative therapeutic strategies aimed at impeding metastatic progression.

2.5.1 | CEMIP-induced angiogenesis

CEMIP has been shown to play a crucial role in angiogenesis, a key process for tumor growth and metastasis.[2] In the TME, conditions of oxygen and glucose deficiency stabilize hypoxia-inducible factors (HIFs) through lactylation, creating a lactate/HIF-1α/CEMIP signaling pathway. This pathway enhances the expression of VEGFA, promotes phosphorylation of EphA2, and increases VE-cadherin levels, while simultaneously suppressing Sema3A, all of which collectively drive angiogenesis and vasculogenic mimicry.[42] This mechanism is not unique to one type of cancer. In PDAC, for instance, CEMIP expression is positively correlated with HIF-1α.[22] Similarly, in ovarian cancer, silencing CEMIP reduces VEGFA levels, along with molecules such as MMPs, which are critical for cell migration and angiogenesis.[35]

In addition to these pathways, CEMIP also contributes to angiogenesis through hyaluronan depolymerization, which aids in ECM remodeling and creates a favorable microenvironment for blood vessel formation.[66] Emerging evidence further suggests that CEMIP directly activates endothelial cells, promoting their ability to form vascular structures, particularly in brain metastasis.[10]

3 | CEMIP AND FUTURE PERSPECTIVES

The following section introduces recent methods for enabling the direct and indirect inhibition of CEMIP and explores the clinical applications of CEMIP modulation.

3.1 | Direct strategies for CEMIP inhibition

RNA interference is a gene-silencing mechanism that involves the application of a microRNA (miRNA), small interfering RNA (siRNA), or short hairpin RNA (shRNA) (Figure 4).[74] A miRNA can be used to control CEMIP as a natural tumor suppression molecule. For example, human genome-encoded miR-216a attaches to the 3′-untraslated region (UTR) of the CEMIP mRNA to impact pancreatic tumors, CRC, and oral squamous cell carcinoma. In CRC cells, miR-216a reduces CEMIP mRNA and protein levels and thereby inhibits cancer cell migration and invasion.[9,67] miR-140-3p downregulates CEMIP, downregulates c-Myc, and upregulates E-cadherin expression in CRC.[68] miR-4677-3p attaches to the 3'-UTR of the CEMIP mRNA to block its expression. Conversely, miR-19A, miR-19B, miR-130 family members, and miR-432 all upregulate CEMIP in lung adenocarcinoma.[65]

shRNA or siRNA may also be used to directly silence CEMIP. In CRC cells, CEMIP shRNA targeting the CEMIP gene mRNA downregulates both β-catenin and its target, snail, resulting in increased levels of E-cadherin and ZO-1 but decreased levels of vimentin and N-cadherin.[20] The siRNA-mediated knockdown of CEMIP inhibits cancer growth in vivo: Reconstituted high-density lipoprotein (rHDL), derived from human HDL, evades the immune system and easily enters endolysosomal sequestration. In

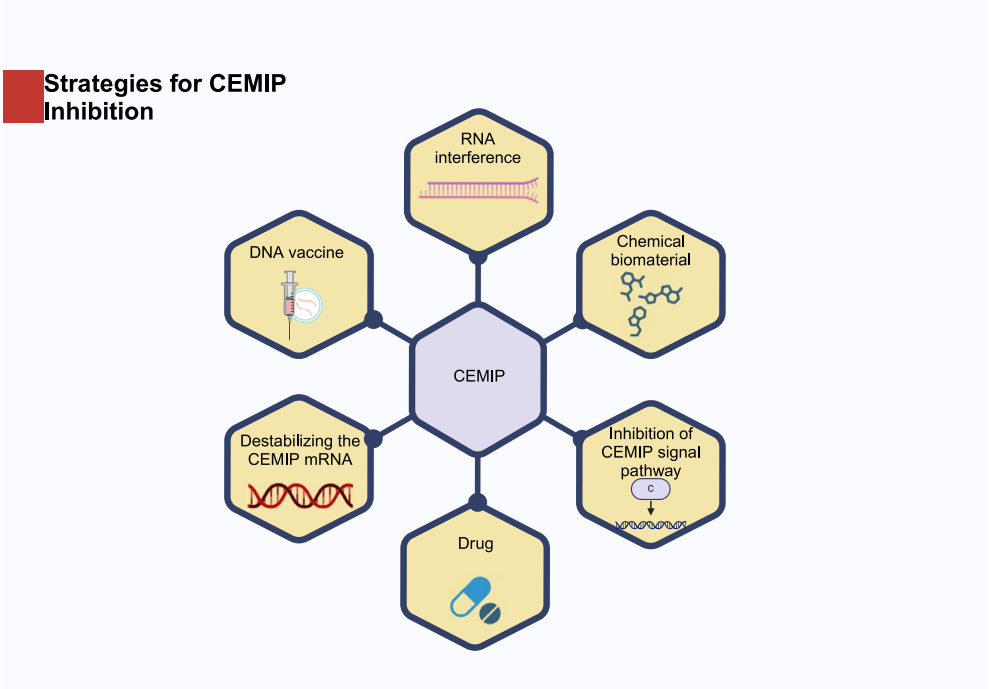

FIGURE 4 CEMIP inhibition methods can be divided into two groups: Direct approaches such as RNA interference,[9,65,67,68] DNA vaccines,[69] and strategies for destabilizing the CEMIP mRNA[70]; and indirect methods such as using a chemical biomaterial (e.g., sulfated hyaluronan),[71,72] altering pathways downstream of CEMIP, and using a pharmacological agent to disrupt CEMIP functions.[2,73] This image was created with BioRender (https://biorender.com/).

a mouse non-small-cell lung cancer (NSCLC) xenograft model, treatment with rHDL/sh-CEMIP decreased the cancer growth rate more effectively than cisplatin alone. Furthermore, combining rHDL/sh-CEMIP with low-dose cisplatin demonstrated synergistic effects, further decreasing cancer growth. These findings suggest that combined therapy with rHDL and an siRNA against CEMIP holds potential for treating cancer.[5]

Chronic fibrosis in obese patients may contribute to renal carcinogenesis. In vitro, VLDL stimulation upregulates CEMIP, activating the Wnt/β-catenin pathway and promoting kidney fibrosis. According to the study, siRNA targeting CEMIP inhibits the VLDL-dependent Wnt/β-catenin/ECM pathway, while the CEMIP DNA vaccine (pcDNA3.1-CEMIP plasmid) increases anti-CEMIP antibody levels via the humoral immune response of B cells. Both therapies show potential for delaying fibrosis in obesity-related chronic kidney disease.[75]

Destabilization of the CEMIP mRNA is another option for directly interrupting the functions of CEMIP (Figure 4). In NSCLC, alkylation repair homolog protein 5 (ALKBH5), which is an m6A demethylase, reduces CEMIP mRNA stability to increase paclitaxel sensitivity.[70] In PDCA cells, ALKBH5 decreases WIF-1 methylation to inhibit Wnt signaling and reduce cell progression, cell migration, tumorigenesis, and metastasis while increasing gemcitabine sensitivity.[76]

3.2 | Indirect strategies for CEMIP inhibition

CEMIP can be indirectly influenced by a chemical biomaterial called sulfated hyaluronan (sHA) (Figure 4). sHA performs the same function as the genetic loss of CEMIP by using the same receptor as endogenous HA and inhibiting CEMIP's hyaluronidase activity. This ultimately increases the HMW-HA level and myofibroblast proliferation.[71] sHA contributes to regulating the secreted HA-binding protein, TSG-6 (encoded by tumor necrosis factor-stimulated gene-6), and modulating HA to alter the cancer cell and anti-angiogenesis microenvironments in breast and lung cancer.[71,72]

CEMIP functions can also be indirectly blocked by inhibiting its downstream pathways (Figure 4). CEMIP acts as a scaffold protein, simultaneously binding GRAF1 (a GTPase-activating protein) and MIB1 (an E3 ubiquitin ligase). This interaction leads to the degradation of GRAF1, which activates the CDC42/PAK1/MAPK pathway and promotes CRC metastasis. Interestingly, a CDC42 inhibitor reduced CEMIP-mediated CRC metastasis in vitro and in vivo, potentially offering a novel therapeutic approach for targeting CEMIP-mediated CRC metastasis.[77]

Drugs can also be used to block CEMIP functions (Figure 4). In hepatocellular carcinoma, CEMIP overexpression activates lung fibroblasts and enhances ECM

TABLE 1 CEMIP's role in cancer and recent research.

Cancer	CEMIP's role	Recent research
Breast cancer	CEMIP and cancer metastasis	• Demethylation of the CEMIP promoter upregulates CEMIP expression.[28] • The enzyme GALNT6 mediates the mucin-type O-glycosylation (O-GalNAc) of coiled-coil domain containing 88C (CCDC88C), and CCDC88C increases CEMIP mRNA expression through c-JUN phosphorylation, leading to lymph node metastasis and poor prognosis.[31] • CEMIP releases calcium ions, activating PKCα and the MAPK/PKC pathway to enhance the motility and invasiveness of cancer cells.[50] • Brain metastatic tumors with higher-level CEMIP expression show poorer survival rates.[56]
	CEMIP and future perspective	• Sulfated hyaluronan (sHA) regulates TSG-6 (the secreted product of tumor necrosis factor-stimulated gene-6, an HA-binding protein) and modulates hyaluronan (HA), thereby altering the cancer cell and anti-angiogenesis microenvironments in breast and lung cancer.[65] • Microglia enhance CEMIP expression and facilitate brain metastasis in breast cancer via the JAK2/STAT3 signaling pathway, suggesting that both microglia and CEMIP may serve as future biomarkers.[54]
Cervical cancer	CEMIP and cancer metastasis	• BCL-3 and p65 attach to the NF-kB site in the CEMIP gene to induce CEMIP expression in human papillomavirus (HPV)- positive cervical cancer cells. In addition, CEMIP activates RAS/MEK1/ERK1/2 signaling and induces epithelial-mesenchymal transition (EMT).[19]
Cholangiocarcinoma/ pancreatic cancer	CEMIP and cancer metastasis	• HIF1α and CEMIP show a significant positive correlation on immunohistochemical analysis.[13] • CEMIP upregulates TGF-β-PI3K-AKT signaling in a SMAD-independent manner to induce EMT.[17] • SLC7A11 is upregulated in pancreatic ductal adenocarcinoma (PDAC), and SLC7A11 deficiency causes ferroptosis.[40]
	CEMIP and future perspective	• Combined use of CEMIP and CA19-9 can provide a better diagnostic tool for early-stage detection of PDAC.[10] • ALKBH5 decreases WIF-1 methylation to inhibit Wnt signaling and reduce PDCA progression.[74] • In patient blood samples, detection of CEMIP autoantibodies demonstrated higher sensitivity than detection of CEMIP protein.[75]
Colorectal cancer	CEMIP and cancer metastasis	• Knockdown of CEMIP downregulates molecules of the Wnt/β-catenin pathway.[30]
	CEMIP and future perspective	• CEMIP is found at high levels in various cancers, including colon.[8] • miR-140-3p downregulates CEMIP.[15] • Silencing of CEMIP with shRNA downregulates β-catenin and snail.[18] • Colon adenocarcinomas with MSI or MSS of stages 2 and 3 show less CpG island methylation.[30] • CEMIP binds to MEK1 to confer resistance to MEK1 inhibitors (e.g., selumetinib) and upregulate phosphorylated MEK1/2, ERK1/2, and RSK1.[36] • Elevated CEMIP is positively correlated with tumor invasion depth, TMN stage, poor prognosis, and mesenchymal phenotype.[61] • miR-216a reduces CEMIP mRNA and protein levels.[61,62] • A CDC42 inhibitor reduces CRC metastasis mediated by CEMIP both in vitro and in vivo.[67] • CEMIP induces cancer cells to internalize major histocompatibility complex class 1 (MHC-I) and thereby escape immune checkpoint blockade (ICB).[70] • Adenoma samples with overexpressed CEMIP showed reversed CRC-associated gene expression patterns under treatment with the selective COX-2 inhibitor, N-(2-cyclohexyloxy-4-nitrophenyl)-methanesulfonamide (NS398).[76]

(Continues)

TABLE 1 (Continued)

Cancer	CEMIP's role	Recent research
Gastric cancer	CEMIP and cancer metastasis	• CEMIP knockdown downregulates members of the Wnt/β-catenin pathway, including β-catenin, cyclin D1, c-myc, and MMP family members.[37]
	CEMIP and future perspective	• High-level expression of the CEMIP mRNA is associated with tumor differentiation, lymph node metastasis, distant metastasis, and peritoneal dissemination and can be monitored to inform decisions on surgery.[12]
Hepatocellular cancer	CEMIP and cancer metastasis	• CEMIP overexpression activates lung fibroblasts and enhances ECM stiffness, leading to lung fibrosis, tumorigenic ECM deposition, and angiogenesis, thereby diminishing the efficacy of sorafenib.[1]
	CEMIP and future perspective	• Pirfenidone, as an anti-angiogenic therapy, blocks Smad2/3 signaling and reduces CEMIP through TGF-β inhibition and enhances the effects of sorafenib by decreasing lung stiffness, pre-metastatic niche formation, and lung metastasis.[1]
Lung cancer	CEMIP and cancer metastasis	• Exosomal CEMIP modulates the WNT signaling pathway and triggers intracellular calcium release. Both of these functions contribute to the formation of pre-metastatic niches and ultimately aid in the colonization of brain metastases.[56] • Alkylation repair homolog protein 5 (ALKBH5) reduces CEMIP mRNA stability, downregulates CEMIP, and increases sensitivity to paclitaxel.[33] • CEMIP modulates immune cells to form the tumor microenvironment.[7]
	CEMIP and future perspective	• Treatment with reconstituted high-density lipoprotein (rHDL)/sh-CEMIP inhibits cancer growth, and combining rHDL/sh-CEMIP with low-dose cisplatin demonstrated synergistic effects, leading to notable cancer growth inhibition.[9] • miR-19A, miR-19B, miR-130 family members, and miR-432 elevate CEMIP expression in lung adenocarcinoma.[7] • Sulfated hyaluronan (sHA) contributes to regulating TSG-6 (the secreted, HA-binding protein encoded by tumor necrosis factor-stimulated gene-6) and modulates HA to alter cancer cell and anti-angiogenic microenvironments in breast and lung cancers.[65] • CEMIP contributes to chemoresistance by activating the oncogenic molecules SRC and YAP.[42] • CEMIP inhibits the interactions among F-box, WD repeat domain-containing 7 (FBXW7), and c-Myc, leading to the stabilization and nuclear accumulation of c-Myc. This upregulates the glutamine transporter, alanine-serine-cysteine transporter 2 (SLC1A5), and promotes glutamine-dependent SCLC growth, suggesting that a targeted therapy to inhibit the FBXW7-mediated degradation of c-Myc could be effective against SCLC.[68]
Ovarian cancer	CEMIP and cancer metastasis	• CEMIP modulates PI3K/AKT/mTOR signaling to induce chemoresistance and cancer metastasis.[26,46] • Silencing of CEMIP leads to the degradation of molecules such as MMPs, which contribute to cell migration, and VEGFA, which is associated with tumor angiogenesis.[26]
Prostate cancer	CEMIP and cancer metastasis	• ATF4/CEMIP/PKCα promotes anoikis resistance.[11] • CEMIP activates the ITPR3/CaMK2/NRF2/SLC7A11 pathway to enable cancer cells to escape ferroptosis.[20] • CircCEMIP (a circular RNA) binds to miR-1248 to activate autophagy and anoikis resistance.[71] • HIF1α lactylation activates CEMIP by inducing angiogenesis and vasculogenic mimicry.[25]
	CEMIP and future perspective	• CEMIP is upregulated in prostate cancer.[11]

stiffness, leading to lung fibrosis and angiogenesis, the establishment of a hospitable pre-metastatic niche, and resistance to sorafenib, which is a standard therapy for hepatocellular carcinoma. The anti-fibrotic drug, pirfenidone, is used to treat idiopathic pulmonary fibrosis; it blocks Smad2/3 signaling and reduces CEMIP through TGF-β inhibition. Pirfenidone enhances the effects of sorafenib by decreasing lung stiffness, pre-metastatic

niche formation, and lung metastasis.[2] CEMIP also contributes to the chemoresistance of SCLC by activating the oncogenic molecules SRC and YAP, which bind to the G8 and second GG domains of CEMIP. Combined treatment of in vitro and in vivo models of SCLC with the SRC inhibitor, dasatinib, or the YAP inhibitor, verteporfin, along with the first-line chemotherapeutic, cisplatin/etoposide, yielded synergistic effects on SCLC.[73]

3.3 | Clinical implications

CEMIP can be utilized to predict cancer progression and could be targeted in developing new therapeutic methods. In lung and breast cancers, CEMIP protein levels were higher in a brain metastasis group than in a no-metastasis group and groups with metastases to other organs. Higher CEMIP levels were associated with a shorter time to brain metastasis, suggesting that CEMIP could be a potential biomarker for brain metastasis, and higher CEMIP levels in brain metastases were associated with poorer survival rates.[10] In CRC, elevated CEMIP was positively correlated with tumor invasion depth, TMN stage, poor prognosis, and a mesenchymal phenotype.[9] In pancreatic intraepithelial neoplasia (PanIN), the detection of CEMIP autoantibodies in patient blood samples demonstrated higher sensitivity for disease diagnosis than detection of the CEMIP protein.[78] In PDAC, CA19-9 is typically used as a cancer biomarker. However, CA19-9 is elevated in both cancer and pancreatitis, whereas CEMIP is elevated specifically in cancer. Therefore, the combined use of CEMIP and CA19-9 can provide a better diagnostic tool for early-stage detection of PDAC.[6]

In gastric cancer, quantification of CEMIP levels can help determine the extent of surgery that will be needed, given that high-level CEMIP mRNA expression is associated with tumor differentiation, lymph node metastasis, distant metastasis, peritoneal dissemination, and poor prognosis.[8] CEMIP can also be used as a marker to predict the potential success of immune checkpoint blockade (ICB) therapy in CRC: CEMIP internalizes major histocompatibility complex class I (MHC-I), preventing CD8+ T cells from recognizing MHC-I and leading to resistance to ICB treatment. MSI-high (MSI-H) CRC is generally more sensitive to ICB therapy than MSS and MSI-low (MSI-L) CRC, Zhang et al. found higher-level expression of CEMIP in MSS and MSI-low (MSI-L) CRC.[79]

4 | CONCLUSION AND FUTURE PERSPECTIVES

Metastasis is one of the most important and lethal adverse events in cancer, making CEMIP, a key player in metastasis, a valuable target for investigation. While CEMIP's roles in cancer have been extensively studied, this article reviews its involvement in tumor cell metastasis, its role in targeting strategies to slow cancer progression, and its clinical implications. CEMIP promotes cancer proliferation by altering signaling pathways, regulating the cell cycle, inducing metabolic reprogramming, and facilitating cancer cell detachment through changes in EMT and cadherin characteristics. Additionally, CEMIP helps cancer cells resist cell death mechanisms like anoikis and ferroptosis, and it plays a pivotal role in the invasion and penetration stages by altering HA through vesicle endocytosis. The transition from HMW-HA to LMW-HA induces the transcription of pro-cancer genes, promoting tumor progression. Finally, CEMIP influences angiogenesis, the TME, and the pre-metastatic niche, contributing to metastasis.

Given its comprehensive roles, CEMIP presents as a potential target for cancer detection and therapeutic inhibition. Various strategies, including RNA interference, CEMIP DNA vaccines, small molecules like sHA, and drugs targeting CEMIP-mediated signaling pathways, are being explored to slow cancer progression and metastasis. This review aims to deepen understanding of CEMIP's role in cancer and provide insights into innovative therapeutic approaches (Table 1).

AUTHOR CONTRIBUTIONS

All authors contributed to the critical analyses and review of the manuscript. Ko, Y. G., and Lee, H. S. wrote the manuscript and designed all figures and tables in consultation with the other authors. Jo, J. H. and Lee, H. S. contributed to funding acquisition.

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Nothing to declare for all authors.

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