

Review

Antimicrobial Peptides as Novel Inhibitors of the Epithelial–Mesenchymal Transition in Cancer Progression

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Abstract

Metastasis is responsible for the majority of cancer-related deaths. During metastasis, cancer cells undergo a series of biological events that allow them to invade surrounding tissues, disseminate through the bloodstream or lymphatic system, and colonize secondary sites. Cancer cells' phenotypic plasticity facilitates this process by enabling them to adapt to diverse microenvironments. Unlike localized tumors, metastasis is more challenging to treat because it represents a systemic disease that can no longer be managed solely through surgery or radiotherapy. Additionally, specific mechanisms underlying metastasis may contribute to resistance to conventional chemotherapy. Therefore, identifying new therapeutic strategies to regulate the key processes underlying metastasis is essential. In recent years, antimicrobial peptides (AMPs) have garnered increasing interest because of their anticancer properties. AMPs are small molecules that are part of the innate immune system of virtually all living organisms and are characterized by their ability to selectively interact with the cell membranes of pathogens and cancer cells. Diverse AMPs have been shown to induce cancer cell death, inhibit proliferation, and interfere with processes associated with metastasis. This review discusses the potential of AMPs as metastasis modulators, highlighting their proposed mechanisms of action, their advantages over conventional therapeutic approaches, and the conceptual framework governing their dual pro- and anti-metastatic activities.

Keywords: metastasis; antimicrobial peptides; anticancer peptides; epithelial-to-mesenchymal transition



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1. Introduction

Cancer remains one of the foremost causes of death globally. In 2024, approximately 9.76 million deaths were attributed to cancer, and this number is projected to increase to 17.5 million by 2050 [1–3]. The majority of cancer-related deaths occur as a consequence of metastasis, which involves the growth of cancer cells in organs distant from the original tumor site [4]. During metastasis, cancer cells undergo a series of biological events that enable them to invade surrounding tissues, disseminate through the bloodstream or lymphatic system, and colonize secondary sites [4–6]. Cancer cells' phenotypic plasticity facilitates each step, allowing them to adapt to diverse microenvironments. Unlike localized tumors, metastases are more challenging to treat because they represent a systemic disease that

cannot be managed solely by surgery or radiation therapy [4]. During invasion, cancer cells also exhibit chromosomal instability and altered gene expression. This mechanism increases genomic heterogeneity at metastatic sites, which complicates the development of effective targeted therapies [7,8]. Additionally, mechanisms underlying metastasis may contribute to resistance to conventional chemotherapy [9–11]. Therefore, identifying novel therapeutic strategies that target key processes involved in metastasis is essential.

In recent years, antimicrobial peptides (AMPs) have attracted increasing interest because of their anticancer properties. AMPs are small molecules that are part of the innate immune system of virtually all living organisms and are characterized by their ability to interact selectively with the cell membranes of pathogens and cancer cells. Diverse AMPs have been shown to induce cancer cell death, inhibit proliferation, and interfere with processes associated with metastasis [12–15]. While conventional modalities often fail due to systemic toxicity, drug resistance, and clonal evolution, AMPs offer distinct biophysical mechanisms that can overcome these clinical bottlenecks. This review discusses the potential of AMPs as metastasis modulators, highlighting their proposed mechanisms of action, comparative therapeutic advantages, the conceptual framework underlying their dual functional roles, and their promising potential as anti-metastatic candidates.

2. Metastasis Overview

Metastasis does not begin as an autonomous event in which tumor cells spontaneously migrate to other parts of the body; instead, it is driven by signals from the tumor microenvironment (TME). The TME is a cellular, molecular, and structural ecosystem comprising cancer cells, fibroblasts, endothelial cells, diverse immune cell populations, and the extracellular matrix (ECM). The interaction among these components induces biochemical signals—such as hypoxia-inducible factors (HIFs), growth factors, and cytokines—that trigger the metastatic cascade [1,2]. Metastasis is a highly complex process that requires coordination of multiple biological events. In the initial stage, tumor cells undergo a phenotypic shift known as the epithelial–mesenchymal transition (EMT), through which they acquire migratory and invasive properties. Subsequently, these cells disseminate via blood or lymphatic vessels to distant sites, where they implant. Finally, following extravasation, they colonize the secondary microenvironment and establish metastatic lesions (Figure 1) [2–4].

2.1. Epithelial–Mesenchymal Transition

During EMT, cancer cells with epithelial characteristics undergo a series of changes: they lose cell–cell adhesion and apicobasal polarity and experience cytoskeletal reorganization, enabling their transformation into mesenchymal cells with migratory and invasive properties [16–21]. However, cancer cells do not always undergo a complete conversion; instead, they may adopt a hybrid state, characterized by the simultaneous expression of both epithelial and mesenchymal markers [21,22]. EMT is induced by various growth factors, including transforming growth factor- β (TGF β), bone morphogenetic proteins (BMPs), epidermal growth factor (EGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), as well as signaling molecules such as Wnt, Notch, and specific integrins [21,22]. These molecules activate a set of EMT-associated transcription factors (EMT-TFs) that regulate the process by repressing epithelial gene expression and promoting mesenchymal gene expression [18,20,21]. Key EMT-TFs include members of the SNAIL family (SNAIL1 and SNAIL2), the ZEB family (ZEB1 and ZEB2), and the TWIST family (TWIST1 and TWIST2) [21,23]. These transcription factors repress epithelial markers such as E-cadherin, claudins, occludins, and Zonula Occludens-1 (ZO-1), thereby disrupting adherents and tight junctions during EMT. They also inhibit filament proteins such as

cytokeratin 18, which usually maintain the structural integrity of epithelial cells [21,24–28]. Conversely, EMT-TFs induce the expression of mesenchymal markers, such as vimentin, a filament protein expressed exclusively in mesenchymal cells, and fibronectin, which facilitates cancer cell invasion. They also promote the expression of matrix metalloproteinases (MMPs), including MMP-2 and MMP-9, which degrade the extracellular matrix and enable cancer cells to migrate and invade distant tissues. Moreover, EMT-TFs enhance their own expression, and the regulatory mechanisms vary depending on the cell type (Table 1) [21,27,29].

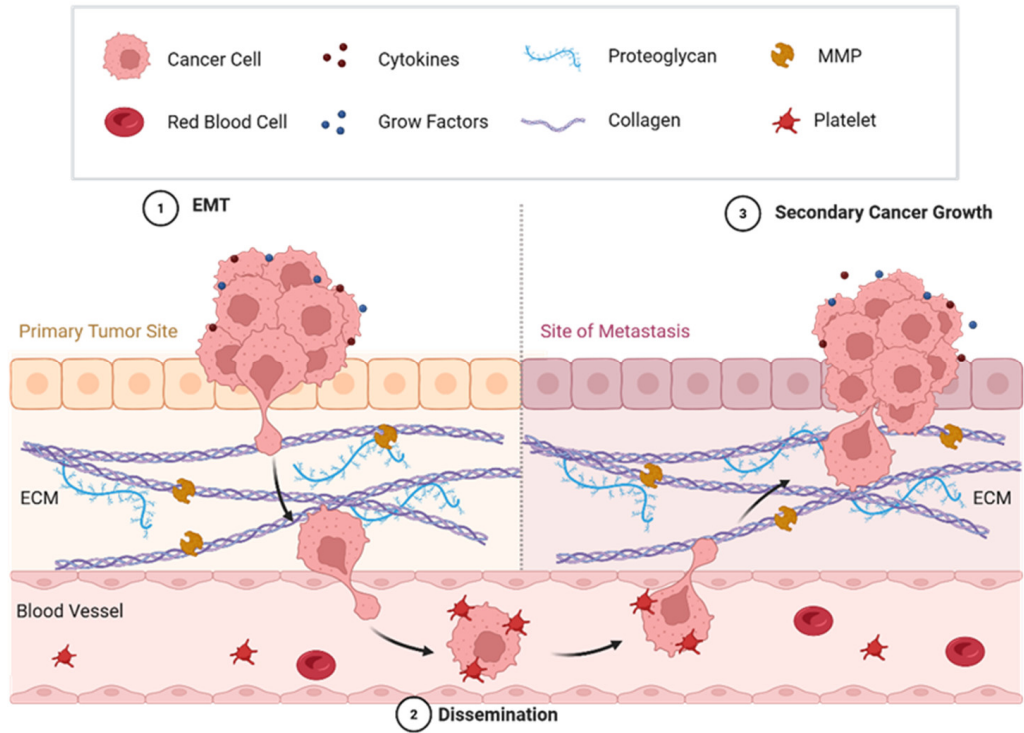


Figure 1. Stages of the metastatic process in cancer. The metastatic process occurs in three main phases: (1) EMT, which involves loss of cell adhesion and apicobasal polarity; in addition, tumor cells invade the extracellular matrix through the action of MMPs. (2) Dissemination, in which tumor cells intravasate into the bloodstream, interact with platelets for protection, and survive in circulation. (3) Secondary cancer growth, which involves extravasation into the extracellular matrix at a distant site and the formation of a new tumor. Figure created with BioRender.com.

Table 1. EMT-inducing Transcription Factors and their principal effector genes.

EMT-TF	EMT-TF Effect	Target Genes	References
SNAIL1	Downregulation	E-cadherin (<i>CDH1</i>), Claudins, Occludin (<i>OCN</i>), ZO-1 (<i>TJP1</i>), Cytokeratin 18 (<i>KRT18</i>)	[21,24,25,27,28,30–33]
	Upregulation	Vimentin (<i>VIM</i>), Fibronectin (<i>FN1</i>), MMP-2 (<i>MMP2</i>), MMP-9 (<i>MMP9</i>), Zeb1 (<i>ZEB1</i>)	[21,24,26,27,29]
SNAIL2	Downregulation	E-cadherin (<i>CDH1</i>), Claudin1 (<i>CLDN1</i>), Estrogen receptor 1 (<i>ESR1</i>)	[21,32,34]
	Upregulation	Vimentin (<i>VIM</i>), Fibronectin (<i>FN1</i>), N-cadherin (<i>CDH2</i>), MMP-2 (<i>MMP2</i>), MMP-9 (<i>MMP9</i>), Zeb1 (<i>ZEB1</i>)	[21,34–36]

Table 1. Cont.

EMT-TF	EMT-TF Effect	Target Genes	References
ZEB1	Downregulation	E-cadherin (<i>CDH1</i>), Crumbs3 (<i>CRB3</i>), Protein associated to junctions (<i>PATJ</i>), Occludin (<i>OCLN</i>), Plakophilin3 (<i>PKP3</i>), Mucin1 (<i>MUC1</i>), miR-190 (<i>MIR190A/MIR190B</i>)	[21,37,38]
	Upregulation	Vimentin (<i>VIM</i>), β -catenin (<i>CTNNB1</i>), N-cadherin (<i>CDH2</i>), Fibronectin (<i>FN1</i>)	[39,40]
ZEB2	Downregulation	E-cadherin (<i>CDH1</i>), Plakophilin2 (<i>PKP2</i>), ZO-3 (<i>TJP3</i>), Connexin26 (<i>GJB2</i>), Rab25 (<i>RAB25</i>)	[21,41]
	Upregulation	N-cadherin (<i>CDH2</i>), Vimentin (<i>VIM</i>), Twist (<i>TWIST1</i>), VEGF-A (<i>VEGFA</i>)	[41]
TWIST1	Downregulation	E-cadherin (<i>CDH1</i>), γ -catenin (<i>JUP</i>)	[21,42]
	Upregulation	Vimentin (<i>VIM</i>), α -tubulin (<i>TUBA1A</i>), Fibronectin (<i>FN1</i>), N-cadherin (<i>CDH2</i>), MMP-1 (<i>MMP1</i>), MMP-2 (<i>MMP2</i>), MMP-9 (<i>MMP9</i>), Snail1 (<i>SNAIL1</i>), Snail2 (<i>SNAIL2</i>), Zeb1 (<i>ZEB1</i>)	[21,42–44]
TWIST2	Downregulation	E-cadherin (<i>CDH1</i>)	[45,46]
	Upregulation	N-cadherin (<i>CDH2</i>), β -catenin (<i>CTNNB1</i>), C-Myc (<i>MYC</i>), Cyclin-D1 (<i>CCND1</i>)	[46]

Source: Modified from [22].

2.2. Dissemination

After crossing the ECM, tumor cells undergo intravasation, a process in which they penetrate the endothelial wall of blood or lymphatic vessels and enter the circulation [47]. During intravasation, tumor cells form invadopodia, actin-rich plasma membrane protrusions that degrade the ECM. Perivascular macrophages induce the formation of invadopodia in tumor cells through activation of the Ras homolog family member A (RhoA) protein [48]. Blood vessels within tumors are often described as chaotic and tortuous, characterized by irregular diameters and high permeability. These features facilitate the passage of cancer cells across the endothelial barrier and are primarily regulated by vascular endothelial growth factor (VEGF) [49]. Once in circulation, tumor cells are called circulating tumor cells (CTCs). CTCs can be found in the bloodstream either as single cells or as multicellular clusters [50]. Although most CTCs travel individually, those that form clusters exhibit significantly higher metastatic potential [51]. These clusters are frequently associated with non-malignant cells such as platelets, leukocytes, endothelial cells, and fibroblasts [50]. The association between neutrophils and CTCs has been linked to enhanced metastatic potential, as neutrophils help CTCs evade immune surveillance by suppressing the activation and responses of leukocytes, natural killer cells, and cytotoxic T lymphocytes [6,52–54]. Moreover, CTCs promote the differentiation of monocytes into tumor-associated macrophages (TAMs), thereby increasing CTC mechanical adhesiveness and facilitating the formation of protective cell clusters [52]. Additionally, platelets play a crucial role in CTC survival in circulation. By coating CTCs, platelets protect them from shear stress and contribute to immune evasion [55].

2.3. Secondary Cancer Growth

As CTCs traverse narrow capillaries, they often become mechanically trapped, leading to microvascular disruption. This mechanical stress facilitates extravasation [17]. Extravasation requires adhesion to the endothelium, modulation of the endothelial barrier, and transendothelial migration to reach target organs. CTC adhesion to the endothelium in-

volves interactions between a wide array of ligands and receptors, including selectins, cadherins, integrins, CD44 receptors, and members of the immunoglobulin superfamily [56]. To facilitate CTC extravasation, platelets bind to CTCs, protect them from the circulation, and release ATP, which increases blood vessel permeability; this ATP opens the endothelial barrier by activating P2Y2 receptors on endothelial cells [57]. Additionally, extravasation can be promoted by angiopoietin-like 4 (ANGPTL4), which disrupts endothelial integrity by interacting with VE-cadherin and claudin-5 and activating the Rac/PAK signaling pathway [56,58]. Other proteins, such as MMPs, EGF, epiregulin (EREG), and cyclooxygenase-2 (COX-2), also contribute to CTC extravasation [59,60].

It might be assumed that once tumor cells successfully extravasate, metastasis is inevitable. However, only 1 in 40 extravasated cells can form micrometastasis; the rest are either eliminated or remain dormant [61]. Therefore, a critical requirement for micrometastasis formation is the tumor-initiating capacity, which is typically restricted to cancer stem cells (CSCs) [6]. In a metastatic breast cancer mouse xenograft model, tenascin C (TNC) was found to modulate Notch and Wnt signaling pathways that support CSC colonization [62].

2.4. Signaling Pathways Involved in Metastasis

As previously mentioned, EMT-TF expression is regulated by extracellular signals that activate various signaling pathways [63]. Receptor tyrosine kinases (RTKs) modulate multiple cellular mechanisms, including proliferation, differentiation, and migration. One example is the epidermal growth factor receptor (EGFR), which can activate several signaling pathways, including MAPK, PI3K/AKT, and JAK/STAT, all associated with tumor progression, metastasis, and the development of therapeutic resistance (Figure 2) [64]. The MAPK signaling pathway is frequently aberrantly activated in cancer cells and has been extensively linked to invasion and metastasis through various mechanisms [64]. Cancer-associated fibroblasts (CAFs) promote tumor cell invasion by secreting IL-32, which binds to integrin β 3 on cancer cells and activates p38 MAPK signaling, thereby increasing mesenchymal marker expression and promoting tumor cell invasion. Likewise, inhibition of the p38 MAPK pathway reduces mesenchymal marker expression and cell invasion [65]. Similarly, integrin α 6 (ITGA6) and ribosomal protein SA (RPSA) have been shown to promote invasion and metastasis by activating the PI3K and MAPK signaling pathways, respectively, in invasive pancreatic cancer cell lines [66]. TGF- β induces EMT in breast, lung, liver, pancreatic, and renal cancer cells by activating the RAS–MAPK signaling pathway [63].

Long non-coding RNAs (lncRNAs) have also emerged as regulators of metastasis; for instance, LINC02167 is overexpressed in colorectal cancer (CRC). LINC02167 acts as a molecular scaffold, forming a complex with the mRNA-binding proteins YBX1 and ILF3. YBX1 stabilizes KSR1 mRNA, thereby activating the ERK/MAPK signaling pathway and driving metastasis in CRC [67]. Similarly, NAT10 overexpression promotes metastasis by enhancing hyperactivation of the MAPK/ERK pathway through stabilization of glycosylated lysosomal membrane protein (GLMP) mRNA via ac4C modification [68]. Another study demonstrated that the transcription factor RUNX1 induces EMT in prostate cancer by activating the Akt/JNK and p38 MAPK signaling pathways. Treatment with the saponin holothurin A (HA) inhibits the RUNX1-induced Akt/JNK and p38 MAPK pathways, thereby suppressing migration and invasion [69]. Collectively, these studies suggest that the MAPK pathway may be a crucial therapeutic target for metastasis treatment. However, direct inhibition of this signaling cascade has been associated with the development of resistance [67]. Therefore, identifying indirect regulators of this pathway could offer a promising alternative for therapeutic intervention.

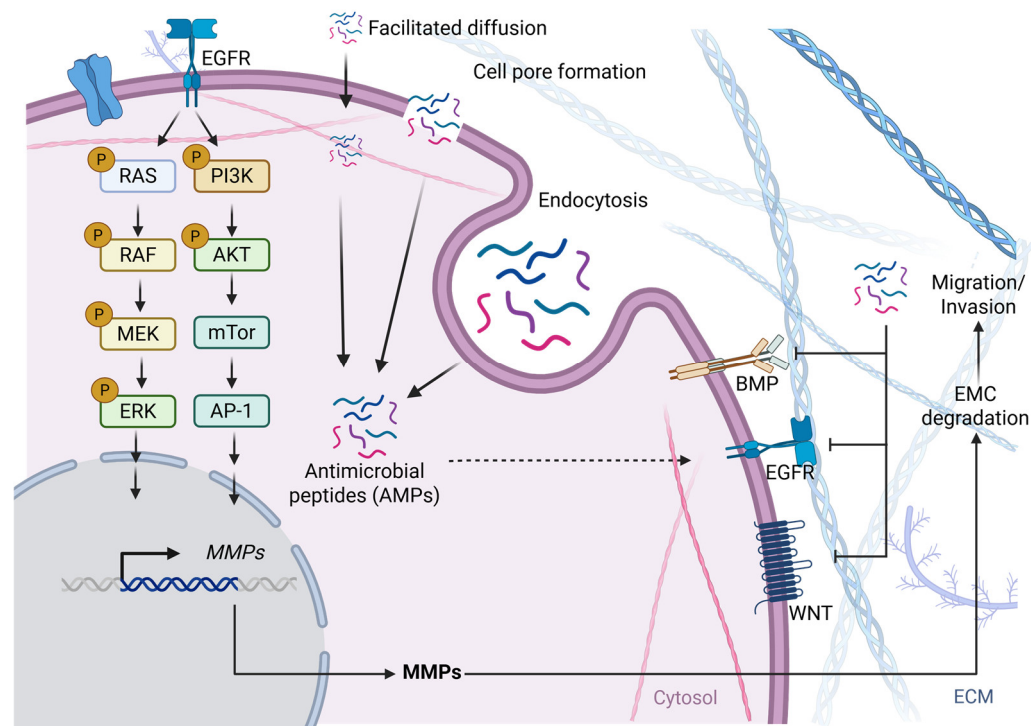


Figure 2. AMPs inhibit signaling pathways involved in metastasis. Growth factor stimulation (e.g., EGFR) activates the RAS and PI3K pathways in cancer cells, triggering EMT and increasing MMP production and subsequent ECM degradation, which facilitates migration and invasion. AMPs can block receptors such as BMP, EGFR, and WNT from outside the cell and, after internalization via facilitated diffusion, pore formation, or endocytosis, can also modulate these receptors intracellularly. Through these mechanisms, AMPs regulate signaling pathways that drive EMT and tumor progression. The dotted arrow represents the intracellular modulation of BMP, EGFR, and WNT receptors mediated by AMPs. Figure created with BioRender.com.

2.5. Conventional Therapeutic Approaches and Unmet Clinical Needs in Metastasis

Clinical management of metastatic disease relies on a combination of local and systemic therapies: local interventions, including surgical resection and radiotherapy, effectively debulk primary tumors and control solitary oligometastatic lesions; however, they cannot eliminate circulating tumor cells or dormant micrometastases that have disseminated to distant organs. By contrast, conventional systemic treatments have major limitations [4,6]. Systemic chemotherapy uses cytotoxic drugs such as paclitaxel, cisplatin, and fluorouracil to eradicate rapidly dividing metastatic cells, but it is severely limited by narrow therapeutic windows, severe systemic off-target toxicities (such as myelosuppression, cardiotoxicity, and nephrotoxicity), and the emergence of multidrug resistance, enhanced DNA repair mechanisms, and evasion of apoptosis [9,11].

Targeted therapies using small-molecule inhibitors and monoclonal antibodies (against EGFR, HER2, BRAF, and ALK) are more specific than chemotherapy, yet genomic heterogeneity, clonal evolution, and bypass signaling in metastatic niches limit their long-term success [7,8,64]. Hormone therapy (tamoxifen, aromatase inhibitors, and androgen receptor antagonists) is standard for hormone receptor-positive breast and prostate cancers, yet metastatic progression often leads to receptor loss or mutations (ESR1, AR), resulting in refractory tumors [10,11,34]. In immunotherapy, immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 have improved outcomes in melanoma and non-small cell lung cancer. However, many patients develop resistance because of an immunosuppressive, or “cold,” tumor microenvironment characterized by poor immune infiltration, defective antigen presentation, and increased regulatory T cells and tumor-associated

macrophages [52,54,70]. Anti-angiogenic therapies such as bevacizumab aim to inhibit tumor vascularization but often cause severe hypoxia, activating HIF-1 α signaling and promoting partial epithelial–mesenchymal transition, invasion, and metastasis. These limitations highlight the need for agents that overcome drug resistance, specifically recognize tumor properties without harming healthy cells, infiltrate and modify the tumor microenvironment, and target multiple networks involved in invasion and survival [4,49].

3. Antimicrobial Peptides as Cancer Therapeutics

AMPs are small molecules that form part of the innate immune system of virtually all living organisms, providing defense against pathogens such as viruses, bacteria, protozoa, and fungi [71]. AMPs are primarily known for their antimicrobial activity, from which the name is derived. However, they have also been widely reported to exhibit antibiofilm, enzyme-inhibitory, immunomodulatory, anti-inflammatory, and anticancer activities [15,72]. To date, 3379 natural AMPs have been identified, of which approximately 5% have demonstrated anticancer effects [73].

AMPs are small peptides composed of fewer than 100 amino acid residues; they are typically cationic (net charge +2 to +9) and amphipathic [74]. AMPs display remarkable structural diversity and can be classified by secondary structure as α -helical, β -sheet, combined α -helix/ β -sheet, linear or unstructured peptides, and cyclic peptides [13,72,75]. The group of α -helical peptides is the most extensively studied. These peptides are rich in Leu, Ala, Gly, and Lys residues and lack cysteine residues, preventing intramolecular disulfide bond formation. These AMPs possess broad-spectrum antimicrobial activity; notable examples include cathelicidins, magainins, and melittin [72,75–78]. β -sheet peptides may also contain α -helical regions and typically have two to four disulfide bonds that stabilize their antiparallel β -sheet structures. These peptides are rich in Cys, Leu, Ala, Gly, and Lys residues and act by binding to specific phospholipids, thereby permeabilizing membranes. The defensin family is the most representative group within this category [72,75,79]. Linear or non-structured AMPs lack defined α -helical or β -sheet structures and are generally rich in Trp, Pro, and Gly residues [74]. Finally, cyclic peptides are unusual AMPs that typically form a ring structure stabilized by one or two disulfide bonds [75].

3.1. Advantages of AMPs over Conventional Anti-Metastatic Modalities

Compared with traditional clinical methods, AMP-based strategies provide unique biophysical and functional benefits that meet key unmet needs in oncology.

- (a) Electrostatic selectivity enables AMPs to target malignant cells by exploiting differences in cell membrane charge and fluidity, sparing normal, cholesterol-rich host membranes, unlike conventional chemotherapeutics, which cause widespread damage [80,81].
- (b) Evasion of Multidrug Resistance: Conventional small-molecule therapies often fail because of efflux pump upregulation or target mutations. Many AMPs, however, rapidly disrupt cell membranes via mechanisms such as barrel-stave, toroidal pore, or carpet. They bypass typical efflux resistance pathways, regardless of intracellular targets [71,82,83].
- (c) Multi-Targeting and TME Modulation: While targeted therapies often develop resistance due to redundant signaling when a single node is blocked, AMPs use multimodal mechanisms. They can directly kill cells by disrupting membranes, block oncogenic cascades (e.g., MAPK/ERK, EGFR, Wnt/ β -catenin), and reprogram the immunosuppressive tumor microenvironment by depleting or repolarizing M2 tumor-associated macrophages [84–87].

- (d) **Broad Bioengineering Versatility:** Unlike rigid antibodies or small molecules, AMPs are highly adaptable. They can be engineered as peptides, conjugated to polymers (e.g., PEGylation), or encapsulated in nanocarriers (e.g., liposomes, silica, or solid lipid nanoparticles) to improve stability, circulation, and targeting of metastatic sites [88–90].

Despite these advantages, clinical translation remains constrained by susceptibility to cleavage by plasma and matrix proteases, rapid systemic clearance, and potential toxicity or hemolysis at high doses. Overcoming these limitations through rational bioengineering is central to the successful clinical development of AMP-based therapeutics [83,88,91].

3.2. Mechanism of Action of AMPs

AMPs can also be classified by their mechanism of action as membranolytic or non-membranolytic peptides [71]. Membranolytic AMPs generally act by inserting into the cell membrane and forming pores, leading to membrane lysis [71,82,92]. Several models have been proposed to describe the action of membranolytic AMPs. In the barrel-stave model, peptide monomers accumulate on the cell membrane. Once they reach a threshold concentration, they undergo conformational changes and aggregate into a barrel-like structure in which the hydrophobic regions interact with membrane lipids. In contrast, the hydrophilic regions face inward, forming aqueous pores that expand as more peptides aggregate [13,71,83,93]. In the toroidal pore model, peptides insert perpendicularly into the membrane at high concentrations, inducing pore formation with diameters of 1–2 nm [13,71,83,93]. In the carpet model, peptides align parallel to the cell membrane, forming a carpet-like covering. When the peptide concentration surpasses a critical threshold, the peptides reorient and disrupt the phospholipid arrangement, ultimately disintegrating the membrane in a detergent-like manner [13,71,83,93]. Non-membranolytic AMPs enter the cell via direct penetration or endocytosis and subsequently target various intracellular components [71,83]. These peptides can inhibit protein biosynthesis by binding to ribosomes and blocking protein translation [83,94,95]. Additionally, AMPs can interfere with nucleic acid synthesis through multiple mechanisms: they may bind directly to nucleic acids, inhibit the activity of topoisomerase or RNA polymerase, induce RNA and DNA degradation, or arrest the cell cycle by binding to DNA [83,93]. AMPs can also inhibit enzymes, disrupt ATP-dependent processes, and interfere with Ca^{2+} homeostasis, thereby generating reactive oxygen species (ROS) and triggering apoptosis [74].

AMPs have emerged as a novel therapeutic alternative for cancer treatment due to their low toxicity, improved selectivity towards cancer cells, and reduced induction of resistance [88,91]. This is attributed to AMPs' specific characteristics, such as positive charge and hydrophobicity, which enable selective interaction with cancer cell membranes. Cancer cells exhibit a negatively charged outer membrane surface and increased membrane fluidity, allowing positively charged peptides to preferentially target them, whereas non-transformed cells possess a neutral charge and more rigid membranes [80,81]. This difference in surface charge arises from the externalization of phosphatidylserine (PS), which accounts for approximately 3–9% of the total phospholipid content in the outer leaflet of cancer cell plasma membranes. In contrast, in non-transformed cells, PS is typically confined to the inner leaflet [81]. Additionally, cancer cell surfaces contain heparan sulfates and O-glycosylated mucins, further contributing to their net negative charge [80,81]. Moreover, cancer cell membranes often display a greater number of microvilli per unit area, further enhancing AMP binding to cancer cells and thereby increasing their anticancer efficacy [74].

3.3. Anticancer Activity of AMPs

To date, numerous AMPs with anticancer activity have been identified, acting through various mechanisms. Some notable examples include the human cathelicidin LL-37, which has demonstrated anticancer activity against colon, ovarian, oral squamous cell, gastric, and leukemic cancers by inducing apoptosis or inhibiting cancer cell proliferation [13,96–101]. Human α -defensins (HNP-1, HNP-3, and HNP-5) exhibit anticancer effects against leukemias, cervical cancer, and lung cancer [13,102,103]. Among plant-derived AMPs, the defensin PaDef from native Mexican avocado (*Persea americana* var. *drymifolia*) has shown cytotoxic activity against breast cancer and leukemia cell lines [104–106]. Among insect-derived peptides, Gomesin (Gm), isolated from a Brazilian spider (*Acanthoscurria gomesiana*), has demonstrated anticancer activity against various cancers, including skin, breast, and cervical cancer cell lines, as well as leukemia cell lines [107]. However, little is known about AMPs that regulate processes involved in cancer metastasis.

4. Role of Antimicrobial Peptides in Metastasis Regulation

Antimicrobial peptides hold significant potential in modulating tumor progression and the metastatic cascade, offering key insights for the development of novel therapeutic strategies.

4.1. AMPs with Anti-Metastatic Activity

4.1.1. Natural AMPs

Some AMPs have been shown to exhibit anti-metastatic activities (Table 2). Among plant-derived peptides, the pea defensin Psd1 (50 μ M) exhibited cytotoxic activity against the B16F10 murine metastatic melanoma cell line, reducing cell viability by up to 60%. Moreover, Psd1 inhibited pulmonary metastatic nodule formation in a murine metastatic melanoma model [108]. To date, Psd1 remains the only plant defensin with experimentally validated anti-metastatic activity, highlighting a largely unexplored area within plant-derived AMPs and suggesting that other plant peptides may have similar properties that have not yet been investigated. Bacterial-derived AMPs, such as the bacteriocin Nisin ZP, inhibit migration in lung cancer cells and suppress proliferation and invasion in melanoma cells [109,110]. Nisin ZP is currently the only bacterial AMP with documented anti-metastatic properties, highlighting bacteriocins as a promising class for metastasis-focused therapies. The fact that only one bacterial AMP has been characterized in this context suggests that their anti-metastatic potential remains underexplored. Psd1 and Nisin ZP are the only plant- and bacterial-derived AMPs with confirmed anti-metastatic activity to date. Their mechanisms remain unknown, but their identification expands the functional roles of AMPs beyond antimicrobial and anticancer activities and opens avenues to discover and optimize AMPs as metastatic modulators. This evidence supports that AMPs from various sources could be a new class of anti-metastatic agents, warranting further investigation into their mechanisms, structure–activity relationships, and therapeutic potential.

In the animal kingdom, AMPs' anti-metastatic activity has been described most extensively. Human defensins have been shown to suppress cancer cell migration. Human β -defensin 1 (hBD1) inhibited the migration of oral squamous cell carcinoma lines by regulating the expression of MMP-2 [111]. Human β -defensin 3 (hBD3) has been shown to inhibit the migration of head and neck cancer cells [112]. Also, human α -defensin 6 (HD6) inhibits migration by interacting with EGFR and blocking the MAPK signaling pathway in colorectal cancer cells [84]. Additionally, bovine lactoferricin (LfcinB) has been shown to inhibit lung and liver metastasis in a murine metastatic melanoma model [113]. The AMP Temporin-SHf isolated from the skin secretions of *Pelophylax saharica* inhibits migration in lung cancer cells and significantly reduces the expression of MMP-2 and MMP-9 [114].

Scorpion AMP Smp24 suppressed lung cancer cell migration and invasion by regulating the expression of MMP-2, MMP-9, TIMP-1, and TIMP-2 [115]. Cecropin from *Musca domestica* inhibited adhesion and migration in human hepatocellular carcinoma cells by downregulating MMP-2 and upregulating TIMP-2 and E-cadherin [116]. PR-39, isolated from pig small intestines, is a proline-rich AMP that suppresses invasive and motile activities in human hepatocellular carcinoma cells [117]. Porcine rpNK-lysin inhibits cell migration, adhesion, and invasion in hepatocellular carcinoma cells by downregulating Fascin 1, which regulates the Wnt/ β -catenin signaling pathway, and reducing β -catenin, MMP-2, and MMP-9 expression [118].

The anti-metastatic activity of melittin has also been extensively studied. Melittin is a small, 26-amino-acid, cationic, amphipathic peptide derived from bee venom, with a structure similar to α -helical AMPs [119]. Melittin suppresses EMT, migration, and invasion through the Wnt/ β -catenin and BMP/Smad signaling pathways, and reduces the activity of MMP-2, MMP-9, and MMP-13 at low concentrations [85,120]. Melittin inhibits migration and invasion in bladder cancer cells by downregulating the ERK5-MAPK signaling pathway [121]. Melittin has also been shown to inhibit the migration and invasion of renal carcinoma cells by downregulating MMP-9 expression via the MAPK pathway [122]. Furthermore, melittin inhibited metastasis in both in vivo and in vitro liver cancer models by suppressing the Rac1-dependent pathway [123].

4.1.2. Synthetic AMPs

Modifications of melittin with anti-metastatic activity have also emerged; for example, TAMpepK is a melittin sequence linked via a peptide linker to the pro-apoptotic dKLA peptide. TAMpepK demonstrated efficacy in reducing tumor burden and preventing metastatic dissemination by selectively targeting and depleting M2-polarized TAMs in murine models of metastatic breast cancer and melanoma [86,124]. M2-type TAMs facilitate metastasis and therapy resistance by secreting anti-inflammatory mediators that establish an immunosuppressive tumor microenvironment, inhibit T-cell proliferation, and activate MAPK signaling, ultimately driving the expression of MMPs involved in EMT [70,125]. However, both melittin and TAMpepK exhibit hemolytic activity [89,126]. This limitation led to the development of a novel formulation, PEG-melittin-dKLA 8–26, which retains the 8–26 amino acid segment of melittin, fused to dKLA, and conjugated to polyethylene glycol. This modification reduced hemolytic potential and conferred improved serum stability compared to the parent melittin-dKLA. Additionally, PEG-melittin-dKLA 8–26 displayed superior efficacy in suppressing pulmonary metastasis in a metastatic breast cancer mouse model [89].

L-K5 is a peptide lysine/leucine-rich AMP designed based on the sequence of temporin-1CEb, isolated from the skin secretions of the Chinese brown frog (*Rana chensiensis*). This peptide exhibited an anti-metastatic effect in a breast tumor mouse model, reducing liver metastasis by 46.73% by regulating M2 macrophage polarization [87].

Another AMP-derived fragment engineered for enhanced anticancer efficacy is merecidin, corresponding to residues 14–32 of human cathelicidin LL-37. Merecidin effectively blocks EMT and suppresses invasion and migration in triple-negative breast cancer cells by modulating miR-30d-5p and vimentin expression. In non-small cell lung cancer, merecidin exerts anti-migratory and anti-invasive effects by regulating the MAPK/ERK signaling pathway [127]. Also, KT2 and RT2 modified antimicrobial peptides derived from *Crocodylus siamensis* Leucrocine I inhibit migration in colon cancer cells [128]. Additionally, KT2 showed anti-metastatic effects by inhibiting migration and invasion in human melanoma cells through reduced MMP-2 and MMP-9 expression and activity, and by mod-

ulating the FAK, uPA, MAPK, PI3K/AKT, NF- κ B, and RhoA–ROCK signaling pathways (Figure 2) [129].

Table 2. Antimicrobial peptides as modulators of metastasis.

Activity	Kingdom	AMP	AMP Origin	AMP Classification	Target	References
Anti-metastatic	Plant	Psd1	Pea	Plant defensin	Unknown	[108]
	Bacteria	Nisin ZP	<i>Lactococcus lactis</i>	Bacteriocin	Unknown	[109,110]
	Animal	Melittin	Bee venom	Melittin	BMP/Smad, MAPK and Rac1 signaling pathways, MMP-2, MMP-9, MMP-13	[85,120–123]
		TAMpepK	Synthetic melittin-derived peptide	Melittin peptide analog	M2-TAMs	[86,124]
		PEG-melittin-dKLA	Synthetic melittin-derived peptide	Melittin peptide analog	M2-TAMs	[89]
		LfcinB	Bovine	Lactoferrin	Unknown	[113]
		Temporin-SHf	Frog	Temporin	MMP-2, MMP-9	[114]
		Smp24	Scorpion venom	Short-chain NDBPs	MMP-2, MMP-9, TIMP-1, TIMP-2	[115]
		Cecropin	Fly	Cecropin	MMP-2, TIMP-1, E-cadherin	[116]
		PR-39	Pig	Cathelicidin	Unknown	[117]
		rpNK-lysin	Pig	Saposin	Fascin 1 Wnt/ β -catenin, MMP-2, MMP-9	[118]
		Merecidin	Synthetic LL-37-derived peptide	Cathelicidin peptide analog	miR-30d-5p, MAPK/ERK signaling pathway	[127]
		L-K5	Synthetic temporin-1CE-derived peptide	Temporin analog	M2-TAMs	[87]
		KT2	Synthetic leucrocin I-derived peptide	Leucrocin-derived peptide analog	Unknown	[128,129]
		RT2	Synthetic leucrocin I-derived peptide	Leucrocin-derived peptide analog	Unknown	[128]
		HD6	Human	α -defensins	EGFR, MAPK signaling pathway	[84]
		hBD1	Human	β -defensins	MMP-2	[111]
		hBD3	Human	β -defensins	Unknown	[112]
		hBD3	Human	β -defensins	EGFR	[130]
Pro-metastatic	Animal	LL-37	Human	Cathelicidin	ERK/EG-MAPK/ERK and NF- κ B signaling pathways, YB1 protein	[131–135]

4.2. AMPs with Pro-Metastatic Activity

Despite their well-documented therapeutic potential, AMPs can also contribute to cancer progression under certain conditions. A notable example is the human cathelicidin LL-37, expressed by macrophages and shown to enhance the proliferation and migration of ovarian cancer cells in co-culture assays [131]. LL-37 also facilitates EMT and pulmonary metastasis in both hepatocellular carcinoma and breast cancer models, through activation of the EGFR/ERK-MAPK signaling cascade and upregulation of mesenchymal markers [132,133]. In melanoma and cutaneous squamous cell carcinoma, LL-37 promotes cellular migration and invasion by inducing Y-box binding protein 1 (YB-1) expression and activating NF- κ B signaling [134,135]. Additionally, in oral squamous cell carcinoma, lipopolysaccharide (LPS)-induced overexpression of hBD-3 has been associated with enhanced cellular mobilization and chemotaxis via EGFR activation [130] (Figure 2).

4.3. The Dual Roles of AMPs in Metastasis (Pro- and Anti-Metastatic)

The dual behavior of AMPs—promoting and inhibiting metastasis—is governed by three key factors that shape their biological impact. First, concentration thresholds act as a functional switch: at low, physiological levels, peptides such as LL-37 and hBD-3 activate signaling pathways (MAPK/ERK, PI3K/Akt, NF- κ B) that drive epithelial–mesenchymal transition (EMT), matrix metalloproteinase expression (MMP-2, MMP-9), cell migration, and invasion [130,131]. By contrast, higher therapeutic concentrations (>micromolar) physically disrupt the lipid bilayer by forming pores and lysing cells [71,82,83]. Second, peptide origin shapes functional outcomes, with endogenous AMPs (produced by tumor cells, CAFs, or immune cells) frequently promoting inflammation, tumor growth, invadopodia, and immunosuppression, whereas synthetic or bioengineered AMPs aim to selectively eliminate tumor cells and target pro-metastatic elements (such as M2 macrophages) without activating invasive pathways [86,130,131,133]. Finally, tumor microenvironment context—including acidosis, hypoxia, protease levels, and extracellular matrix components—ultimately determines whether AMPs act as pro-metastatic drivers or anti-metastatic agents [70,83,90,91].

5. Strategies to Enhance the Anti-Metastatic Activity of AMPs

AMPs have certain limitations for clinical application. Some AMPs can damage healthy cell membranes and cause hemolysis; they are also expensive and challenging to produce. Additionally, pH fluctuations can affect AMP stability; they may lose activity in the presence of iron and serum, be susceptible to proteolytic degradation, exhibit low bioavailability, and elicit immunogenic responses [83,91]. To address these limitations, researchers have developed several strategies. Reducing peptide length can lower production costs, improve peptide stability against proteolytic degradation, and enhance anti-metastatic activity (e.g., mercedin) [12,87]. Other approaches to improve proteolytic stability include protecting the amino and carboxyl termini through N-acylation or C-amidation, cyclization, substitution of amino acid residues with non-proteinogenic residues, and designing pseudopeptides by replacing peptide bonds with other chemical linkages. Additional methods include removal of residues most susceptible to proteolytic cleavage (peptides ending in Arg, Asp, Leu, Lys, or Phe are generally more prone to degradation); use of protease inhibitors; conjugation of the peptide to polymers, which not only protect against degradation but also improve pharmacokinetics; and formulation modifications using liposomes, solid lipid nanoparticles, or gold nanoparticle conjugation [88,90,91]. Examples showing that these modifications enhance anti-metastatic activity include the peptides KT2 and RT2, which were designed based on Leucocrocin I. These peptides incorporate tryptophan (W) and

lysine (K) or arginine (R) substitutions to increase their hydrophobicity and hydrophilicity, respectively, along with C-terminal amidation [87].

Another strategy to enhance the anti-metastatic activity of AMPs is to incorporate linkers that direct peptides toward target cells. One example is TAMpepK, which was designed to specifically bind tumor-associated macrophages with an M2-like phenotype [86]. Another example is PEG-Melittin-dKLA 8–26, in which the peptide is linked to a membrane-binding sequence that targets negatively charged membranes and is PEGylated at the N-terminus to increase its stability in the body [89]. Furthermore, rational peptide design has been implemented to optimize the discovery of novel molecules through *in silico* analysis. Tools such as data mining identify patterns and build predictive models from databases, helping to predict whether a sequence exhibits anticancer activity and design *de novo* peptides with anti-metastatic properties [88].

6. Conclusions and Future Perspectives

AMPs represent a versatile and promising class of bioactive molecules with significant potential as modulators of cancer metastasis. While conventional therapeutic modalities—such as chemotherapy, targeted therapies, and anti-angiogenic agents—are frequently hampered by systemic toxicities, narrow therapeutic windows, and rapid development of multidrug resistance, AMPs offer unique biophysical advantages, including electrostatic selectivity for malignant cell membranes, low susceptibility to efflux pumps, multi-targeting capabilities, and TME-modulating properties. Integrating rational *de novo* peptide design, chemical stabilization, and advanced nano-delivery systems with a clear understanding of microenvironmental signaling will be essential to translate AMPs into safe, selective, and potent anti-metastatic therapeutics.

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Abbreviations

The following abbreviations are used in this manuscript:

AMP	Antimicrobial peptide
TME	Tumor microenvironment
ECM	Extracellular matrix
HIF	Hypoxia-inducible factors
EMT	Epithelial–mesenchymal transition
TGFβ	Transforming growth factor-β
BMP	Bone morphogenetic protein
EGF	Epidermal growth factor
FGF	Fibroblast growth factor

PDGF	Platelet-derived growth factor
EMT-TF	EMT-associated transcription factor
ZO-1	Zonula Occludens-1
MMP	Matrix metalloproteinases
RhoA	Ras homolog family member A
VEGF	Vascular endothelial growth factor
CTC	Circulating tumor cell
TAM	Tumor-associated macrophage
ANGPTL4	Angiopoietin-like 4
EREG	Epiregulin
COX-2	Cyclooxygenase-2
CSC	Cancer stem cell
TNC	Tenascin C
RTK	Receptor tyrosine kinase
EGFR	Epidermal growth factor receptor
CAF	Cancer-associated fibroblast
ITGA6	Integrin alpha 6
RPSA	Ribosomal protein SA
CRC	Colorectal cancer
GLMP	Glycosylated lysosomal membrane protein
HA	Holothurin A
ROS	Reactive oxygen species
PS	Phosphatidylserine
Gm	Gomesin
hBD1	Human β -defensin 1
hBD3	Human β -defensin 3
HD6	Human α -defensin 6
LfcinB	Bovine lactoferricin
YB-1	Y-box binding protein 1
LPS	Lipopolysaccharide

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