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REVIEW

Regulation of matrix metalloproteinase-13 in cancer: Signaling pathways and non-coding RNAs in tumor progression and therapeutic targeting

Deekshaa Chidambaram, Velan Subashini, Muthuvairaprasath Nanthanalaxmi, Iyyappan Saranya, Nagarajan Selvamurugan

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Deekshaa Chidambaram, Velan Subashini, Muthuvairaprasath Nanthanalaxmi, Iyyappan Saranya, Nagarajan Selvamurugan, Department of Biotechnology, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur 603203, India

Corresponding author: Nagarajan Selvamurugan, PhD, Professor, Department of Biotechnology, School of Bioengineering, SRM Institute of Science and Technology, Tamil Nadu, Kattankulathur 603203, India. selvamun@srmist.edu.in

Abstract

Matrix metalloproteinases (MMPs) are essential enzymes involved in extracellular matrix degradation and remodeling. Such processes are integral to normal tissue homeostasis and several pathological conditions such as cancer. Among these MMPs, MMP-13 plays a key role in cancer progression, driving tumor invasion, metastasis, and angiogenesis. Despite significant advancements in understanding its biology, therapeutic targeting of MMP-13 remains challenging owing to its complex and multifaceted regulatory mechanisms. Recent studies have underscored the pivotal role of non-coding RNAs (ncRNAs), including long ncRNAs, microRNAs, and circular RNAs, in modulating MMP-13 expression. This review provides a comprehensive analysis of MMP-13 regulation by several signaling pathways, the influence of ncRNAs on these signaling pathways, and MMP-13 expression during cancer progression and metastasis. Furthermore, we explored the clinical relevance of ncRNA-mediated regulatory networks, highlighting their potential as diagnostic biomarkers and therapeutic targets in various cancers. By unraveling these regulatory mechanisms, this review offers valuable insights into innovative strategies for cancer diagnosis and treatment and emphasizes the translational significance of ncRNA-mediated MMP-13 regulation in oncology.

Key Words: Matrix metalloproteinase-13; Cancer; MicroRNAs; Long non-coding RNAs; Circular RNAs

Core Tip: Matrix metalloproteinase-13 (MMP-13) is an important collagenase that plays a critical role in cancer development and metastasis. Several signaling pathways and non-coding RNAs (ncRNAs) regulate MMP-13 expression in various types of cancer. This review explores the mechanisms by which various signaling pathways and different types of ncRNAs, such as long ncRNAs, microRNAs, and circular RNAs, modulate MMP-13 expression in cancer.

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INTRODUCTION

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases involved in the degradation and remodeling of the extracellular matrix (ECM). Such processes are integral to normal tissue homeostasis and several pathological conditions such as cancer. MMP-13, a major collagenase, is involved in ECM turnover; it preferentially cleaves type II collagen, but also hydrolyzes type I and III collagen[1]. Under physiological conditions, MMP-13 is necessary for skeletal growth and tissue remodeling. However, dysregulated expression of MMP-13 is strongly associated with cancer progression and metastasis[2,3].

The overexpression of MMP-13 has been reported in several cancers, including breast, lung, and head and neck squamous cell carcinoma (HNSCC), where MMP-13 largely contributes to increased aggressiveness in tumors[1]. The release of MMP-13 degrades ECM components, thus facilitating the local invasive growth of a tumor and colonization of metastatic colonies, as it allows the production of secondary tumor sites by cancer cells. Different mechanisms and regulation of MMP-13 result in aggressive tumor formation and poor clinical performance[4]. The growing cancer burden worldwide, with over 20000000 new cases and 10000000 deaths reported in 2022, underscores the critical role of MMP-13 in cancer biology. These trends are projected to increase to 35000000 new cases by 2050, making it urgent to develop innovative therapeutic strategies to counteract cancer progression and improve patient survival rates[5]. Developing targeted interventions against MMP-13 is a promising approach to address this challenge.

Traditionally, MMP-13 regulation has been approached through three main strategies: Controlling its transcriptional and translational expression and directly inhibiting its catalytic domain by utilizing endogenous tissue inhibitors of metalloproteinases[6]. Despite promising preclinical findings, MMP inhibitors have shown limited clinical success due to their off-target effects and toxicity concerns. To overcome these limitations, a deeper understanding of the structure of MMPs, or protein engineering, can be used to develop efficient and selective MMP inhibitors[7]. Notably, alternative regulatory mechanisms, particularly those involving non-coding RNAs (ncRNAs), have garnered increasing attention.

The ncRNAs, such as microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs), are functional RNA molecules that regulate gene expression at multiple levels[8,9]. Such molecules play pivotal roles in homeostasis as well as in the development of the disease and act as both tumor suppressors and oncogenes[10,11]. The mechanisms of MMP-13 regulation through ncRNAs include transcriptional modulation and post-transcriptional silencing. For example, the expression of the MMP-13 gene is suppressed by miRNAs, such as miR-27a and miR-140[12,13], whereas certain lncRNAs, such as hypertrophic chondrocyte angiogenesis-related lncRNA, function as competing endogenous RNAs by sponging miR-15b-5p, leading to MMP-13 upregulation in hypertrophic chondrocytes[14].

This article discusses the role of ncRNAs in the regulation of MMP-13 and their effects on tumor invasion, metastasis, and angiogenesis in different types of cancers. Recent developments in ncRNA-based therapeutic approaches that modulate MMP-13 expression have also been investigated. Understanding the regulation of MMP-13 by ncRNAs may provide insights into the development of more precise and effective molecular interventions for cancer treatment.

PHYSIOLOGICAL ROLE OF MMP-13

MMP-13, a key collagenase, plays a fundamental role in ECM remodeling, particularly in bone biology. Studies using MMP-13-deficient models have demonstrated its crucial functions in bone integrity and repair. For instance, mice lacking MMP-13 exhibit cortical bone fragility, impaired cartilage resorption, and delayed fracture healing, highlighting its indispensable role in bone strength, angiogenesis, and cellular recruitment during tissue repair[15,16]. The absence of MMP-13 in fractures leads to reduced vascular penetration and defective chondroblast recruitment, thereby impairing cartilage clearance. Additionally, chondrocyte pellets derived from MMP-13-deficient mice showed diminished angiogenic potential, further underscoring their role in vascularization during fracture repair[17].

MMP-13 expression is tightly regulated by key transcription factors including osterix, runt-related transcription factor 2 (RUNX2), activating transcription factor 3 (ATF3), and cellular Fos proto-oncogene. Osterix directly binds to the MMP-13 promoter, enhancing its expression in osteoblasts[18]. Similarly, ATF3 and cellular Fos proto-oncogene coordinate to regulate MMP-13 transcription in chondrocytes[19]. MMP-13 also interacts with collagen I by exposing cryptic ligands, which activate integrin α3β1 signaling, leading to RUNX2 nuclear translocation and the subsequent upregulation of

MMP-13 expression[20].

In addition to its regulatory functions, MMP-13 also plays a crucial role in supporting osteogenic differentiation in three-dimensional environments. In type I collagen hydrogels, increased MMP-13 expression enhances the osteogenic potential of bone marrow mesenchymal stem cells[21]. Additionally, recombinant MMP-13-treated collagen sponges improved *in vivo* bone formation by increasing the bone volume, reducing porosity, and enhancing bone mineral density [20]. These findings highlight the potential therapeutic applications of MMP-13 in bone tissue engineering.

In addition to bone remodeling, MMP-13 is involved in muscle repair and regeneration. Satellite cells deficient in MMP-13 exhibited impaired migration and reduced regenerative capacity, indicating their broad role in ECM remodeling and tissue integrity[22]. MMP-13 contributes to osteogenic differentiation by regulating osteoblast activity. For example, exogenous MMP-13 has been shown to enhance bone morphogenetic protein 9-induced osteogenesis in fibroblasts by activating Wnt/β-catenin signaling *via* the upregulation of hypoxia-inducible factor 1[23]. Thus, MMP-13 plays a vital role in ECM remodeling and facilitates tissue development, repair, and regeneration. It is essential for bone formation, fracture healing, angiogenesis, and muscle regeneration, highlighting its broad physiological significance (Figure 1). Understanding the precise regulatory mechanisms governing MMP-13 function may provide valuable insights into its therapeutic applications, particularly in regenerative medicine and tissue engineering.

PATHOPHYSIOLOGICAL ROLE OF MMP-13

Tissue reorganization that occurs during wound healing, cancer, and inflammatory responses is regulated by the vital enzyme MMP-13, and its dysregulation has been associated with a broad spectrum of pathological conditions, such as osteoarthritis, rheumatoid arthritis, fibrosis, neurodegenerative disorders, and cardiovascular diseases[24]. Its central role in disease progression is primarily attributed to its proteolytic activity and intricate regulatory mechanisms. In osteoarthritis, MMP-13–enhanced cartilage degradation by degrading key matrix components, thereby accelerating tissue deterioration[25]. Elevated MMP-13 Levels, with concomitant pro-inflammatory mediators, such as interleukin-1β and nuclear factor-kappa B (NF-κB) p65 in synovial fluid, suggested an inflammation-mediated cartilage degradation pathway by NF-κB signaling[26]. Notch signaling also modulates MMP-13 through RUNX2 activation, leading to the hypertrophy of chondrocytes and further augmenting the damage inflicted on the cartilage[27]. Other pathways, such as p38/cyclic adenosine monophosphate-response element binding protein (CREB)/MMP-13 and transforming growth factor (TGF) beta 1 signaling, contribute to increased MMP-13 expression, amplifying inflammation and ECM degradation[28,29]. In rheumatoid arthritis, MMP-13 plays a key role in ECM degradation within the synovial joints, leading to progressive joint damage and inflammation. Normal T-expressed and secreted/CC ligand 5 activates MMP-13 *via* the protein kinase C delta-Jun N-terminal kinase/extracellular signal-regulated kinase (ERK) pathway in fibroblasts, driving cartilage destruction[30]. Additionally, increased serum levels of MMP-13 are correlated with disease severity, linking its activity to joint erosion and systemic inflammation[31].

In addition to joint diseases, MMP-13 is involved in fibrosis and chronic inflammatory disorders. During liver fibrosis, MMP-13 enhanced the expression of fibrotic genes and promotes disease progression. Additionally, MMP-13 contributed to the cleavage of connective tissue growth factors, generating fragments that further drive fibrosis[32,33]. In Crohn's disease, *MMP-13* promotes fibrostenotic complications *via* interleukin (IL)-36R signaling, and its deletion reduces fibrosis severity in intestinal tissues, highlighting its role in intestinal inflammation and remodeling[34]. Similarly, in ulcerative colitis, Fos-like antigen-1 mediated MMP-13 inhibition alleviates inflammatory damage and strengthens the intestinal barrier integrity, suggesting a potential therapeutic approach[35].

MMP-13 has been implicated in neurodegenerative diseases where it contributes to neuroinflammation and ECM degradation. In Parkinson's disease, mutant α-synuclein induced *MMP-13* expression in microglia, leading to lysosomal dysfunction and neuronal damage[36]. Additionally, rare mutations in *MMP-13* have been associated with Alzheimer's disease, indicating its involvement in disease progression[37]. These findings suggest that MMP-13-mediated ECM remodeling plays a role in neuroinflammatory and neurodegenerative disorders.

In respiratory and cardiovascular diseases, MMP-13 contributes to tissue damage and ECM destabilization. In cystic fibrosis, persistent *Pseudomonas aeruginosa* infection induces *MMP-13* expression *via* NF-κB activation, which contributes to chronic inflammation and lung tissue damage. Targeting this pathway may help mitigate disease progression[38]. In influenza-induced atherosclerosis, MMP-13-mediated collagen degradation destabilizes plaques, thereby increasing the risk of cardiovascular events[39]. However, in pulmonary fibrosis, MMP-13 exerts antifibrotic effects, playing a pivotal role in lung repair and maintaining tissue integrity during fibrosis resolution[40]. These findings indicated that the role of MMP-13 is highly context-dependent, with both pathological and protective functions depending on the disease setting.

MMP-13 is also involved in periodontal disease and ECM homeostasis. Its excessive activity accelerates bone resorption and inflammation, which cause tissue destruction in periodontal disease; however, inhibition of *MMP-13* decreases such effects, preserving the integrity of the ECM while reducing inflammation[41]. Overall, MMP-13 has been established as a pivotal regulator of ECM homeostasis, and its dysregulation contributes to the pathogenesis of joint degeneration, fibrosis, neuroinflammation, and cardiovascular instability (Figure 2). Its proteolytic activity can drive tissue destruction and disease progression under multiple pathological conditions, suggesting that it is an exciting therapeutic target. In this context, further research is required to identify selective MMP-13 inhibitors and their regulatory mechanisms as effective treatment approaches for chronic and degenerative diseases.

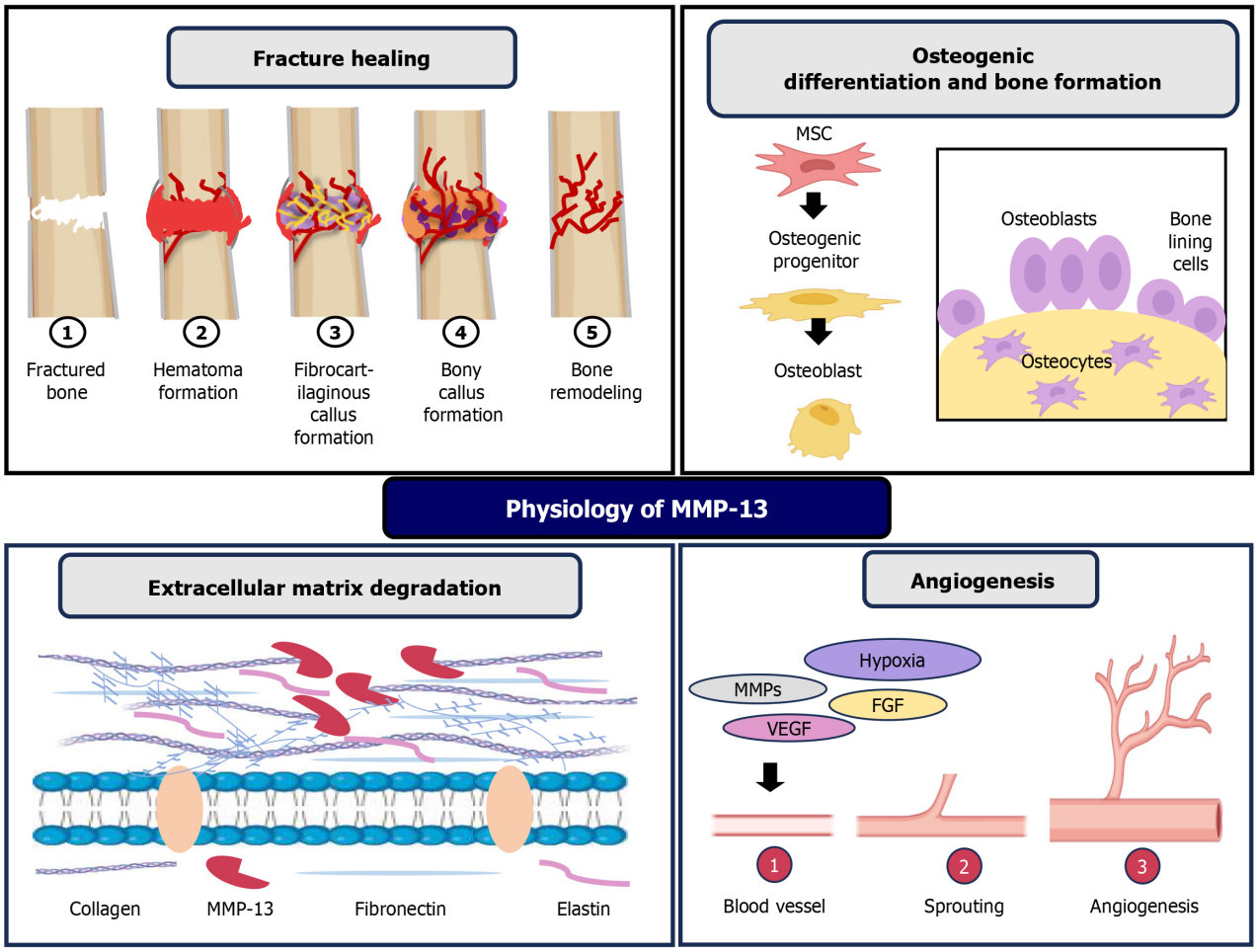

Figure 1 Physiological role of matrix metalloproteinase-13. A schematic diagram illustrates the diverse functions of matrix metalloproteinase-13 in various physiological processes. MSC: Mesenchymal stem cells; MMP: Matrix metalloproteinase; FGF: Fibroblast growth factor; VEGF: Vascular endothelial growth factor.

ROLE OF MMP-13 IN CANCER PROGRESSION AND METASTASIS

MMP-13 is a key regulator of the tumor microenvironment that drives cancer progression through its role in ECM degradation, invasion, and metastasis. Aberrant expression across various malignancies has been linked to increased tumor aggressiveness and poor patient prognosis[42]. In oral squamous cell carcinoma (OSCC), *MMP-13*, C-X-C motif chemokine ligand 8 and *MMP-12*, are crucial biomarkers associated with tumor progression. It has been linked to inflammatory signaling pathways, including IL-17, chemokines, and cytokine-cytokine receptor interactions, offering potential diagnostic and prognostic targets[43]. Similarly, in tongue squamous cell carcinoma, bioinformatics analyses have implicated MMP-13 in tumor behavior through the tumor necrosis factor signaling pathway, further reinforcing its role in disease progression[44]. In cutaneous squamous cell carcinoma (CSCC), the serum MMP-13 levels can distinguish between invasive and non-invasive cases and predict lymph node metastasis, underscoring its utility in diagnosis and disease monitoring[45].

Similarly, in esophageal squamous cell carcinoma (ESCC), *MMP-13* regulated epithelial-mesenchymal transition (EMT) *via* the *TWIST 1-CD44-MMP-13* axis, promoting tumor invasion and metastasis[46]. In melanoma, elevated MMP-13 expression correlated with aggressive tumor phenotypes, particularly nodular melanomas, and its expression varied based on BRAF mutation status, suggesting a role in invasive progression[47]. In breast cancer (BC), *MMP-13* was upregulated by TGF-β *via* the β6 integrin-EP300 pathway, significantly contributing to stromal invasion in ductal carcinoma *in situ*, thereby facilitating the transition to invasive BC[48]. MMP-13 also plays a significant role in bone-related malignancies, particularly multiple myeloma, in which it contributes to osteolytic lesions. The MMP-13/programmed death-1 homolog axis is integral to myeloma-associated osteolysis, suggesting a potential therapeutic avenue for mitigating bone destruction[49,50]. In lung cancer, MMP-13 was regulated by IL-6-induced ataxia telangiectasia mutated protein (ATM) phosphorylation and the hypoxia-inducible factor 1/Janus kinase 2/signal transducer and activator of transcription 3 (STAT3) pathway under hypoxic conditions, promoting invasion and metastasis (Figure 3). The pharmacological inhibition of these pathways has been shown to reduce MMP-13 levels and suppress metastatic potential, highlighting a promising therapeutic strategy[51,52].

MMP-13 facilitates metastatic progression in hepatocellular carcinoma, where it is upregulated *via* Golgi protein-73 mediated CREB activity, enhancing tumor invasiveness and metastatic potential[53]. In colorectal cancer, C-C motif chemokine receptor 4 activated MMP-13 through the ERK/NF-κB/MMP-13 axis, promoting tumor invasion and

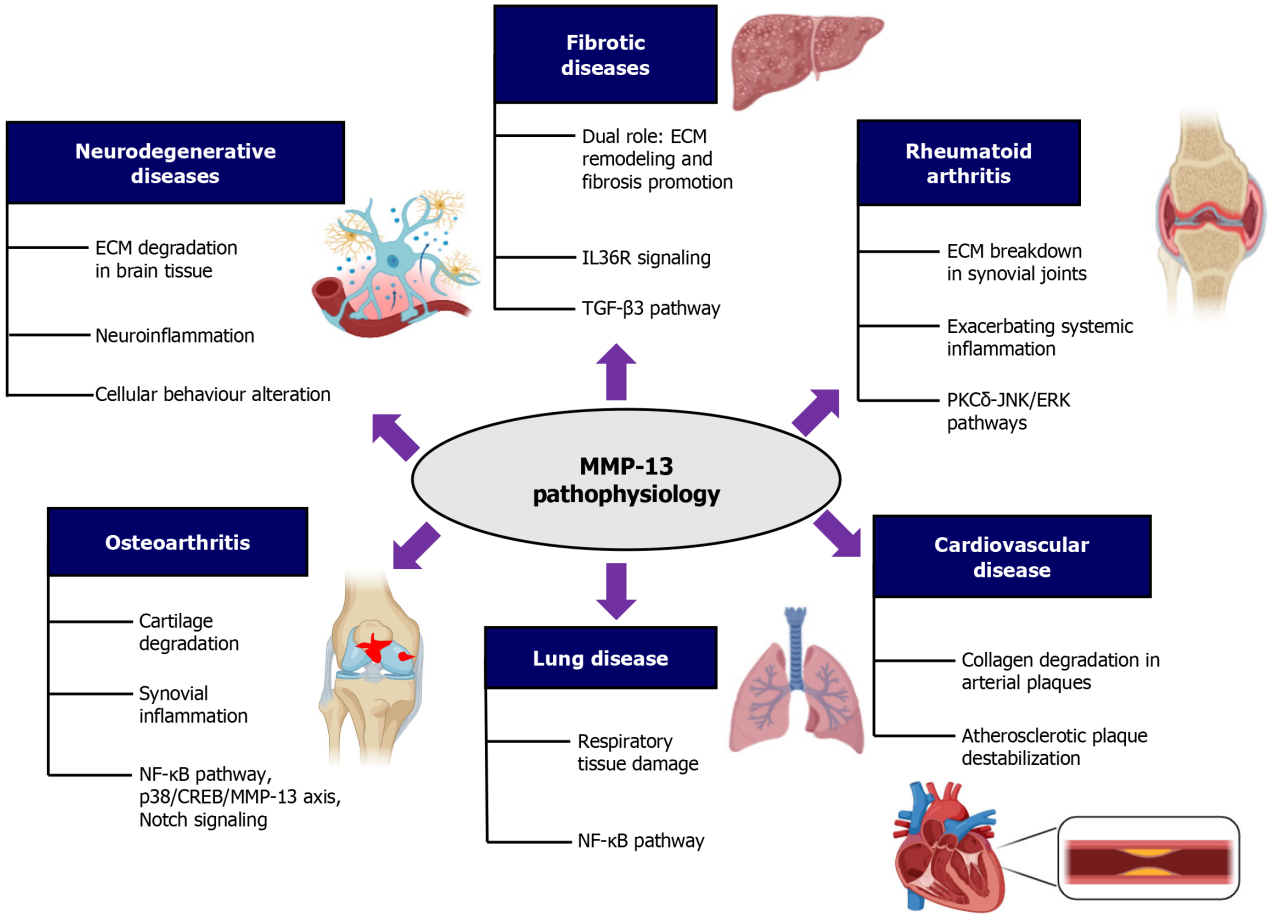

Figure 2 Pathophysiological role of matrix metalloproteinase-13 in various diseases. A schematic diagram illustrates the involvement of matrix metalloproteinase-13 (MMP-13) in the development and progression of various diseases. ECM: Extracellular matrix; PKC: Protein kinase C delta; JNK: Jun N-terminal kinase; ERK: Extracellular signal-regulated kinase; NF-κB: Nuclear factor kappa B; CREB: Cyclic adenosine monophosphate-response element binding protein; IL36R: Interleukin 36R; TGF-β3: Transforming growth factor-beta 3; MMP-13: Matrix metalloproteinase-13.

associated with poor prognosis[54]. In summary, these studies highlight MMP-13 as an important biomarker and therapeutic target in various cancers. Its role in tumor invasion, EMT, and metastasis presents several avenues for intervention. Therefore, it is necessary to investigate targeted therapies aimed at modulating MMP-13 activity (Table 1) [55-68].

SIGNALING PATHWAYS REGULATING MMP-13 IN CANCER

MMP-13 expression in cancer is strictly regulated by several signaling pathways that control its role in tumor invasion, metastasis, and progression[1,69]. For example, the TGF-β signaling pathway enhances the transcription of MMP-13 through ATF3 activation. ATF3 associates with c-Jun and JunB to form a transcriptional complex at the activator protein-1 site on the MMP-13 promoter, resulting in increased MMP-13 expression, thus increasing the invasive potential of tumor cells, especially in BC[69]. In the prostate cancer system, melatonin has been recently identified as an MMP-13 expression regulator, which acts on the MT1 receptor to control the phospholipase C and p38 signaling cascades, thus diminishing the migration and invasive capacity of cancer cells. Therefore, the dose-dependent inhibition of MMP-13 by melatonin underlines the potential therapeutic benefits of controlling metastasis through this pathway[70].

Another important pathway involves gremlin-1 and STAT3 signaling. Gremlin-1 led to the expression of MMP-13 in BC cells through tyrosine phosphorylation at Tyr705 of STAT3. Inhibition of STAT3 phosphorylation significantly reduced the levels of MMP-13, making this pathway a potential target in STAT3-driven malignancies[71]. Similarly, the protein kinase B (Akt)-B-CREB pathway plays a significant role in regulating MMP-13 expression. This axis mediates TGF-β-induced MMP-13 transcription. Sauchinone, a bioactive compound, suppresses Akt and CREB activity, thus decreasing MMP-13 Levels and offering a targeted approach for cancers with hyperactive Akt-CREB signaling[72].

Another important pathway that regulates MMP-13 is the ERK signaling pathway. In ESCC, the scaffold protein AJUBA induces the expression of MMP-13 through enhanced activation of ERK1/2. Silencing AJUBA results in reduced ERK1/2 phosphorylation and MMP-13 Levels, suggesting its therapeutic relevance[73]. In bladder cancer, the C-C motif chemokine ligand 17/C-C motif chemokine receptor 4 axis upregulates MMP-13 through ERK signaling. Blocking this pathway impairs tumor cell invasiveness, highlighting the role of ERK signaling in cancer progression[74].

Table 1 Role of matrix metalloproteinase-13 as a biomarker in various disease conditions

Number	Disease condition	Biological source	MMP-13 expression	Role in disease	Global statistics	Ref.
1	OSCC	Saliva and serum samples	Upregulated	MMP-13 expression level in serum was associated with the invasion of OSCC	New cases in 2020: 377713	[55, 56]
2	OSCC	Tumor tissues, tumor-adjacent tissues, and saliva	Upregulated	Promotes tumor progression and metastasis	New cases in 2020: 377713	[56, 57]
3	ESCC	ESCC tissue and serum	Upregulated	Elevated MMP-13 expression in the serum was linked to tumor progression and reduced survival rates	New cases in 2020: 512500	[58, 59]
4	GC	Serum	Upregulated	A combined identification of Ephrin A1 and MMP-13 was found to be potential biomarkers for the early detection of GC	New cases in 2022: 968000	[60, 61]
5	GC	Tumor tissues and tumor-adjacent tissues	Upregulated	Associated with cancer progression, metastasis and invasion	New cases in 2022: 968000	[61, 62]
6	Ovarian cancer	Ovarian cancer tissue	Upregulated	High levels of MMP-13 were associated with worse overall survival in patients with ovarian cancer	New cases in 2020: 313959	[63, 64]
7	BC	Stromal fibroblast of invasive ductal carcinoma and benign epithelial breast lesions	Upregulated	MMP-13 played a critical role in the tumorigenesis of human BC, acting as a key modulator of tumor invasion and metastasis. It was also an independent predictor of poor prognosis	New cases in 2020: 2300000	[65, 66]
8	BC in Egyptian women	Serum	Upregulated	Elevated MMP-13 Levels in the serum were linked to tumor growth, metastasis, and poor treatment response, particularly in TNBC cases	New cases in 2020: 2300000	[66, 67]
9	Pan-cancer (BC, HNSCC, LAD, lung squamous cell carcinoma)	Cancer tissue, serum	Upregulated	MMP-13 was associated with tumor immune infiltration, EMT pathway activation, and poor prognosis	Not applicable	[68]

OSCC: Oral squamous cell carcinoma; MMP-13: Matrix metalloproteinase-13; ESCC: Esophageal squamous cell carcinoma; GC: Gastric cancer; BC: Breast cancer; HNSCC: Head and neck squamous cell carcinoma; TNBC: Triple negative breast cancer; LAD: Lung adenocarcinoma; EMT: Epithelial-mesenchymal transition.

Inflammatory pathways have been shown to control MMP-13 expression. For instance, tumor necrosis factor-activated MMP-13 expression in lung cancer through an ATM-ERK/p38-NF-κB cascade. Activation of ATM is the core of this pathway because it promotes TNF-induced phosphorylation of ERK and p38, and NF-κB signaling activities, which contribute to the increase in MMP-13 transcription. ATM inhibition blocks this signaling network, thereby decreasing MMP-13 Levels and restricting the invasiveness of cancer cells[75]. A study by Zhang *et al*[76] on Kaposi's sarcoma showed that miR99a suppresses MMP7 and MMP-13 *via* the phosphatidylinositol 3-kinase/Akt and ERK/MAPK signaling pathways, respectively. This could be regulated by targeting miR99a or modulating Akt/ERK phosphorylation to impact MMP-7 and MMP-13- dependent Kaposi's sarcoma invasiveness[76]. Likewise, the study by Yang *et al*[77] highlighted the feedback loop of miR-127 regulating the TGF-β/c-Jun cascade by suppressing MMP-13 expression in hepatocellular carcinoma progression[77]. Thus, ncRNAs are associated with various signaling pathways involved in regulating gene expression in cancer[78]. The complexity of these signaling pathways demonstrates their potential to regulate MMP-13 expression in various types of cancers (Figure 4). Targeting these networks presents a promising avenue for the development of therapies focused on reducing metastasis and enhancing survival in several cancers.

OVERVIEW OF NCRNAS

The majority of the human genome comprises ncRNAs, which amount for only 2%-3% of the coding genes that produce proteins. These ncRNAs regulate gene expression by controlling transcription, translation, and post-transcriptional processes[79]. They can be divided into housekeeping ncRNAs, such as rRNA and tRNA, which are used in protein synthesis, or regulatory ncRNAs that alter the levels of gene expression[80]. In terms of size, ncRNA categories include small ncRNAs less than 200 nucleotides like miRNAs and siRNAs, and lncRNAs that consist of more than 200 nucleotides, which are linear and circular forms. Linear and circular lncRNAs serve as gene regulators through protein interactions, and act as sponges for miRNAs. Several diseases, such as cancer and neurodegenerative, cardiovascular, and metabolic disorders, are associated with ncRNA dysregulation. The abundance and ease of ncRNA detection in body fluids renders them suitable candidates as biomarkers for disease diagnosis and treatment[81,82]. The following sections analyze the functions of lncRNAs, miRNAs, and circRNAs in the regulation of MMP-13 expression in cancer and present these ncRNAs as therapeutic candidates.

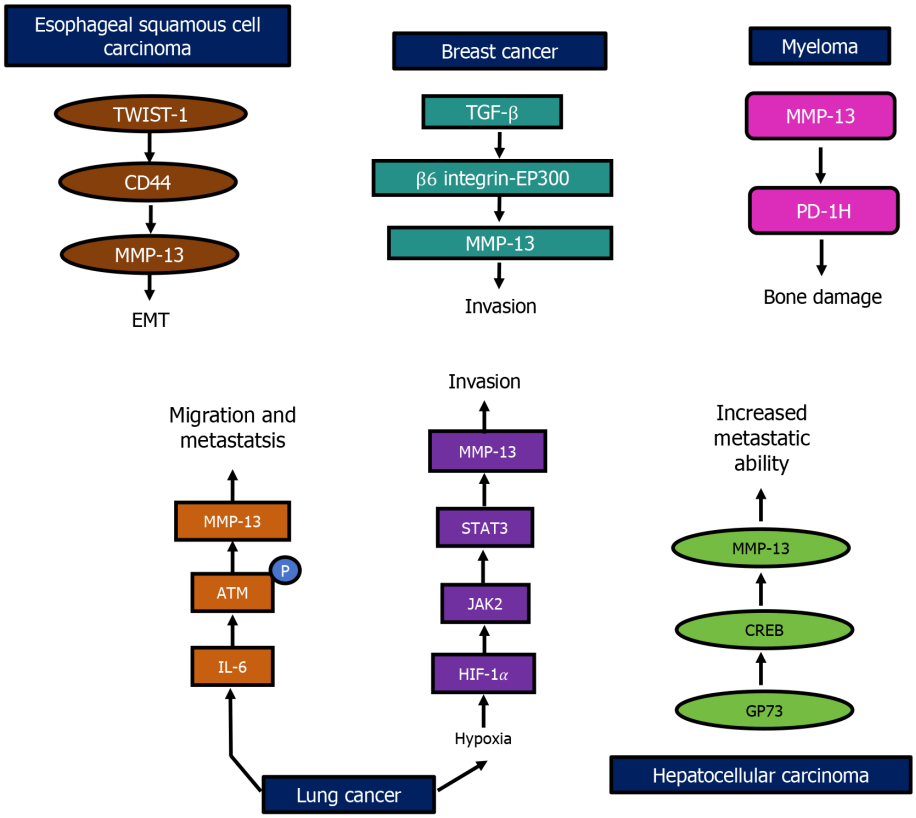

Figure 3 Matrix metalloproteinase-13-mediated cancer progression. The overexpression of matrix metalloproteinase-13 (MMP-13) has been associated with increased invasion, migration, and metastasis in different types of cancer. In breast cancer, transforming growth factor-β/β6 integrin-histone acetyltransferase p300/MMP-13 axis increases the invasive potential, and in lung cancer, hypoxia-inducible factor 1/ Janus kinase 2/signal transducers and activators of transcription 3/MMP-13 and interleukin 6/ataxia telangiectasia mutated protein/MMP-13 axes are involved in tumor aggressiveness. Then, the Golgi protein 73/cyclic adenosine monophosphate response element-binding protein/MMP-13 axis in hepatocellular carcinoma further accelerates metastasis. TWIST 1: Twist family basic helix-loop-helix transcription factor 1; MMP-13: Matrix metalloproteinase-13; TGF-β: Transforming growth factor-β; EP-300: Histone acetyltransferase p300; PD-1H: Programmed death-1 homolog; ATM: Ataxia telangiectasia mutated protein; EMT: Epithelial mesenchymal transition; IL-6: Interleukin 6; HIF-1: Hypoxia-inducible factor 1; JAK2: Janus kinase 2; STAT3: Signal transducers and activators of transcription 3; GP73: Golgi protein 73; CREB: Cyclic adenosine monophosphate response element-binding protein.

lncRNAs regulating MMP-13 in cancer

lncRNAs have emerged as key regulators of MMP-13 expression in various cancer types, influencing tumor progression, metastasis, and treatment resistance. These lncRNAs mediate their effects through diverse mechanisms, including transcriptional regulation, epigenetic modifications, protein or RNA stability, translation, and post-translational modifications[83]. In gastric cancer (GC), the lncRNA gastric progression-associated ncRNA enhanced invasion and metastasis through the RUNX2-MMP-13 axis. Overexpression of lncRNA gastric progression-associated ncRNA in AGS and SK-GT2 cell lines leads to the upregulation of *RUNX2* and *MMP-13* expression[84]. In contrast, LINC00332 was inversely correlated with *MMP-13* expression in GC tissues, suggesting a tumor-suppressive role[85].

In OSCC, a study by Huang *et al*[86] using the TCA8113 tongue carcinoma cell line revealed that esophageal cancer-related gene-4 downregulates MMP-9 and MMP-13 expression, while BC200 lncRNA upregulates these metalloproteinases. esophageal cancer-related gene-4 suppresses BC200 lncRNA expression and mitigates the malignant phenotype of OSCC by targeting MMP-9 and MMP-13 signaling in TCA8113 cells[86]. Additionally, LINC01133 inhibits metastasis in OSCC by forming a feedback loop with growth and differentiation factor 15, which downregulates *MMP-13* expression and suppresses invasive tumor behavior in CAL27 and HN4 cell lines[87].

In CSCC, BRD3OS (LINC00094), also known as lncRNA SERLOC (super enhancer-regulated LINC00094), promoted invasiveness by regulating cell-matrix adhesion, basement membrane integrity, and metalloendopeptidase activity. Knockdown of BRD3OS reduces MMP-1 and MMP-13 expression and inhibits cell invasion, highlighting its role in enhancing ECM degradation and tumor progression[88]. Similarly, lncRNA cancer susceptibility candidate 9 upregulates laminin subunit gamma 2, resulting in activation of the focal adhesion kinase phosphoinositide 3-kinase/Akt signaling pathway. Activation of this signaling pathway elevates MMP-13 expression and promotes ESCC[89]. In osteosarcoma (OS), overexpression of the lncRNAs human leukocyte antigen complex group 11 (HCG11) and MMP-13, coupled with decreased miR-579 Levels, promotes malignancy. The lncRNA HCG11 acts as a competing endogenous RNA by sponging miR-579, which leads to the upregulation of MMP-13. Knockdown of the lncRNAs HCG11 or MMP-13 or overexpression of miR-579 suppressed OS cell proliferation, migration, invasion, and EMT. miR-579 directly targets and negatively regulates MMP-13, and its overexpression reduces MMP-13 Levels and suppresses OS progression[90]. Li *et al*[91] found that lnRNA nicotinamide nucleotide transhydrogenase antisense RNA 1 promotes OS progression by downregulating

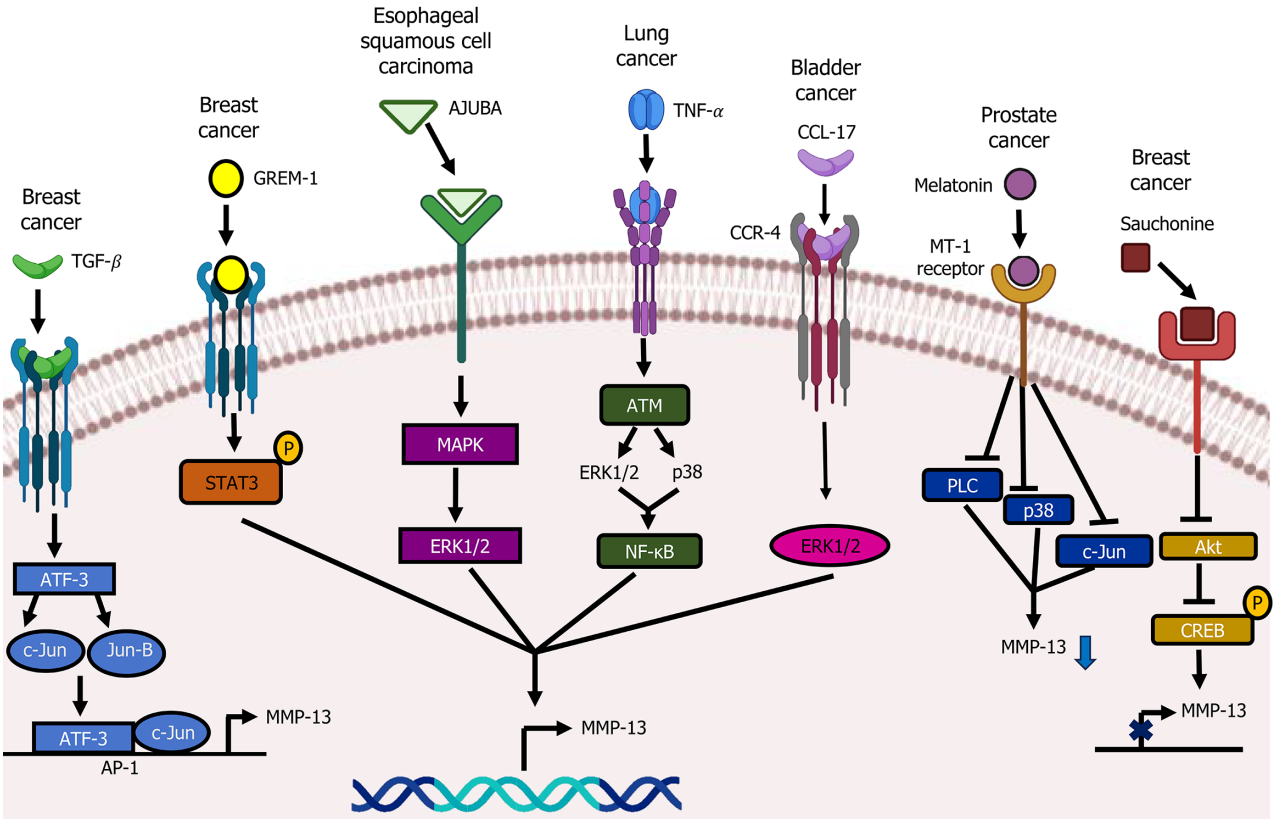

Figure 4 Signaling pathways controlling matrix metalloproteinase-13 in cancer. This figure shows the most important signaling pathways regulating matrix metalloproteinase-13 expression in various cancers, such as breast cancer, esophageal squamous cell carcinoma, lung cancer, bladder cancer, and prostate cancer. MMP-13: Matrix metalloproteinase-13; ATF3: Activating transcription factor 3, STAT3: Signal transducer and activator of transcription 3; AP1: Activating protein 1; GREM1: Gremlin-1, TNF-α: Tumor necrosis factor α; ATM: Ataxia telangiectasia mutated protein; TGF-β: Transforming growth factor-β; MAPK: Mitogen activated protein kinase; ERK: Extracellular signal-regulated kinase; NF-κB: Nuclear factor kappa B; PLC: Phospholipase C; Akt: Protein kinase B; CREB: Cyclic adenosine monophosphate response element-binding protein; c-Jun: Cellular Jun; CCR4: C-C motif chemokine receptor 4; CCL-17: C-C motif chemokine ligand 17.

miR-320a and increasing the expression of oncogenic proteins, such as β-catenin, RUNX2, and their downstream targets, including insulin growth factor 1 receptor, cellular MYC proto-oncogene, cyclin D1, and MMP-13. This process activates the phosphoinositide 3-kinase/Akt signaling pathway, facilitating OS progression[91].

LncRNA RP3-326I13.1 was found to be highly expressed in cisplatin-resistant cells and lung adenocarcinoma (LAD) tissues. It promoted cell migration, invasion, and cisplatin resistance by binding to heat shock protein-90 beta, which reduced apoptosis and upregulated MMP-13 expression. MMP-13 acted as a downstream target, promoting tumor proliferation and cisplatin resistance. Knockdown of RP3-326I13.1 induced G1 phase cell cycle arrest, reducing tumor growth, and improved cisplatin sensitivity. The synergistic effect of heat shock protein-90 beta and MMP-13 with RP3-326I13.1 drove tumor progression and cisplatin resistance in LAD cells[92]. In renal cell carcinoma, the tumor suppressor lncRNA suppressing androgen receptor in renal cell carcinoma (SARCC) binds and destabilizes the androgen receptor (AR) protein, leading to transcriptional suppression of miR-143-3p and inhibition of downstream targets, including MMP-13, Akt, Kirsten rat sarcoma viral oncogene homolog proto-oncogene guanosine triphosphatase, and phospho-ERK. Elevated expression of SARCC lncRNA prevents renal cell carcinoma cells from becoming resistant to sunitinib therapy[93].

In bladder cancer, the lncRNA metastasis-associated LAD transcript 1 sponged miR-125b, resulting in increased protein expression of MMP-13 and Bcl-2, which inhibited apoptosis and promoted invasion. This process facilitated bladder cancer progression[94]. Furthermore, lncRNA colon cancer-associated transcript 2 functions as an oncogene in pituitary adenoma progression. It affected the expression of downstream genes regulated by pituitary tumor transforming gene 1, such as *SRY-box transcription factor 1*, *delta like non-canonical notch ligand 1*, *MMP-2*, *and MMP-13* in HP75 cells[95]. In prostate cancer, lncRNA PCAT7 (Prostate cancer-associated transcript 7) activated the TGF-β signaling by upregulating *MMP-13*, contributing to bone metastasis through suppression of miR-324-5p[96].

Metastasis-associated LAD transcript 1 has been shown to promote ovarian cancer progression by upregulating MMP-13 and downregulating MMP-19 and ADAMTS1 (metallopeptidase with thrombospondin type-1 motif), thus facilitating invasion[97]. Another study showed that the lncRNA SNHG12 (small nucleolar RNA host gene 12), located in the cytoplasm, enhanced cell migration and invasion in triple-negative BC (TNBC) by upregulating *MMP-13*[98].

In summary, these studies highlighted the importance of lncRNAs in the regulation of MMP-13 expression in different types of cancer and their subsequent effects on tumor growth, metastasis, and response to treatment (Figure 5). The multifaceted interactions of lncRNAs are likely to be important biomarkers and therapeutic targets. In-depth studies on the molecular mechanisms of MMP-13 regulation by lncRNAs are essential for improving cancer treatment approaches.

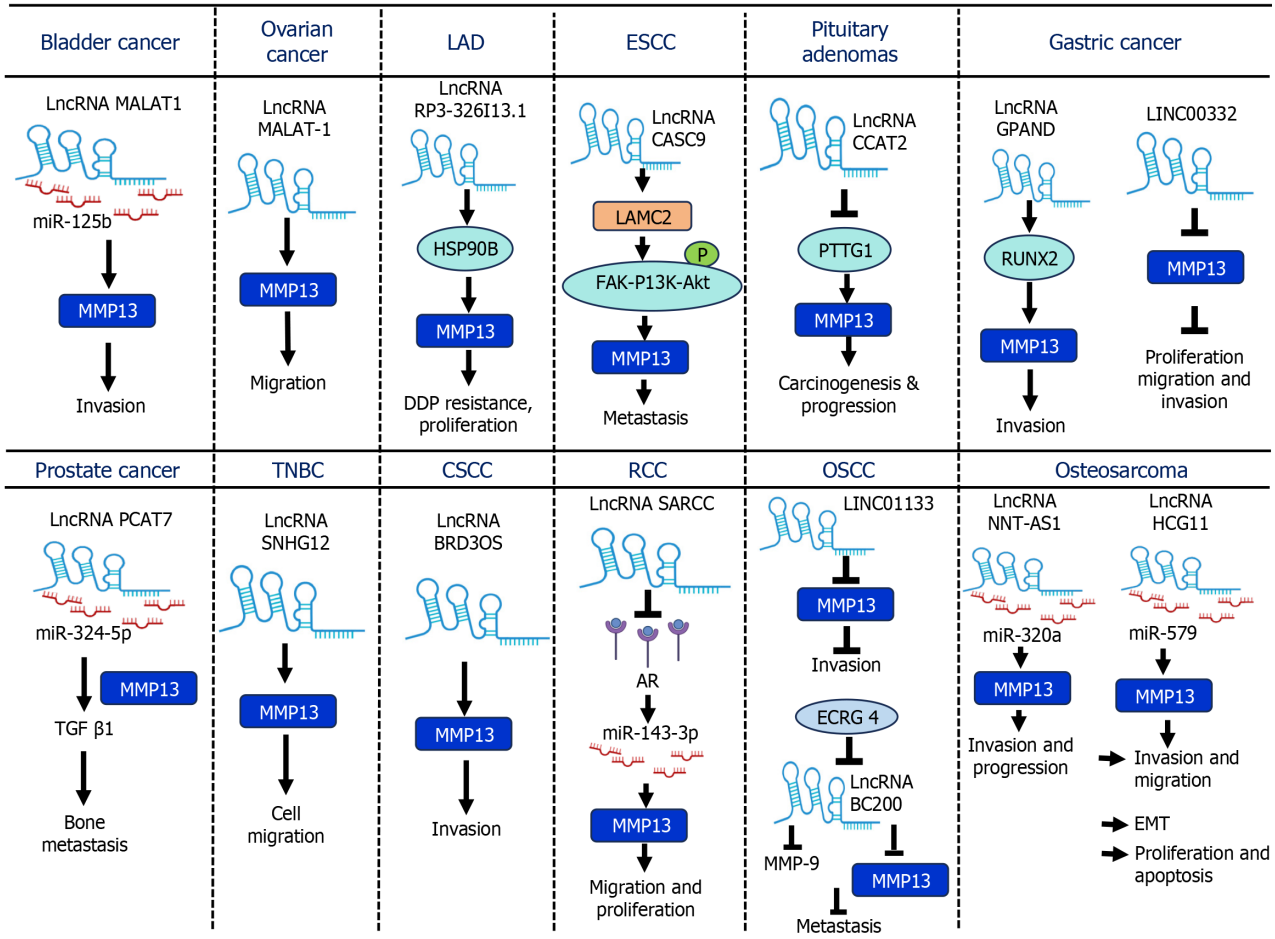

Figure 5 Involvement of long non-coding RNAs in regulating matrix metalloproteinase-13 expression in cancer. This figure illustrates the role of long non-coding RNAs in regulating matrix metalloproteinase-13 expression across various cancer types. LncRNAs: Long non-coding RNAs; MMP: Matrix metalloproteinase; LAD: Lung adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; TNBC: Triple negative breast cancer; CSCC: Cutaneous squamous cell carcinoma; RCC: Renal cell carcinoma; OSCC: Oral squamous cell carcinoma; HSP90B: Heat shock protein-90 beta; LAMC2: Laminin subunit gamma 2; PTTG1: Pituitary tumor transforming gene 1; RUNX2: Runt-related transcription factor 2; TGF-β1: Transforming growth factor beta 1; AR: Androgen receptor; ECRG4: Esophageal cancer related gene 4; EMT: Epithelial mesenchymal transition; MALAT1: Metastasis associated lung adenocarcinoma transcript 1; CASC9: Cancer susceptibility candidate 9; CCAT2: Colon cancer associated transcript 2; GPAND: Gastric progression associated non-coding RNA; PCAT7: Prostate cancer-associated transcript 7; SNHG12: Small nucleolar RNA host gene 12; SARCC: Suppressing androgen receptor in renal cell carcinoma; NNT-AS1: Nicotinamide nucleotide transhydrogenase antisense RNA 1; HCG11: Human leukocyte antigen complex group 11; FAK: Focal adhesion kinase; P13K: Phosphoinositide 3-kinase; Akt: Protein kinase B.

miRNAs influencing MMP-13 expression in cancer

miRNAs, a class of endogenous ncRNAs, play a crucial role in gene regulation by modulating various biological processes, including tumor progression. Dysregulation is increasingly recognized as a key factor in the pathogenesis[99, 100]. In the context of cancer, tumor-suppressing miRNAs are frequently downregulated, whereas oncogenic miRNAs, or "oncomiRs", are often upregulated compared to their expression in normal cells[101].

Regulatory network analysis identified ten differentially expressed miRNAs associated with MMP-13 regulation in OSCC. Among these, miR-7109-5p and miR-34b were downregulated in metastatic OSCC tissues, correlating with increased *MMP-13* expression, suggesting their tumor-suppressive roles[102]. Similarly, in CSCC, miR-27b-3p was found to inhibit tumor progression by targeting the 3' untranslated region of both epidermal growth factor receptor and MMP-13. This regulation led to a decrease in N-cadherin expression and an increase in E-cadherin expression, thereby enhancing cell adhesion and suppressing EMT and metastasis[103]. In TNBC, inhibition of miR-941 increases E-cadherin levels and reduces MMP-13 expression, thereby suppressing migration and invasion, indicating its oncogenic role in this aggressive BC subtype[104]. Similarly, in gliomas, the downregulation of miR-4262 was linked to decreased MMP-2 and MMP-13 Levels, leading to reduced tumor invasiveness, highlighting its role in MMP regulation[105].

The functional interplay between miRNAs and signaling networks further emphasizes their impact on cancer progression. For instance, miR-217 targets neurofibromatosis type 1, leading to the activation of ATF3 and the subsequent upregulation of MMP-13 in BC cells. This interaction promoted tumorigenicity and chemoresistance by inducing autophagy[106]. In esophageal cancer, miR-145-5p downregulated the specificity protein 1/NF-κB pathway, leading to decreased *MMP-13* expression and reduced cell migration, invasion, and EMT, underscoring its potential as a therapeutic target[107].

Oncogenic miRNAs contribute to cancer progression by promoting MMP-13 expression. In prostate cancer, the upregulation of miR-210-3p enhanced metastasis by activating NF-κB signaling and increasing the expression of *TWIST 1* and *MMP-13*[108]. Likewise, loss of the miR-148/152 family in colon cancer resulted in MMP-13-mediated ECM disruption, acti twist family basic helix-loop-helix transcription factor 1ating the NF-κB pathway and exacerbating inflammation and tumor progression[109].

The role of miRNAs in MMP-13 regulation extends beyond primary tumor growth to metastatic control. In OS, the knockdown of plasminogen activator inhibitor-1, a direct target of miR-143, reduces MMP-13 expression, suggesting that both plasminogen activator inhibitor-1 and MMP-13 may serve as potential biomarkers and therapeutic targets for metastasis prevention[110]. In BC, AR signaling has been linked to miRNA regulation; AR activation downregulates miR-100 and miR-125b, leading to increased MMP-13 expression and EMT, thereby enhancing TNBC cell invasiveness[111]. These findings highlight that miRNAs play a crucial role in the regulation of MMP-13 in different types of cancers, as well as in the response to tumors and their therapeutic interventions. The multifaceted roles of miRNAs suggest that they serve as valuable tools for cancer diagnosis and treatment. However, further studies are needed to understand the molecular details of MMP-13 regulation by miRNAs and determine their utility in cancer management.

CircRNAs and MMP-13 regulation in cancer

CircRNAs are a novel class of ncRNA molecules that are of paramount importance in cancer biology. They are produced by the back-splicing of precursor mRNAs, allowing them to exist as covalently closed-loop structures, and are thereby highly resistant to exonucleases, implying that their formation is tightly controlled by cis-acting elements and trans-acting factors. Functionally, circRNAs play various roles in biological phenomena, such as acting as sponges for miRNAs, modulating gene expression, decoys for proteins, and as templates for peptide synthesis. CircRNAs can be classified into three categories according to their genomic origin: Exonic, exon-intron circRNAs and intron-derived circRNAs[112]. Notably, circRNAs exhibit dual roles in oncogenesis, functioning as either tumor suppressors or oncogenic drivers, depending on the cellular and molecular context.

In BC tissues, elevated chondrocyte ECM-related circRNA (circRNA-CER) levels correlated with increased MMP-13 expression and reduced miR-136. Functional studies showed that circRNA-CER knockdown suppressed the proliferation and migration of MCF-7 cells, whereas miR-136 overexpression inhibited MMP-13 expression. Silencing circRNA-CER enhances miR-136 Levels and downregulated MMP-13 expression, highlighting its role in BC invasion and metastasis *via* the circRNA-CER/miR-136/MMP-13 axis[113].

In HNSCC, circRFWD3 (hsa_circ_101877) was significantly upregulated and promoted metastasis by modulating the peroxisome proliferator activated receptor gamma (PPARγ)/NF-κB/MMP-13 signaling axis. Its knockdown reduced PPARγ expression and key NF-κB components, including p65, p-p65, and RelB, leading to decreased MMP-13 Levels. This effect was reversed by miR-27a/b inhibitors, indicating that circRFWD3 regulates MMP-13 expression *via* miR-27a/b-mediated control of the PPARγ/NF-κB pathway in HNSCC[114]. Collectively, circRNAs are significant regulators that post-transcriptionally influence the expression MMP-13 are involved in all types of cancer. The function of regulating core pathways related to ECM remodeling and metastasis positions circRNAs as potential candidates for establishing new biomarkers and targeted drugs.

ADVANCES IN THE DELIVERY OF NCRNAS FOR CANCER THERAPY

The use of ncRNAs for therapeutic purposes presents several challenges including poor delivery efficiency, limited stability under physiological conditions, and potential off-target effects, which hinder their clinical applicability[115]. Recent studies have increasingly focused on the development of advanced drug delivery systems to overcome these barriers and improve the effectiveness of ncRNA-based therapies. For instance, the delivery of LINC00589 through polyethyleneimine-modified mesoporous silica nanoparticles effectively suppressed the peritoneal metastasis of GC[116]. Various studies have investigated combinatorial treatment approaches that integrate existing therapeutic approaches with ncRNA delivery to improve therapeutic efficacy and address limitations. For example, miR-23b-3p, miR-126-3p, and lncRNA growth arrest-specific 5 were delivered by extracellular vesicles combined with sorafenib treatment, resulting in a significantly reduced BC xenograft tumor area, suppressed angiogenesis, and decreased number of micrometastases in the tail[117]. In another study, the lncRNA mediator of DNA damage checkpoint protein 1 (MDC1)-antisense and oxaliplatin were co-delivered by a magnetic thermosensitive cationic liposome drug carrier. This approach achieved effective targeted delivery and thermosensitive drug release, and allowed MDC1-antisense to regulate MDC1, ultimately leading to the inhibition of cervical cancer[118].

CONCLUSION

MMP-13 is important for normal tissue homeostasis, and its regulation is highly implicated in pathological conditions, including cancer invasion and metastasis. Dysregulated expression of this gene is influenced by multiple factors, including several signaling pathways and their components. ncRNAs regulate MMP-13 expression either directly or indirectly *via* various signaling pathways. ncRNAs function as oncogenic drivers or tumor suppressors depending on the cancer context. A complex network of ncRNAs, lncRNAs, and circRNAs, along with miRNAs, regulates the expression of MMP-13 across cancers, thus affecting tumor progression and metastatic capability through ECM remodeling. Because of

their effects on MMP-13 regulation, these ncRNAs are promising candidates for novel therapies. However, the challenges in translating preclinical studies to clinical is essential, such as immunogenicity, delivery efficiency, and targeting the tumor site. Advances in RNA-based therapeutic strategies, including the development of precise delivery systems and combinatorial approaches that enhance specificity but reduce the likelihood of off-target effects, are required to overcome these barriers. Future research should focus on clinical trials of the above-mentioned ncRNAs, such as circRFWD3, lncRNA SARCC, lncRNA HCG11, miR-941, and miR-100, to uncover their therapeutic potential and clinical significance in cancer treatment. Certain pathways, such as NF-κB, JAK/STAT, WNT, phosphatidylinositol 3-kinase, and ERK, are heavily dysregulated in cancer. Hence, targeting these pathways by regulating MMP-13 through ncRNAs is a potential area of future research. Current research on ncRNAs has predominantly focused on their diagnostic and prognostic capabilities, particularly their utility as biomarkers of various diseases. Conversely, investigations into the therapeutic applications of ncRNAs remain largely within the preclinical and early clinical phases, thereby impeding the comprehensive understanding of treatment outcomes and their associated effects.

FOOTNOTES

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Country of origin: India

ORCID number: Nagarajan Selvamurugan 0000-0003-3713-1920.

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