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Review Article

Matrix Metalloproteinases-3, -9, and Prolidase: A Promising Therapeutic Strategy Targeting Breast Cancer

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Abstract

Matrix metalloproteinases (MMPs) are tightly regulated enzymes that play a significant role in tissue remodeling. They are produced by normal and tumor cells and participate in extracellular matrix remodeling and degradation of basement membrane barriers. During tumor progression, cancer cells invade surrounding tissues, accompanied by numerous alterations, leading to microenvironmental stress and breakdown of the extracellular matrix, including loss of basement membrane integrity caused by dysfunction of metalloproteinase activity. This review summarizes the significant roles of MMP-3, -9, and prolidase in different stages of breast cancer progression to offer a comprehensive understanding of the main contributions of these enzymes in breast tumors. Studies have indicated that elevated expression and enzymatic activity correlate with tumor progression through the modulation of transcription factor activity and metastasis mechanisms. MMP-3 is involved in angiogenesis; inhibition of MMP-3 activity is considered a potential therapeutic strategy. In contrast, MMP-9 plays a restrictive role in angiogenesis. Numerous studies have shown that targeting tissue inhibitors of MMPs or silencing these enzymes represents a promising therapeutic strategy to suppress tumor growth and enhance apoptosis. MMP-3, MMP-9, and prolidase should not be considered independent regulators of extracellular matrix remodeling; they function through interconnected mechanisms that govern the dynamic remodeling of cancer progression. Few studies have investigated prolidase activity and its role in pathological processes, and its precise association with MMP-3 and MMP-9 in breast cancer remains poorly understood. Currently, no studies have directly discussed the relationship between MMP-3 and prolidase; however, few mechanistic studies have indicated that prolidase acts as an upstream regulator of MMP-3 and MMP-9 in breast cancer. Further experimental investigations are needed to clarify the interplay of these enzymes in extracellular matrix remodeling within the breast tumor microenvironment to support the development of a prospective therapeutic approach.

Keywords
Angiogenesis, Breast cancer, Matrix metalloproteinases, Prolidase, Target therapy

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Introduction

Breast cancer is the predominant cancer diagnosed in females. It is characterized by complex interactions among genetic, environmental, and lifestyle factors [1]. Among the numerous biochemical pathways involved in tumor progression, metalloproteinases (MMPs) are key regulators of collagen metabolism [2]. The extracellular matrix (ECM) plays a main role in maintaining tissue architecture and physiological balance, as well as in cell growth regulation, cell proliferation, and apoptosis [3]. In cancer progression, malignant transformation is generally associated with profound variations in tumor cell–ECM interactions within normal tissue. The tumor remodels the surrounding microenvironment, resulting in ECM dysfunction via the loss of basement membrane integrity mediated by the dysregulation of matrix metalloproteinase activity. These alterations lead to the formation of fibrillar collagen crosslinking within the ECM. Consequently, cell invasion, metastasis, and resistance to therapy increase [3, 4].

Structure and Biological Activity

Metalloproteinases are a zinc-dependent endopeptidase family secreted by both malignant and normal cells and are involved in the remodeling of the extracellular matrix and in the degradation of basement membrane barriers [5]. Twenty-eight members of the human metalloproteinase family have been characterized and categorized into subfamilies on the basis of structure, proteolytic function, and substrate, involving collagenases, metalloelastases, gelatinases, matrilysins, stromelysins, and enamelysin. The enzymatic activity of MMPs is tightly controlled to preserve tissue structural integrity [6]. In cancer, this regulation is disrupted; numerous studies have reported the overexpression of multiple MMPs in several malignant types, such as breast cancer [7].

MMP-3, or stromelysin-1, has unique features that facilitate its interaction with multiple substrates, enabling the breakdown of E-cadherin-mediated adherens junctions. This process leads to tumor cells losing contact with adjacent cells, increasing tumor cell invasion ability. MMP-3 enhances epithelial–to-mesenchymal transformation, a mechanism connected with morphological and functional modifications in epithelial cells, allowing invasion through the basement membrane [8]. It degrades different collagen types (II, IV, and IX) and, furthermore, fibronectin, proteoglycans, elastin, and laminin. Interestingly, MMP-3 is responsible for tissue remodeling through the activation of MMP-1, -7, and -9 [9]. In vivo, MMP-3 has been identified in normal and osteoarthritic chondrocytes and in cultured nuclei from both chondrocytic cells and hepatocytes. In cancer, several studies have demonstrated that MMP-3 can have dual functions, antitumor or protumorigenic, depending on tumor stage and type [10]. MMP-9, commonly known as gelatinase B, plays a significant role in the remodeling of the ECM and protein breakdown and is involved in invasion, metastasis, and remodeling of the tumor microenvironment. In particular, it cleaves various collagen types, particularly collagen type IV. MMP-9 is produced by neutrophils, endothelial cells, macrophages, and fibroblasts [11]. MMP-9 is secreted in its inactive form (zymogen), and its proteolytic function depends on its proteolytic activity. MMP-3 is a protease that can detach the N-terminal peptide segment and activate MMP-9 [12]. Several signaling pathways, including the phosphoinositide-3-kinase–protein kinase (PI3K)/mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), and p53 pathways, are responsible for regulating the expression of MMP-9. Elevated expression of epidermal growth factor receptor (EGFR) is associated with the upregulation of MMP-9 [13]. Notably, in vitro and in vivo experimental studies have revealed that the overexpression of MMP-9 in humans is strongly linked to tumor progression and disease development [14]. Prolidase is a fundamental enzyme that facilitates the controlling step in collagen metabolism and plays a key role in protein synthesis, degradation, and matrix remodeling. Structurally, it is a homodimeric enzyme with hydrophobic and hydrophilic residues that are equally located throughout its amino acid sequence. Prolidase structural analysis revealed conserved sequences and motifs comparable to those of methionine aminopeptidase, aminopeptidase P (APPro), and creatinase. Moreover, the crystal structure of human prolidase is characterized by a “pita-bread fold”, with the active site cleft containing a bimetallic core composed of two identical domains, namely, two α-helices and an antiparallel β-sheet, which are essential for enzymatic activity [15]. A disulfide bond links two monomers between residues Cys58A and Cys158B. Structurally, prolidase activity depends on the presence of a hydroxide ion, which acts as a bridging moiety that connects the two manganese ions; this configuration is essential for catalytic activity [15, 16]. In addition to its metabolic role, prolidase plays a regulatory role in enzymatic activity and controls signaling pathways. Notably, its activity is linked to the overexpression of EGFR and HER2, which are typically associated with malignancy via the PI3K/Akt/mTOR, ERK1/2, and JAK/STAT3 pathways [17].

Methodology

The data were collected between January and September 2025 using the PubMed, Scopus, Web of Science, and Google Scholar databases. The studies included in this review focused mainly on clinical prevalence and targeted therapy in patients with breast cancer. Non-English publications and conference abstracts were excluded. The following keywords were used in various combinations: MMP-3, MMP-9, prolidase, breast cancer, and extracellular matrix.

Activation Factors of MMP-3, MMP-9, and Prolidase

The activation of MMPs is influenced by several factors, such as microenvironmental signaling molecules, growth factors such as fibroblast growth factor, cytokines, and stress-related proteins such as heat shock proteins and metal ions. Their activity is closely controlled by tissue inhibitors of metalloproteinases (TIMPs) [18]. In inflammatory and tumor-associated conditions, cytokines such as TNF-α and IL-1β act as major inflammatory mediators that typically increase

MMP-3 activity [19]. Upregulation of the NF-κB signaling pathway is strongly associated with increased MMP-3 expression. The MAPK pathway and the PI3K/Akt pathway regulate MMP-3 expression. TNF-α induces the NF-κB pathway by binding to either TNFRI or TNFRII receptors. The transcription factor NF-κB binds to the regulatory region of the MMP-3 gene and regulates its expression [20]. Conversely, MMP-3 expression can be downregulated by glucocorticoids, protein kinases, and cyclic AMP-dependent pathways. E26 transformation-specific proto-oncogenes 1 and 2, which are signaling proteins, modify MMP-3 activity [21]. The binding of the catalytic zinc ion with the cysteine 99 residue in an active form is essential for the activation of MMP-9. A spherical active domain of MMP-9 composed of 170 amino acids is responsible for its proteolytic activity. Three histidine residues bind to zinc in the functional site in the preserved domain: HEXXHXXGXXH, where H: histidine, E: glutamic acid, G: glycine, and X: different amino acids. In the catalytic domain, two zinc ions contribute to structural integrity and enzymatic specificity. Moreover, the availability of five calcium ions stabilized the catalytic domain. In the context of inhibiting MMP-9 activity through obstructing the interaction of zinc ions with water, preventing the binding of water molecules in the active site [22]. In general, prolidase requires a manganese ion for activation; moreover, amino acids containing a sulfur group play a regulatory role, especially the cysteine residue, which is essential for activation [23]. β1-integrin receptor signaling controls the prolidase activity and biosynthesis of collagen [21]. Several processes are involved in the signaling of β1-integrin receptors, such as the stimulation and activation of Sos, Ras, and Raf proteins and the mitogen-activated protein (MAP) kinases ERK1 and ERK2 by autophosphorylation of focal adhesion kinase pp125FAK (FAK) and Grb2, especially SHc or Src proteins, and nonreceptor proteins [24]. Consequently, stimulation of transcription factors leads to the induction of the expression of genes involved in cellular biochemical regulation [21]. Tissue inhibitors of metalloproteinases (TIMPs) orchestrate the activity of four types of TIMPs: TIMP-1 regulates the activity of MMP-1, MMP-3, MMP-7, and MMP-9, while TIMP-2 is a key regulator of MMP-2; TIMP-3 can restrain the activity of both MMP-2 and MMP-9; and TIMP-4 can inhibit MT-1 and MMP-2 [25]. In mammals, TIMPs are small proteins and share a conserved structural organization of approximately 22–28 kDa. TIMPs, with a wedge-shaped form formed by folding, consist of two main domains. The N-terminal domain links the active site of MMPs, forming a ridge that is essential for inhibiting metalloproteinase activity, whereas the role of the C-terminal domain of TIMPs is limited; it is confined to protein–protein communication in the context of metalloproteinase inhibition, such as the communication of pro-MMPs with the hemopexin domain. TIMP-1 and TIMP-3 can interact with proMMP-9; tissues express various TIMPs, stimulating or inhibiting the synthesis of TIMPs under numerous conditions, such as development, tissue repair, and injury [21, 26]. Moreover, four TIMPs bind and suppress MMP activity; the binding constants are very low, approximately in the picomolar range. Notably, certain members of the MMP family, especially MMP-3 and MMP-9, stimulate tumor development in patients with cancer, blood vessel formation, epithelial–mesenchymal transition (EMT), and premetastasis [27]. MicroRNAs have been shown to increase breast cancer growth, invasion, and migration by altering the expression of certain MMPs. Javadian et al. reported that miRNAs downregulate TIMP-1 and TIMP-3 expression in breast cancer, resulting in decreased MMP activity through the targeting of histone deacetylases (HDACs), which modify chromatin. Under healthy conditions, the expression of TIMPs and MMPs maintains a physiological balance of activating and suppressing proteolytic breakdown in contrast to that in cancer conditions [28]. MMP-9 mRNA levels were found to be higher in breast cancer tissues than in nontumour tissues. Kaplan–Meier analysis revealed that a higher level of MMP-9 was associated with a reduced relapse-free survival (RFS) rate. On the basis of bioinformatics analysis, Xio et al. suggested that MMP-9 represents a promising therapeutic target [29]. Previous studies have investigated the connection between MMP-9 levels and cancer development. Chu et al. reported that MIR-182 regulates breast cancer progression by indirectly promoting cell spreading and migration through the upregulation of MMP-9 activity [30]. Liu et al. reported that the expression of MMP-9 is downregulated by miR-206 and thereby positively affects tumor growth suppression [31]. Previous studies have shown that miR-21 plays a crucial role in breast cancer. In this context, miR-21 controls the expression of MMP-3, thereby governing breast cancer [32]. As noted in breast cancer, MMP-3 is commonly associated with advanced stages and aggressive breast cancer, including pregnancy-related cases [33]. Chu et al. reported a significant reduction in breast cancer cell migration caused by the stimulation of miR-519d through the downregulation of MMP-3, suggesting a novel positive correlation between miR-519d and MMP-3 and suggesting a new suitable strategy for breast cancer treatment [30]. A therapeutic strategy focused on breast cancer treatment aimed at inhibiting MMP-9 was proposed, and the results confirmed that a low expression level of MMP-9 was strongly associated with reduced tumor invasion and drug resistance [34]. In particular, several strategies targeting breast cancer, focusing on expanding inhibitors of specific MMPs as potential treatments, have been suggested by the Shoari team [35]. MMP-3 is expressed in physiological breast tissue and has been detected in glandular and myoepithelial cells by immunochemical labeling. Evidence suggests that MMP-3 levels are elevated during the early stages of the disease [36]. Several studies have reported elevated MMP-3 levels, and some other types of MMPs are expressed in a variety of types of breast cancer histology [37]. In particular, elevated plasma levels of MMP-3 have been observed in patients with the luminal A subtype of early-stage breast cancer before and after surgery. Moreover, its level positively

correlated with cancer stage. Mainly, the use of MMP-3 as a biomarker for disease recurrence may improve therapeutic decisions. The data demonstrated that the MMP-3 level remained elevated 3 months after surgery. Ławicki and his colleagues reported high concentrations of MMP-3 in patients with stage III-IV disease relative to those with stage I disease [38]. Suhaimi et al. suggested that in breast cancer, MMP-3 polymorphisms are regarded as predictive biomarkers and more precise prognoses; furthermore, the identification of MMP-3 gene polymorphisms as potential biomarkers of metastasis may facilitate the development of therapeutic strategies [39]. In contrast, Benson et al reported that there are no significant differences between the mRNA levels of MMP-3 in normal breast tissue and malignant tumor tissue [40]. On the other hand, Mehner et al demonstrated that high MMP-3 expression was correlated with poor prognostic parameters and advanced disease stages [41]. Discrepant findings were reported by Balkhi et al., who reported that compared with healthy women, patients with breast cancer in Iran had increased circulating levels of MMP-3. In serum samples, high concentrations of MMP-3 were linked to a homozygous MMP-3 genotype [42]. Other researchers reported similar associations between copious polymorphic variants and the MMP-3 gene and lymph node metastasis in a population study among South Indian women [43]. Slattery et al. reported that MMP-3 and MMP-9 are correlated with malignant breast tumor risk among those with in situ carcinoma and invasive ductal carcinoma, particularly among ER−/PR− tumors and Native American ancestry, which was confirmed by histological classification of breast cancer subtypes [44]. In a pilot study in which pre- and postradiotherapy treatment was monitored, Olivares-Urbano and his colleagues reported that MMP-3 expression was closely related to advanced grades of breast tumors and negative estrogen/progesterone receptor patients. However, no significant difference was detected between MMP-3 levels and menopausal status or lymph node involvement [45]. Argote et al. conducted a cohort study and reported that MMP-3 expression is higher in breast cancer tissue than in normal breast epithelial cells [46]. Taha et al. demonstrated that knocking out MMP-3 suppressed solid tumors, reduced tumor size, and limited the development of necrotic areas within tumors [47]. Indeed, several studies have reported elevated MMP-9 expression in breast cancer cells compared with that in fibroadenoma cells; some investigators reported higher MMP-9 protein expression in breast cancer cells than in fibroadenoma cells [48]. An Iraqi study revealed that MMP-9 expression is higher in breast cancer samples than in control samples. Furthermore, the data indicated a 71.7% overexpression rate of MMP-9 [49]. Moreover, Mahmood et al. focused on the association of MMP-9 levels with the stage of breast cancer. The results confirmed that MMP-9 levels were substantially greater in stage II-III tumors than in noncancerous tumor tissues. Immunohistochemistry revealed that MMP-9 protein levels were 64% higher in Iraqi patients with stage II-III breast cancer than in those with benign breast tumors [50]. In Slovakia, the data revealed a high prevalence of MMP-9 expression among stage I-III breast cancer patients compared with circulating tumor cells (CTCs). Primary breast cancer samples were subjected to immunohistochemistry, and the data revealed that stromal MMP-9 expression was lower than that detected in cancerous cells. Notably, stromal MMP-9 expression is a poor prognostic tool. In contrast, MMP-9 expression correlated significantly with hormone-positive status and proliferation rate in tumor cells. Furthermore, the expression of MMP-9 is low in triple-negative tumor cells and stromal cells; mainly, its expression is positively correlated with survival rate according to subgroup analysis. Thus, all the results revealed that MMP-9 expression in tumor cells could serve as a prognostic tool to facilitate the detection of a greater risk of disease recurrence in these subgroups [51]. In Nottingham, Joseph et al. reported that MMP-9 expression was detected within both the stroma and cytoplasm of early-stage (operable) primary invasive breast cancer cells. Elevated MMP-9 levels were negatively correlated with the expression of hormonal receptors, a high Nottingham prognostic index, and tumor grade. The overexpression of MMP-9 correlated substantially with proliferation biomarkers (Ki67), cell division control protein 42 (CDC42), cell surface adhesion receptor (CD44), cytokeratin 17 (CK17), and epidermal growth factor receptor (EGFR). The results confirmed that shorter breast cancer-specific survival was linked to cytoplasmic MMP-9 expression, which served as an independent predictor tool for poor patient outcomes in the external validation cohort. Transcriptomic research revealed that the expression of MMP-9 and ECM remodeling biomarkers was positively correlated. Gene set enrichment analysis (GSEA) was used to validate the links among MMP-9 expression and cytoskeletal and extracellular matrix-associated pathways [52]. Bayhan et al. reported a significant association between increased serum prolidase activity and tumor stage. Additionally, the data showed that increased serum prolidase activity was strongly linked to oxidative stress [53]. In a separate Turkish study, the authors reported elevated activity of prolidase as a diagnostic marker in the sera of patients with different grades of breast cancer (I, II, and III), and the results confirmed that prolidase might be a reliable indicator for detecting oxidative status and strongly correlated with oxidative stress parameters, particularly the thiol/disulfide ratio [54]. A purified prolidase from Escherichia coli that plays a role similar to that of human prolidase had a substantial effect on multiple measures, including cell survival, nuclear signal intensity, mitochondrial membrane potential, membrane integrity alteration, and cytochrome C release at a concentration of 200 µg/ml. In the MCF-7 cell line, increasing the prolidase concentration greatly increased the activity of caspases (8 and 9) and reactive oxygen species. The results of this study revealed that prolidase has significant effects on cancer cells and various biological parameters and is considered one of the therapeutic strategies [55].

The role of enzymes in the apoptosis pathway

With respect to therapeutic strategies for breast cancer, MMP-3 plays a significant role in therapeutic response mechanisms. Zareba et al. reported that treatment of the EO771 cell line with tamoxifen resulted in increased MMP-3 levels. Moreover, tamoxifen induces the expression of the pro-apoptotic JNK and p38-MAPK pathways. These pathways are crucial for promoting cell death in cancer cells. An increase in MMP-3 levels may oppose these effects by facilitating metastatic spread [56]. Activator protein-1 (AP-1) and nuclear factor-κB (NF-κB) are key regulators associated with MMP-9. The MAPK pathway, which regulates MMP-9 expression, is involved in both cellular survival and proliferation. Following DNA damage, ERK stimulation, independent of p53, resulted in apoptosis and cell cycle arrest. A decrease in ERK phosphorylation is associated with reduced MMP-9 expression. Triptolide has been shown to reduce MMP-9 expression and reduce the invasiveness of the MCF7 cell line through suppression of the ERK pathway and activation of NF-κB and AP-1 signaling [57]. Celastrol, a plant extract, suppresses antiapoptotic proteins such as cIAP1 and cIAP2, induces TNF-α, and downregulates NF-κB signaling, thereby promoting apoptosis and preventing invasion by decreasing MMP-9 expression, enhancing apoptosis, and altering caspase-8, caspase-3, and PARP cleavage in MDA-MB-231 cells [58]. By treatment with methylglyoxal and glyoxalase I, Guo et al. reported that apoptosis is strongly enhanced by the activation of MAPK family signaling and the downregulation of Bcl-2 and MMP-9 expression in MCF-7, T47D (estrogen receptor ER positive), and MDA-MB-231 (ER negative) breast cancer cell lines [59]. Prolidase also plays a regulatory role in the PRODH/POX pathway. Prolidase overexpression increases the cytoplasmic proline concentration through PRODH/POX-dependent mechanisms, which may be essential for regulating apoptotic and survival signaling cascades in MCF-7 cells. The data revealed that the overexpression of prolidase reduced apoptotic indicators, inhibited DNA synthesis, and enhanced cell survival [60, 56]. Zareba et al. reported that the MCF-7 cell line promoted autophagic cell death, which depended on the overexpression of a prolidase that modified the PRODH/POX pathway. Stimulation of the overexpression of Atg7, LC3A/B, Beclin-1, and HIF-1α and a reduction in PRODH/POX expression stimulate caspase-3 and -9 activation [56]. Previously, estrogens have been shown to stimulate prolidase activity and collagen synthesis. Prolidase promotes proline production in estrogen-positive receptors in breast cancer, decreasing its ability to induce apoptosis mediated by PRODH or POX. Furthermore, a lack of free proline (which has been shown to increase hypoxia-inducible factor 1, HIF-1) restricts HIF-1-dependent pro-survival activity. Therefore, ProDH/POX expression is transcriptionally activated by P53 and posttranscriptionally regulated by AMP-activated protein kinase [60].

Enzymatic role in Angiogenesis

Angiogenesis is vital for malignant cell proliferation and progression. MMP-3 plays a key role in promoting angiogenic phenotypes through the remodeling of the extracellular matrix. Experimental evidence suggests that inhibiting MMP-3 may be a possible treatment for breast cancer by reducing tumor growth. However, further clinical studies are needed to establish their clinical applicability, particularly in aggressive tumors [46]. MMP-9 inhibition decreased neoplastic angiogenesis and greatly reduced both local and metastatic tumor development in mice [61]. Mechanistically, MMP-9 stimulates tumor vascularization by degrading ECM components and generating and forming specialized blood arteries via endothelial cells, thereby inducing the expression of angiogenic factors such as vascular endothelial growth factor and facilitating endothelial cell migration and the formation of new vessels. Conversely, MMP-9 can restrict angiogenesis under specific conditions. MMP-9 cleaves plasminogen and releases angiostatin and disassembles collagen type XVIII to release endostatin, which promotes cell death via the apoptotic pathway [62]. This finding reflects the dual role of MMP-9 in angiogenesis, generating either proangiogenic or antiangiogenic effects depending on the tumor microenvironment. MMP-9 exhibits both pro-angiogenic and anti-angiogenic effects depending on the tumor microenvironment. The anti-apoptotic effect is associated with Fas ligand cleavage, leading to activation of protein kinase B (AKT) signaling pathways [63]. In fact, studies that address the role of prolidase in angiogenesis are limited and are included in this review.

Interplay between MMP-3, MMP-9, and Prolidase

Prolidase may interact with MMPs under inflammatory conditions. Recombinant human prolidase (rhPEPD), particularly under inflammatory conditions such as IL-1β stimulation, has been reported to stimulate the functional proteolytic activity of MMP-2 and MMP-9 through EGFR signaling. This activation promotes extracellular matrix degradation and fibroblast migration, suggesting that prolidase can amplify proteolytic activity under proinflammatory conditions [64]. Furthermore, MMP-mediated collagen degradation produces proline-rich peptides that are directly hydrolyzed by prolidase activity, thereby linking extracellular matrix remodeling to intracellular proline metabolism [65]. Increased prolidase activity in breast cancer may enhance MMP-driven invasion by supporting proline-dependent metabolic reprogramming and redox signaling. However, the interactions among MMP-3, MMP-9, and prolidase in breast cancer have not been fully elucidated; studies on the relationship between MMP-3 and prolidase are limited.

Conclusion

Recent investigations have focused on multiple signaling pathways that regulate the activity of MMP-9 and prolidase in breast cancer. Prolidase is involved in cellular proliferation, metastasis, angiogenesis, and apoptosis through its role in collagen turnover and proline metabolism. Moreover, MMP-3 is an essential upstream activator of metalloproteinases. MMP-3 plays an important regulatory role in the pro-

teolytic cascade. Therefore, targeting MMP-3 activity may represent a strategic therapeutic approach because of its ability to modulate the activation of other MMP family members. Collectively, MMP-3, MMP-9, and prolidase should not be regarded as independent regulators of extracellular matrix remodeling; rather, they work together through interconnected mechanisms that govern the dynamic remodeling of cancer progression. Notably, few studies have investigated prolidase, and the pathological processes and their precise associations with MMP-3 and MMP-9 in breast cancer are still unclear. Ongoing research aims to elucidate the activity of these enzymes through different targeted pathways and provide an integrative overview of the connected functions of these enzymes. In fact, no study has directly discussed the relationship between MMP-3 and prolidase. Furthermore, few mechanistic studies have investigated whether prolidase plays a role as an upstream regulator of MMP-3 and MMP-9 in breast cancer. This review does not directly answer this question; therefore, additional experimental investigations are needed to clarify the interplay of these enzymes in extracellular matrix reorganization within the breast cancer microenvironment to support the development of a promising therapeutic approach.

Author Declarations

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Conflict of Interest Statement

The authors declare that they have no competing financial or non-financial interests related to this work.

Ethics Statement

This article is a review study and does not involve human participants, human samples, animal experiments, or identifiable personal data; therefore, ethical approval was not required.

Consent for Publication

All authors have reviewed and approved the final version of the manuscript and consent to its publication.

Data Availability Statement

No new datasets were generated or analyzed during this study. Data sharing is not applicable to this article.

Author Contributions

S.A.J. conducted the literature search and drafted the manuscript. O.H.F. organized, analyzed, and summarized the collected literature and data. N.A.M. supervised the study, critically revised the manuscript for important intellectual content, and approved the final version for publication.

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