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# Understanding the Regulation of Breast Cancer by TGF-β/Smad Signaling and Matrix Metalloproteinases (MMPs): A Molecular Perspective

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***Abstract***

*Breast cancer is a complex and heterogeneous disease, with metastasis being the primary cause of mortality. The intricate molecular mechanisms governing breast cancer progression are critical areas of research, particularly the roles of the Transforming Growth Factor-beta (TGF-β) signaling pathway and Matrix Metalloproteinases (MMPs). TGF-β signaling, mediated through Smad proteins, is known for its dual role in cancer biology. In the early stages of breast cancer, TGF-β acts as a tumor suppressor, inhibiting cell proliferation and promoting apoptosis. However, in advanced stages, it switches roles to promote tumor progression, invasion, and metastasis. This switch is largely influenced by the tumor microenvironment and the complex cross-talk between TGF-β/Smad signaling and other molecular pathways. One such pathway involves MMPs, a family of zinc-dependent enzymes responsible for degrading the extracellular matrix (ECM). MMPs facilitate tumor invasion by breaking down ECM barriers, allowing cancer cells to disseminate and establish metastases. TGF-β is known to upregulate MMP expression, thereby enhancing the invasive capabilities of breast cancer cells. The interplay between TGF-β/Smad signalling and MMP activity creates a pro-metastatic environment that not only supports tumor growth but also contributes to therapeutic resistance. Targeting these pathways could offer new therapeutic strategies for managing breast cancer, particularly in combating metastasis and overcoming drug resistance. Understanding the molecular dynamics of TGF-β/Smad signaling and MMPs in breast cancer provides valuable insights into the development of more effective treatments, potentially improving patient outcomes.*

***Keywords:*** *Breast Cancer, Matrix Metalloproteinases, Molecular Mechanisms, TGF Signalling.*

## Introduction

Breast cancer is a highly complex and heterogeneous disease characterized by the uncontrolled proliferation of abnormal cells in the breast tissue. It remains the most common cancer among women worldwide and a leading cause of cancer-related mortality. The significant advances in early detection and treatment have led to increased survival rates; however, the management of breast cancer is still challenged by issues such as treatment resistance, metastasis, and recurrence. A deeper understanding of the molecular mechanisms driving breast cancer progression is crucial to developing more effective therapies [1]. One of the key molecular pathways implicated in breast cancer is the Transforming Growth Factor-β (TGF-β) signaling pathway. TGF-β is

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a multifunctional cytokine that plays a dual role in cancer. In the early stages of tumor development, TGF-β acts as a tumor suppressor, inducing cell cycle arrest and promoting apoptosis. This is achieved through the regulation of various cellular processes, including the release of growth factors, cytokines, and extracellular matrix (ECM) proteins that help maintain tissue homeostasis. However, as breast cancer progresses, the role of TGF-β becomes paradoxical. Due to genetic and epigenetic alterations within the tumor microenvironment, TGF-β signaling switches from tumor-suppressive to tumor-promoting, contributing to the initiation, invasion, metastasis, angiogenesis, and immune evasion of the cancer cells [2].

This functional shift, often referred to as the "TGF-β paradox," is driven by dynamic changes in the tumor microenvironment and is associated with poor prognosis in advanced breast cancer. At the molecular level, the TGF-β signaling cascade is mediated by SMAD proteins, which are intracellular molecules that transduce signals from the cell membrane to the nucleus. Upon activation by TGF-β, these SMAD proteins form complexes that regulate the transcription of target genes involved in various cellular functions, including cell proliferation, differentiation, and migration [3]. In the context of breast cancer, the dysregulation of TGF-β/Smad signaling is a critical factor that contributes to the aggressive behavior of tumors [4]. In addition to TGF-β/Smad signaling, matrix metalloproteinases (MMPs) play a pivotal role in breast cancer pathogenesis. MMPs are a family of zinc-dependent proteolytic enzymes that are primarily responsible for the degradation of ECM components. This degradation is essential for normal tissue remodeling and repair; however, in cancer, MMPs facilitate tumor invasion and metastasis by breaking down the ECM barriers that confine tumor cells. Among the MMPs, MMP-14 has been shown to be particularly important in breast cancer. It not only promotes tissue remodeling and ECM degradation but also affects cell-matrix communication, which is crucial for cancer cell invasion and metastasis [5, 6].

The interplay between TGF-β/Smad signaling and MMPs creates a pro-tumorigenic environment that enhances the invasive and metastatic potential of breast cancer cells. MMPs can modulate TGF-β signaling by cleaving ECM components that sequester TGF-β, thereby increasing its availability and activation. Conversely, TGF-β can upregulate the expression of MMPs, further contributing to the breakdown of the ECM and the promotion of tumor spread. This crosstalk between TGF-β/Smad signaling and MMPs underscores the complexity of the tumor microenvironment and highlights the need for therapeutic strategies that target both pathways [7]. Given the critical roles of TGF-β/Smad signaling and MMPs in breast cancer progression, understanding the molecular mechanisms underlying their regulation is essential for the development of new therapeutic approaches. Targeting these pathways could potentially prevent or reduce metastasis, overcome treatment resistance, and improve the overall prognosis for breast cancer patients. This review aims to provide a comprehensive overview of the TGF-β/Smad signaling pathway and MMPs in breast cancer, with a focus on their interconnections and implications for therapeutic intervention. By elucidating these molecular interactions, the review seeks to offer insights into novel strategies that could be employed to combat the aggressive nature of breast cancer.

## TGF-β/Smad Signaling in Critical Pathways of Breast Cancer

The TGF-β/Smad signaling pathway plays a crucial role in breast cancer progression by interacting with key pathways such as MAPK and PI3K/Akt. MAPKs, including Erk1/2, JNK1/2/3, and p38/MAPK, regulate various cellular processes through a phosphorylation cascade initiated by an external signal, starting

from MAPKKK to MAPKK and ultimately leading to MAPK activation. This cascade is vital for the activation of the TGF-β family and is regulated through both Smad-dependent and Smad-independent mechanisms, making MAPKs essential conduits for non-Smad TGF-β signaling [8]. The HER2/Neu/ErbB2 signaling pathway, which activates the MAPK and PI3K/Akt pathways, interacts closely with TGF-β/Smad signaling to regulate mammary epithelial cell biology and breast cancer development. In breast cancer cells overexpressing ErbB2, TGF-β recruits TACE and ErbB3 to activate PI3K/Akt, leading to reduced sensitivity to trastuzumab. The HER2/Ras pathway can counteract TGF-β-induced apoptosis and cell cycle arrest while promoting proliferation and pro-invasive effects. These interactions result in both synergistic and antagonistic regulatory outcomes, contributing to the complexity of these pathways [9].

The interplay between TGF-β and HER2/Ras/MAPK pathways often leads to the release of additional growth factors and cytokines, including TGF-β itself, further promoting epithelial-mesenchymal transition (EMT) and cell invasion. The activation of the Ras/MAPK pathway by TGF-β is required for TGF-β1 production via a Smad-dependent mechanism. Moreover, TGF-β1 and Ha-Ras collaborate to regulate the phenotypic plasticity and invasiveness of epithelial tumor cells [10]. Pharmacological studies indicate that PI3K inhibitors or mTOR kinase, which operate downstream in the PI3K/Akt pathway, play a role in regulating Smad3 activation by the TGF-β receptor. However, conflicting evidence suggests that PI3K/Akt signaling can either enhance or diminish the response to TGF-β. The PI3K/Akt pathway is modulated by TGF-β/BMP, with TGF-β treatment increasing Akt activity, which is critical for various TGF-β-induced functions, including the migration of HER2-expressing breast cancer cells [11, 12].

## Regulation of TGF-β/Smad Signaling in Cancer Progression

Transforming Growth Factor (TGF)-β is a multifunctional cytokine that regulates crucial cellular processes, including cell growth, differentiation, apoptosis, migration, adhesion, and immune responses. The classical TGF-β signaling pathway involves the activation of Smad proteins through receptors TGF-βR, TβRII, and ALK5/TβRI [13]. Binding of TGF-β to these receptors leads to the phosphorylation of receptor-regulated Smads (R-Smads) like Smad2 and Smad3, which then form a complex with Smad4. This complex translocates to the nucleus to regulate gene transcription [14]. TGF-β signaling is tightly regulated by inhibitory Smads, such as Smad6 and Smad7, which provide negative feedback. They prevent R-Smad phosphorylation, promote receptor degradation via E3 ubiquitin ligases like Smurf1/2, and disrupt Smad-DNA interactions in the nucleus. Smad7's expression is modulated by various stimuli, and its dysregulation is linked to diseases including fibrosis, inflammation, and cancer [15].

MicroRNAs (miRNAs) play a significant role in the post-transcriptional regulation within the TGF-β pathway. EMT-related miRNAs function as molecular switches, influencing cell state transitions and cancer cell diversity through feedback loops with transcription factors. This mechanism is critical for understanding epithelial-to-mesenchymal transition (EMT) and cancer cell behavior. TGF-β exhibits a dual role in cancer, functioning both as a tumor suppressor and promoter, depending on the tumor stage and cellular context. Initially, TGF-β can induce cell cycle arrest and apoptosis, but it later promotes tumor growth, invasion, and metastasis. It influences the tumor microenvironment, ECM remodeling, and immune responses, contributing to its oncogenic potential [16]. In summary, the TGF-β/Smad signaling pathway is essential in cancer progression, with its regulation involving inhibitory Smads and

miRNAs. Understanding these mechanisms and the dual role of TGF-β provides valuable insights into potential therapeutic targets for cancer treatment.

## Matrix Metalloproteinases (MMPs) in Breast Cancer

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases essential for extracellular matrix (ECM) remodeling, impacting processes like embryonic development, angiogenesis, and tissue repair. Abnormal MMP expression can lead to ECM degradation, contributing to chronic diseases, vascular complications, neurodegeneration, and cancer progression [17]. TGF-β signaling has a dual role in cancer, inhibiting early tumor growth while promoting invasion in advanced stages. Despite various inhibitors being developed, TGF-β's role in cancer resistance to treatments remains complex. Combining anti-TGF-β therapies with other treatments may help address therapy-resistant cancers [18].

MMPs, especially MMP-14, are crucial in cancer for degrading ECM components and affecting tissue integrity, immune cell recruitment, and turnover. They facilitate cancer invasion and metastasis by remodeling the ECM and releasing growth factors. For example, MMPs enhance tumor growth and invasion through the cleavage of α1-antitrypsin products [19]. During angiogenesis, MMPs aid in degrading the vascular basement membrane and remodeling the ECM, supporting new blood vessel formation. Tissue Inhibitors of MetalloProteases (TIMPs) regulate MMP activity, and an imbalance between MMPs and TIMPs is linked to vascular diseases and cancer progression. MMPs, influenced by factors such as oxidative stress and inflammation, play a significant role in metastasis, affecting the metastatic potential of cancer cells and contributing to treatment resistance. In breast cancer, MMPs are key in tumor invasion, metastasis, and resistance to therapy, highlighting their importance as targets for cancer treatments [20].

## TGF-β/Smad-MMP Interplay in Breast Cancer

The interplay between TGF-β/Smad signaling and matrix metalloproteinases (MMPs) is crucial for regulating tumor progression, invasion, and metastasis (Table 1). TGF-β, a multifunctional cytokine, significantly impacts various aspects of cancer biology, including extracellular matrix (ECM) remodeling. This signaling pathway, primarily mediated by Smad proteins, plays a pivotal role in modulating MMP activity and thereby influencing tumor behavior (Table 1). Upon binding of TGF-β to its receptors TβRII and ALK5/TβRI, a receptor complex is formed that activates receptor-regulated Smads (R-Smads) such as Smad2 and Smad3. These R-Smads then bind with the common mediator Smad4, forming a complex that translocates to the nucleus. Inside the nucleus, this Smad complex initiates the transcription of target genes, including those encoding MMPs. MMPs, including MMP-2, MMP-9, and MMP-14, are essential for ECM remodeling, facilitating cancer cell invasion and metastasis. For instance, Smad3 activated by TGF-β directly binds to the promoters of MMP-2 and MMP-9, enhancing their transcription. This increased expression of MMPs promotes the degradation of the basement membrane and ECM components, aiding in tumor cell invasion and migration [21, 22].

**Table 1.** Role of Matrix Metalloproteinases in Breast Cancer

| S. No | MMP | Study Model | Methods Used | Key Findings | Signaling Pathway/Factor | Reference |
|---|---|---|---|---|---|---|
| 1 | MMP-13 | In vivo (direct injection onto calvaria) | Immunohistochemistry, Tartrate-Resistant Acid Phosphatase Staining | MMP-13 was identified in breast carcinomas, with IL-1α and IL-1β inducing MMP-13 expression. | IL-1α and IL-1β | 23 |
| 2 | MMP-11 | In vivo (right flank region of male BALB/c nude mice) | Colony Formation Assay, Western Blot, Immunohistochemistry | MMP-11 knockdown inhibited tumor proliferation and growth. MMP-11 stabilizes Smad2 and activates TGF-β signaling. | TGF-β, Smad2 | 24 |
| 3 | MMP-9 | In vivo (CA1a cells in nude mice) | Immunocytochemistry | TNF-α and TGF-β strongly induced MMP-9 expression, independent of the TGF-β pathway in Smad4 negative breast cancer cells. | TNF-α, TGF-β | 25 |
| 4 | MMP-2, 9 | In vivo (MDA-MB-231 cell line) | Gelatin Zymography Assays, Migration and Invasion Assays | TGF-β1 induces MMP-2 and MMP-9 expression, promoting invasion in premalignant breast cancer cells. | TGF-β1, ERK1/2 | 26 |
| 5 | MMP-9 | In vivo (MDA-MB-231 and T47D cells) | Immunohistochemistry, Migration, Invasion Assays | USP4 promotes MMP-9 expression via Relaxin/TGF-β1/Smad2 signaling, enhancing breast cancer cell migration and invasion. | Relaxin/TGF-β1/Smad2 | 27 |
| 6 | MMP-7 | In vitro | Scratch Wound Healing Assay, Boyden Chamber Invasion Assay | TGF-β induces Wnt3 and MMP-7 expression, promoting epithelial-mesenchymal transition (EMT) in HER2-overexpressing breast cancer cells. | Wnt3 | 28 |
| 7 | MMP-9 | In vivo (MDA-MB-231 cells) | CCK-8 Assay, Immunohistochemistry | TGF-β1 regulates MMP-9 expression via Smad and ERK pathways; curcumin inhibits MMP-9 and invasive phenotypes. | ERK, Smad | 29 |
| 8 | MMP-9 | In vivo (MDA-MB-231 and MCF7 cells) | Immunohistochemistry, Cell Viability, Migration, Invasion Assays | Overexpression of MMP-9 in breast cancer cell lines significantly increases cell malignancy via activation of TGF-β/SMAD signaling. | SMAD4, SMAD2/3 | 30 |
| 9 | MMP-9 | In vitro | Invasion and Motility Assays | TGF-β signaling might be crucial for enhancing MMP-9 activity, leading to increased cell motility and invasion. | F-actin | 31 |
| 10 | MMP-2 | In vitro | Invasion Assay, Transwell Migration Assay, Luciferase Reporter Assay, Electrophoretic Mobility Shift Assay (EMSA) | TGF-β-induced transcriptional activation of MMP-2 is mediated by activating transcription factor (ATF2), contributing to invasive and migratory phenotypes. | ATF2, TGF-β | 32 |

Additionally, TGF-β modulates MMP activity indirectly by regulating tissue inhibitors of metalloproteinases (TIMPs), which bind to MMPs to inhibit their activity and maintain ECM balance. In cancer, TGF-β signaling often disrupts this balance, leading to increased ECM degradation and tumor progression. For example, TGF-β-induced Smad3 activation can downregulate TIMP-1 expression, reducing its inhibitory effect on MMPs and thus facilitating ECM remodeling and tumor invasion [33]. Moreover, TGF-β/Smad signaling can enhance MMP expression through interactions with additional transcription factors and signaling pathways. Smad3 can interact with transcription factors such as AP-1 and Sp1, further promoting MMP gene expression [34]. This interaction amplifies the effects of TGF-β on ECM remodeling and tumor progression.

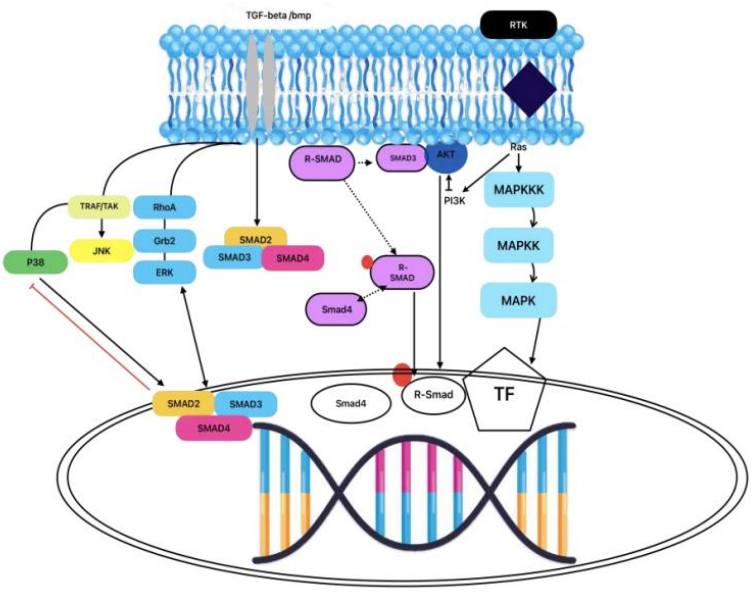


**Figure 1.** TGF-β/Smad-MMP Interplay in Breast Cancer

The TGF-β/Smad-MMP axis also impacts the tumor microenvironment and therapy resistance. Disruption of ECM integrity and promotion of invasive behaviors through MMP activity can influence the effectiveness of various treatments, including chemotherapy, targeted therapy, and immunotherapy. Targeting the TGF-β/Smad-MMP pathway presents a promising strategy for overcoming therapy resistance and improving treatment outcomes [35]. In conclusion, the TGF-β/Smad signaling pathway is integral to the regulation of MMP expression and activity, driving ECM degradation and tumor invasion (Figure 1). Understanding the complex interactions between TGF-β/Smad signaling and MMPs is essential for developing targeted therapies aimed at inhibiting tumor progression and overcoming treatment resistance.

## Conclusion

In conclusion, the interaction between TGF-β/Smad signaling and matrix metalloproteinases (MMPs) is pivotal in regulating breast cancer progression, invasion, and metastasis. TGF-β orchestrates ECM remodeling by modulating MMP activity through Smad proteins, enhancing the expression of MMPs such as MMP-2, MMP-9, and MMP-14, which facilitate tumor cell invasion and migration. The balance between MMPs and tissue inhibitors of metalloproteinases (TIMPs) is crucial, with TGF-β often disrupting this equilibrium to promote ECM degradation and tumor advancement. Additionally, TGF-β/Smad signaling interacts with other transcription factors, further amplifying MMP expression

and reinforcing its role in cancer progression. Understanding these complex interactions provides critical insights into the mechanisms driving tumor invasion and metastasis, highlighting the potential for developing targeted therapies aimed at modulating TGF-β/Smad signaling and MMP activity to effectively combat breast cancer.

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