REVIEW

Editorial Process: Submission:08/30/2024 Acceptance:04/14/2025

The Role of Twisted Gastrulation 1 (*TWSG1*) Gene in TGF-β Signaling Linked to Cancer: A Comprehensive Review

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Abstract

Background: Transforming Growth Factor-beta (TGF-β) signaling is a crucial pathway in cancer development, affecting key processes such as cell growth, differentiation, and the spread of cancer cells. Recent research highlights the role of Twisted Gastrulation Protein Homolog 1 (*TWSG1*) as an important regulator of TGF-β signaling, showing both tumour-promoting and tumour-suppressing activities depending on the type of cancer and its specific context. **Objective:** This review provides a detailed overview of how *TWSG1* influences TGF-β signaling in different cancers, including breast, colorectal, pancreatic, and lung. It also explores the potential of *TWSG1* as a therapy target and as a biomarker for predicting patient outcomes. **Methods:** A thorough review of the current literature was conducted to understand how *TWSG1* affects TGF-β signaling and its role in cancer progression. Studies were chosen based on their relevance to *TWSG1*'s dual role in TGF-β signaling and its implications for cancer treatment. **Results:** *TWSG1* has been found to either enhance or inhibit TGF-β signaling. It can promote processes like epithelial-to-mesenchymal transition (EMT), cancer cell invasion, and metastasis by boosting interactions between TGF-β ligands and receptors and increasing SMAD protein phosphorylation. On the other hand, *TWSG1* can also suppress TGF-β signaling by binding to the ligands, preventing them from interacting with receptors. High levels of *TWSG1* are often associated with worse outcomes in several types of cancer, suggesting its potential as a biomarker and a target for cancer therapy. **Conclusion:** *TWSG1* plays a complex role in TGF-β signaling that varies with the type of cancer and the surrounding environment. Targeting *TWSG1*, either alone or alongside TGF-β inhibitors, could offer new avenues for treating cancers driven by TGF-β signaling. More research is needed to fully understand how *TWSG1* is regulated and to explore its potential for use in clinical settings.

Keywords: Twisted Gastrulation Protein Homolog 1- Transforming Growth Factor-beta- SMAD Phosphorylation

Asian Pac J Cancer Prev, **26 (4)**, 1129-1138

Introduction

Overview of TGF-β Signaling Pathway

The Transforming Growth Factor-beta (TGF-β) signaling pathway is a complex network of intracellular and extracellular components that regulate cellular processes essential for cancer development and progression [1, 2]. The TGF-β signaling pathway involves a variety of molecules, such as ligands, receptors, and intracellular messengers, all of which regulate different aspects of cell behaviour. *TWSG1* was initially discovered for its role in controlling BMP signaling during embryonic development. However, recent research has shown that *TWSG1* also plays a significant part in regulating TGF-β signaling in various cancers [3]. Twisted Gastrulation, known as *TWSG1* or BMP signaling modulator 1, plays a versatile role in the body by both promoting and inhibiting BMP signaling. It is involved in critical biological functions like developing thymocytes, producing red blood cells, embryonic development, and even cancer progression. The fact that *TWSG1* shows different levels of expression in various types of tumours suggests it could be a promising target for cancer treatments [3, 4].

Role of TWSG1 in TGF-β Signaling

TWSG1 is a secreted glycoprotein vital in regulating the TGF-β signaling pathway [5]. This protein is expressed across various tissues and stages of development, highlighting its importance in numerous biological processes, including in muscle cells [6]. The regulation of the TGF-β signaling pathway by *TWSG1* is crucial for controlling cellular activities such as differentiation, programmed cell death (apoptosis), cell proliferation, and the production of the extracellular matrix [2, 7]. Bone morphogenetic proteins (BMPs), which belong to the TGF-β superfamily, have their activity modulated by

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TWSG1; by binding to BMPs, *TWSG1* influences how these molecules interact with their receptors, thereby indirectly affecting the TGF-β signaling pathways. Interestingly, *TWSG1* can enhance and inhibit signaling, depending on the specific context [8, 9]. It has a dual purpose since, depending on the situation, it can either increase or decrease signaling [10].

During embryonic development, *TWSG1* is essential for forming and differentiating various tissues and organs [9]. Abnormalities in the expression or function of *TWSG1* have been associated with several conditions, such as cancer and fibrosis, where TGF-β- signaling plays a critical role. These disruptions can lead to developmental abnormalities [11]. These disorders can cause developmental abnormalities [12]. Understanding how *TWSG1* regulates TGF-β signaling is crucial for identifying potential therapeutic targets for diseases associated with disrupted TGF-β signaling [5]. This review aims to provide a comprehensive overview of the current understanding of *TWSG1*'s role in TGF-β signaling, particularly in various types of cancer (Table 1).

TGF-β signaling pathway components and mechanism in cancer

The TGF-β signaling system is a crucial pathway in regulating cell functions such as growth, division, and apoptosis (programmed cell death). This system includes TGF-β ligands, SMAD proteins (like SMAD2, SMAD3, and SMAD4), and specific receptors (TGF-βRI and TGF-βRII). When TGF-β ligands bind to the TGF-βRII receptor, it recruits and activates TGF-βRI. This activation leads to the phosphorylation of receptor-regulated SMADs (R-SMADs), which then form a complex with SMAD4 and move into the cell nucleus to regulate the expression of target genes [2, 5, 7, 13]. TGF-β acts as a tumour suppressor in normal cells and early stages of cancer by preventing cell division, inducing apoptosis, and maintaining genomic stability [14, 15]. However, in advanced cancer stages, TGF-β can promote tumour growth, angiogenesis (formation of new blood vessels), immune evasion, and metastasis (spread of cancer cells) [16]. It achieves this by influencing the cell cycle and apoptosis, such as upregulating cyclin-dependent kinase inhibitors and downregulating c-Myc, a gene involved in cell proliferation [5, 17, 18]. TGF-β also helps maintain DNA stability and supports DNA repair mechanisms, highlighting its dual role in cancer progression [19].

Role in EMT and Tumor Microenvironment

TGF-β plays a key role in promoting cancer by inducing a process called Epithelial-to-Mesenchymal Transition (EMT). During EMT, epithelial cells can move and adopt mesenchymal traits, making it easier for them to spread or metastasise to other parts of the body [20, 21]. TGF-β also modifies the tumour environment to suppress the body's immune response against the tumour, enhancing the activity of regulatory T-cells (which can dampen immune responses) and reducing the effectiveness of cytotoxic T-cells (which are involved in killing cancer cells) [5]. Additionally, TGF-β promotes the growth of new blood vessels (angiogenesis) by increasing the levels of pro-angiogenic factors like VEGF, which is essential for providing tumours with the nutrients they need to grow [22-25]. It also facilitates tumour invasion by increasing the production of enzymes called matrix metalloproteinases (MMPs), which break down the surrounding tissue, allowing cancer cells to invade neighbouring areas [26]. Mutations in TGF-β receptors (TGFBR1, TGFBR2) and SMAD proteins (like SMAD4), along with abnormal methylation (a DNA modification process), can disrupt the normal tumor-suppressing functions of the TGF-β-pathway [14]. Dysregulation methylation of TGF-β signaling components can lead to dysregulation of the system. Changes in the expression of regulatory proteins, such as TGIF1, can further influence the dynamics of TGF-β signaling [2, 27].

Targeting TGF-β signaling, small molecule inhibitors, neutralising antibodies, and receptor kinase inhibitors are being investigated as potential targets for cancer treatments [28-30]. The anti-tumour efficaciousness of TGF-β inhibitors may be increased when combined with other therapies (such as immune checkpoint inhibitors) [31, 32]. Determining biomarkers for TGF-β pathway activity can aid in forecasting the reaction of patients to medicines that target TGF-β [33, 34]. However, one of the main challenges is overcoming resistance to TGF-β-targeted therapies and finding ways to block the tumour-promoting effects of TGF-β while preserving its ability to suppress tumours. This requires a balanced and precise approach to therapy.

Modulation of TGF-β Signaling by TWSG1
Enhancement of TGF-β Signaling by TWSG1

TWSG1 (Twisted Gastrulation 1) is known to regulate the TGF-β signaling pathway and modulate the activity of BMP ligands, which are part of the TGF-β superfamily [35]. *TWSG1* has been shown to modulate TGF-β signaling through various mechanisms, viz., *TWSG1* acts as a positive regulator of TGF-β signaling by enhancing the binding of TGF-β ligands to their receptors, thereby promoting downstream signaling events [3, 7, 9]. Conversely, *TWSG1* acts as a negative regulator in other cellular contexts by sequestering TGF-β ligands, preventing their interaction with receptors, and inhibiting downstream signaling [3, 36]. The dual role of *TWSG1* in TGF-β signaling highlights its context-dependent function in cancer biology.

TWSG1 gene involved in TGF-β ligands binds to their specific type II receptors on the cell surface. It helps in the activation of type I receptor phosphorylating type II receptor. Play a significant role in SMAD activation (Type I receptor phosphorylates receptor-regulated SMADs (R-SMADs, such as SMAD2/3)) [37]. It is involved in the phosphorylation of R-SMADs, which form complexes with SMAD4 and translocate to the nucleus [38]. The SMAD complex regulates the transcription of target genes involved in cell proliferation, differentiation, and apoptosis. Further, *TWSG1* can bind directly to BMPs, regulating their availability and activity [39]. Modulates BMP signaling by either enhancing or inhibiting the interaction of BMPs with their receptors [40]. This modulation affects the downstream effects of the TGF-β

signaling pathway, impacting cellular processes such as embryonic development, tissue homeostasis, and immune responses [5, 41]

Role of TWSG1 in regulating TGF-β Signaling
TWSG1 enhances TGF-β signaling

TWSG1 is an essential glycoprotein that plays a crucial role in regulating the TGF-β signaling pathway, which controls important cell functions [42]. *TWSG1* helps enhance the stability and availability of TGF-β ligands, the molecules that start the signaling process. By doing this, it facilitates the activation of TGF-β receptors on the cell surface, ensuring that the signaling cascade can proceed efficiently [43, 44]. *TWSG1* can also influence co-receptors like beta glycan (TGFBR3), which are involved in the production and activation of TGF-β receptors. Moreover, *TWSG1* promotes the activation of latent (inactive) TGF-β ligands, making them ready to trigger the signaling process. The TGF-β signaling pathway mainly operates through the Smad pathway. In this pathway, activated receptors cause the phosphorylation (a chemical modification) of specific proteins known as receptor-activated Smads (R-Smads) [7, 45]. These phosphorylated R-Smads then form complexes with other Smad proteins and move into the cell nucleus, where they regulate the expression of target genes. *TWSG1* may enhance this phosphorylation process, aiding in the transport of R-Smads to the nucleus and boosting the activation of TGF-β target genes [46]. Additionally, *TWSG1* might interact with other signaling pathways, such as the Wnt or BMP pathways, which can also influence TGF-β signaling. If *TWSG1* or TGF-β signaling becomes dysregulated, it can contribute to the progression of various diseases, including cancer [47]. *TWSG1* overexpression could lead to stronger TGF-β signaling responses, whereas reducing *TWSG1* levels, either through genetic knockout or specific RNA techniques, results in weaker TGF-β signaling [48].

TWSG1 inhibits TGF-β signaling activation

TWSG1 can act as an inhibitor in the TGF-β signaling pathway by binding to TGF-β ligands and preventing them from interacting with their receptors on the cell surface. By doing this, *TWSG1* reduces the availability of active TGF-β ligands, which in turn inhibits the initiation of the TGF-β signaling cascade [3]. *TWSG1* also blocks the activation of latent (inactive) TGF-β ligands by inhibiting the activity of proteases and other components in the extracellular matrix that normally activate these ligands. Additionally, *TWSG1* prevents the phosphorylation of receptor-activated Smads (R-Smads), a crucial step in the TGF-β signaling process [36]. Without this phosphorylation, the Smads cannot activate the transcription of target genes, leading to a reduction in TGF-β's effects on the cell.

Moreover, *TWSG1* may enhance its inhibitory effect by interacting with other molecules that suppress TGF-β signaling, such as SMAD7. This inhibitory role of *TWSG1* is essential for regulating processes like cell differentiation and tissue development. However, when *TWSG1*'s function is disrupted, it can lead to various pathological conditions, including cancer, fibrosis, and inflammation [3, 49].

Context-dependent regulation of TGF-β signaling by TWSG1

TWSG1 is a protein involved in several cellular processes, including development, differentiation, and homeostasis. It promotes TGF-β signaling by increasing the availability of active TGF-β ligands and activating latent TGF-β through interactions with extracellular matrix components and proteases [50]. TGF-β activity is crucial for tissue healing and fibrosis, increasing extracellular matrix synthesis and cell proliferation [51]. *TWSG1* can decrease TGF-β signaling by sequestering ligands or preventing their interaction with receptors [36]. This is critical for avoiding undesired fibrosis and regulating cellular proliferation during development. *TWSG1* can interact with inhibitory molecules such as Smad7, leading to negative control of TGF-β signaling. *TWSG1* promotes TGF-β signaling for fast proliferation in developing tissues and inhibits it for differentiation [52]. Interactions with other signaling pathways, such as the BMP and Wnt pathways, can alter *TWSG1* regulation [9]. *TWSG1*'s impact on TGF-β signaling is context-dependent, as studies involving animal models [53], cell culture [36], and genetic modification revealed [54].

Facilitation of TGF-β Ligand-Receptor Interactions

TWSG1 enhances the TGF-β signaling cascade by increasing the affinity between TGF-β ligands and their respective receptors, TGF-βRII and TGF-βRI [55]. This facilitation likely occurs through *TWSG1*-mediated stabilisation of the ligand-receptor complex, which optimises the spatial orientation and conformation of both the ligands and receptors, thereby enhancing the efficiency of receptor dimerisation and activation [56]. The increased ligand-receptor interactions lead to a higher rate of receptor phosphorylation and subsequent activation of downstream signaling pathways [57].

Promotion of SMAD Phosphorylation and Nuclear Translocation

Upon ligand-receptor interaction facilitated by *TWSG1*, the activated TGF-β receptor complex phosphorylates receptor-regulated SMADs (R-SMADs, specifically SMAD2 and SMAD3) [58]. *TWSG1* appears to play a role in optimising the phosphorylation efficiency of these R-SMADs, which is critical for signal propagation. Following phosphorylation, SMAD2/3 forms a heteromeric complex with SMAD4, essential for translocation into the nucleus [59]. *TWSG1*'s influence on this process may involve enhancing the stability of the SMAD complex or altering the nucleocytoplasmic transport mechanisms, leading to more efficient nuclear translocation. In the nucleus, the SMAD complexes regulate the transcription of target genes involved in cell cycle regulation, differentiation, and extracellular matrix production [60, 61]

Role of TWSG1 in Specific Cancer Types

The recent evidence suggests that dysregulation of *TWSG1* expression is associated with various cancers,

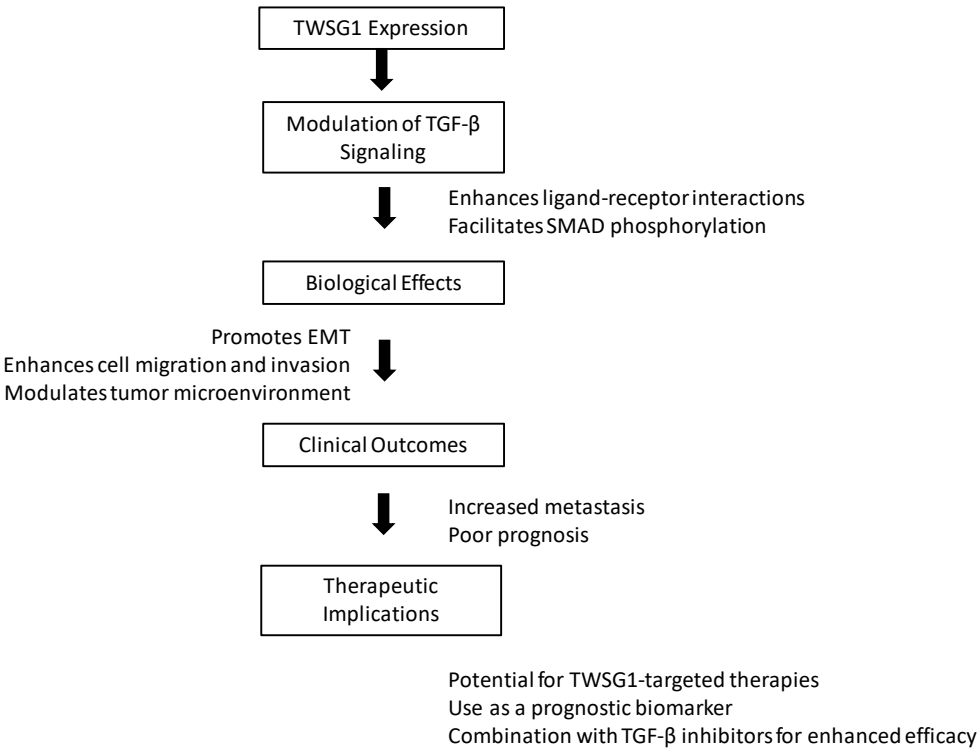

Figure 1. Schematic Representation of Showing the Role of *TWSG1* in different cancers. *TWSG1* interacts with the TGF-β signalling pathway in different cancers. In breast cancer, *TWSG1* facilitates EMT by upregulating transcription factors like Snail and Slug, decreasing E-cadherin, and increasing vimentin expression. In colorectal cancer, it promotes metastasis by activating SMAD pathways, enhancing cell motility and invasion of organs like the liver. *TWSG1* interacts with latent TGF-β ligands in pancreatic cancer to enhance SMAD phosphorylation, driving EMT and metastasis to distant organs such as the lungs. *TWSG1* fosters immune evasion and metastatic spread in lung cancer by activating SMAD-dependent and independent TGF-β pathways, reshaping the tumour microenvironment to favour aggressive cancer progression.

including breast, colorectal, pancreatic, and lung cancers [3, 4]. *TWSG1* has been implicated in cancer progression by promoting epithelial-mesenchymal transition (EMT), cancer cell invasion, and metastasis through its effects on TGF-β signaling [62]. Additionally, *TWSG1* may play a role in modulating the tumour microenvironment, influencing immune cell infiltration and angiogenesis needs further evaluation.

Breast Cancer: Role of TWSG1

Promotion of EMT and Metastasis

TWSG1 plays a significant role in promoting breast cancer progression by enhancing TGF-β signaling pathways that drive the epithelial-to-mesenchymal transition (EMT) [63]. EMT is a key process where cancer cells change from an epithelial state (less mobile) to a mesenchymal state (more mobile), enabling them to migrate and invade other tissues. *TWSG1* influences this transformation by regulating the expression of specific EMT-related transcription factors, including Snail, Slug, and ZEB1 [64]. This shift is marked by a decrease in epithelial markers such as E-cadherin and an increase in mesenchymal markers like N-cadherin and vimentin, which helps the cancer cells become more migratory and invasive [65]. High levels of *TWSG1* in breast cancer cells are associated with greater metastatic potential, facilitating

Table 1. The role of *TWSG1* across different cancer types, including breast, colorectal, pancreatic, and lung cancers. The table shows how *TWSG1* modulates TGF-β signalling to promote processes like EMT, invasion, and metastasis, showing context-dependent effects. The table also outlines the therapeutic implications of targeting *TWSG1* to inhibit metastasis or use its expression as a prognostic biomarker. This concise overview emphasises *TWSG1*'s potential as a target for cancer therapies and personalised treatment approaches.

Cancer Type	Role of *TWSG1*	Impact on TGF-β Signaling	Therapeutic Implications
Breast Cancer [86]	Promotes EMT and metastasis	Enhances TGF-β signaling	Potential target for inhibiting EMT
Colorectal Cancer [87]	Modulates EMT and invasion	Dual role: suppressor/promoter	Targeting *TWSG1* may reduce metastasis
Pancreatic Cancer [88]	Increases invasiveness	Facilitates SMAD phosphorylation	Biomarker for predicting therapy response
Lung Cancer [89]	Promotes metastasis	Enhances ligand-receptor interaction	Target for reducing metastatic spread

the spread of cancer to distant organs [66, 67]

Regulation of Tumor Microenvironment

TWSG1 also affects the tumour microenvironment (TME), which consists of not only cancer cells but also the surrounding stromal cells, including fibroblasts, immune cells, and blood vessels [68]. By enhancing TGF-β signaling, *TWSG1* influences the interaction between tumour cells and these surrounding stromal cells [11]. This can lead to the recruitment and activation of cancer-associated fibroblasts (CAFs), which produce components of the extracellular matrix (ECM) and secrete pro-tumorigenic cytokines, substances that can promote tumor growth [69]. Furthermore, *TWSG1* can create conditions that suppress the immune response within the tumour microenvironment, allowing the tumour to grow and evade detection by the immune system.

TWSG1 association with clinical outcomes in breast cancer correlating prognosis

Clinical studies have shown that high levels of *TWSG1* expression are linked to a poor prognosis for breast cancer patients. Elevated *TWSG1* levels are associated with more advanced tumour grades, a higher likelihood of lymph node metastasis, and reduced overall survival. These findings suggest that *TWSG1* could serve as a useful biomarker for predicting breast cancer outcomes, helping to identify patients who may be at higher risk of aggressive disease progression [3, 4]. This association suggests that *TWSG1* could serve as a prognostic biomarker for breast cancer, helping to identify patients at higher risk of aggressive disease progression. Moreover, targeting *TWSG1* for therapeutic intervention could potentially disrupt the TGF-β-driven pathways that promote cancer, offering a strategy to mitigate breast cancer progression and improve patient outcomes.

Colorectal Cancer

*Role of TWSG1 in TGF-β Signaling and Metastasis in Colorectal Cance*r

In colorectal cancer, *TWSG1* plays a role in modulating the TGF-β signaling pathway, which has a dual function: it acts as a tumour suppressor in the early stages of cancer development but promotes metastasis in later stages [14]. *TWSG1* enhances TGF-β-mediated signaling by activating downstream SMAD pathways, which drive the epithelial-to-mesenchymal transition (EMT) [70]. During EMT, cancer cells lose epithelial characteristics, marked by reduced expression of markers like E-cadherin, and gain mesenchymal traits, indicated by increased markers like vimentin and fibronectin [71]. This transformation boosts the mobility and invasiveness of colorectal cancer cells, facilitating their spread to distant organs, particularly the liver [72]. Additionally, *TWSG1*'s enhancement of TGF-β signaling may influence the tumour microenvironment by promoting the recruitment of myofibroblasts (cells that play a role in wound healing) and immunosuppressive cells. These changes further support tumour progression and metastasis, contributing to the aggressive nature of colorectal cancer in its advanced stages [73].

Potential Therapeutic Implications of Targeting TWSG1 in Colorectal Cancer

Due to its role in enhancing TGF-β-mediated EMT and metastasis, *TWSG1* is a promising target for therapeutic intervention in colorectal cancer. By inhibiting *TWSG1*, it may be possible to disrupt TGF-β signaling pathways, thereby reducing EMT and the spread of cancer cells while potentially restoring the tumour-suppressing effects of TGF-β in early-stage cancers [74]. Potential therapeutic strategies could include using small molecule inhibitors, monoclonal antibodies, or RNA interference techniques designed to lower *TWSG1* expression or block its interaction with TGF-β ligands [75]. These targeted therapies could be used alongside existing cancer treatments, providing a novel approach to managing colorectal cancer, especially in cases where abnormal TGF-β signaling driven by *TWSG1* leads to aggressive tumour behaviour and metastasis. Continued research into developing and testing *TWSG1* inhibitors may offer valuable insights into effective strategies for slowing down or halting colorectal cancer progression.

Pancreatic Cancer

TWSG1-Mediated Modulation of TGF-β Signaling in Pancreatic Cancer Cells

In pancreatic cancer, *TWSG1* plays a critical role in modulating TGF-β signaling pathways that are essential for tumour growth and metastasis. *TWSG1* enhances the TGF-β-induced EMT, increasing pancreatic cancer cells' invasiveness and metastatic potential. By interacting with TGF-β ligands, *TWSG1* promotes the phosphorylation of SMAD proteins. These SMAD proteins then move into the cell nucleus, where they initiate gene expression changes associated with EMT [76, 77] These changes include an increase in mesenchymal markers such as vimentin and N-cadherin and a decrease in epithelial markers like E-cadherin. Such molecular alterations contribute to a shift in cell characteristics, making pancreatic cancer cells more mobile and capable of invading surrounding tissues. This shift ultimately facilitates the metastasis of cancer cells to distant organs, including the liver and lungs. Understanding *TWSG1*'s role in these processes highlights its importance in promoting pancreatic cancer progression and its potential as a target for therapeutic intervention [20, 65]

TWSG1 as a Potential Biomarker for Predicting Response to TGF-β-Targeted Therapies in Pancreatic Cancer

The expression levels of *TWSG1* could serve as a valuable biomarker for predicting the effectiveness of TGF-β-targeted therapies in pancreatic cancer. Since high *TWSG1* expression is associated with enhanced TGF-β signaling and aggressive tumour behaviour, patients with elevated *TWSG1* levels may respond better to therapies that inhibit TGF-β signaling [3]. Directly targeting *TWSG1* or modulating its activity might make pancreatic tumours more sensitive to TGF-β inhibitors, potentially slowing down tumour progression and reducing metastasis. Evaluating *TWSG1* expression in tumour biopsies could help identify patients who are more likely to benefit from TGF-β-targeted treatments,

allowing for a more personalised therapy approach and improving clinical outcomes [78]. Further research into *TWSG1* as a biomarker could lead to the development of diagnostic tools and tailored therapeutic strategies that match the molecular characteristics of pancreatic cancer.

Lung Cancer

TWSG1 Expression and Its Correlation with TGF-β Signaling in Lung Cancer

In lung cancer, *TWSG1* expression is closely linked to the activation of TGF-β signaling pathways, which play a crucial role in tumour growth and metastasis. High levels of *TWSG1* have been detected in lung cancer tissues, where it enhances TGF-β signaling by promoting the interaction between TGF-β ligands and their receptors [79]. This interaction activates both SMAD-dependent and SMAD-independent pathways, leading to processes that drive cancer, such as increased cell proliferation, EMT (epithelial-to-mesenchymal transition), and immune evasion [80]. The connection between *TWSG1* and TGF-β signaling indicates that *TWSG1* may mediate TGF-β's cancer-promoting activities in lung cancer, supporting tumour growth and leading to more aggressive cancer behaviour.

Role of TWSG1 in lung cancer metastasis and potential therapeutic strategies

TWSG1 plays a significant role in promoting metastasis in lung cancer by enhancing TGF-β-induced EMT, which gives cancer cells the ability to migrate and invade other tissues. This process involves the downregulation of epithelial markers like E-cadherin and the upregulation of mesenchymal markers like vimentin, enabling cancer cells to detach from the primary tumour and invade surrounding tissues and blood vessels [76]. Targeting *TWSG1* could help disrupt this EMT process, potentially inhibiting the spread of cancer. Therapeutic strategies may include developing *TWSG1* inhibitors, such as small molecules, monoclonal antibodies, or RNA interference-based therapies, to reduce *TWSG1* activity and block its interaction with TGF-β ligands [81, 82]. By limiting *TWSG1*-mediated TGF-β signaling, these strategies could effectively slow down tumour progression and metastasis, providing new treatment options for lung cancer.

Clinical implications of targeting TWSG1 in TGF-β-driven cancers

Therapeutic potential with inhibitors

Given *TWSG1*'s role in enhancing TGF-β signaling, targeting *TWSG1* alongside TGF-β pathway inhibitors may present a new therapeutic strategy for cancers driven by abnormal TGF-β activity. Inhibiting *TWSG1* could reduce TGF-β-mediated processes such as epithelial-to-mesenchymal transition (EMT), invasion, and metastasis by decreasing the availability of TGF-β ligands for receptor activation [76]. Combining *TWSG1* inhibitors with existing TGF-β receptor kinase inhibitors or blockers of the SMAD pathway could offer a more comprehensive approach to blocking the signaling cascade [83]. This combined strategy could potentially improve the effectiveness of treatments by overcoming the limitations of single-agent therapies and reducing the chance of tumour resistance, providing a more robust option for patients with aggressive and metastatic cancers.

Use of TWSG1 expression as a prognostic biomarker in TGF-β-driven cancers

The expression levels of *TWSG1* in tumour tissues could serve as a valuable biomarker for predicting the aggressiveness of TGF-β-driven cancers. High *TWSG1* expression is associated with enhanced TGF-β signaling, increased EMT, and more significant potential for metastasis, all of which correlate with worse clinical outcomes. Measuring *TWSG1* expression in cancer patients could help identify those at higher risk and those more likely to benefit from targeted therapies that inhibit the TGF-β pathway [84]. This biomarker approach could improve personalised treatment strategies, ensuring patients receive the most suitable and effective therapeutic interventions [85]. This biomarker-based approach could improve personalised treatment strategies, ensuring patients receive the most appropriate and effective therapeutic interventions.

Challenges and clinical translation of TWSG1-targeted therapies

Developing *TWSG1*-targeted therapies presents several challenges, such as identifying specific inhibitors that can effectively block *TWSG1* activity without causing off-target effects. Additionally, it is crucial to understand the precise mechanisms by which *TWSG1* influences TGF-β signaling in various types of cancer to design effective combination therapies. Future research should focus on conducting preclinical studies to validate the safety and effectiveness of *TWSG1* inhibitors and investigate their potential synergistic effects with existing TGF-β pathway inhibitors. Clinical trials will be necessary to evaluate the therapeutic potential of these approaches in cancer patients, ultimately paving the way for incorporating *TWSG1*-targeted strategies into standard cancer treatment practices (Figure 1).

In conclusion, *TWSG1* has emerged as a pivotal regulator of TGF-β signaling in various cancer types, demonstrating both tumour-promoting and suppressive roles depending on the context of its expression and the specific cancer environment. *TWSG1* modulates TGF-β-induced processes such as epithelial-to-mesenchymal transition (EMT), immune evasion, and tumour microenvironment remodelling. These actions facilitate cancer cell invasion, metastasis, and resistance to therapy, underscoring *TWSG1*'s role in cancer progression. Moreover, elevated *TWSG1* expression has been linked to poor prognosis in several cancers, suggesting its potential as a prognostic biomarker and a therapeutic target.

Further research is necessary to delineate the precise molecular mechanisms *TWSG1* regulates TGF-β signaling in cancer. Understanding the context-specific effects of *TWSG1* how it can switch from tumour-suppressive to tumour-promoting roles will be crucial for developing targeted therapies. Future studies should focus on identifying the upstream regulators and downstream effectors of *TWSG1* in different cancer types. Additionally,

preclinical and clinical investigations into *TWSG1* inhibitors, either alone or combined with TGF-β pathway inhibitors, are needed to explore their efficacy and safety. Developing reliable diagnostic tools to measure *TWSG1* expression in tumour tissues will also be critical for its application as a prognostic biomarker.

Overall, *TWSG1* plays a complex yet crucial role in regulating TGF-β signaling pathways in cancer progression and metastasis. Its dual role, depending on the tumour type and microenvironment, highlights the need for a nuanced understanding of its function in cancer biology. Targeting *TWSG1*, alone or in combination with other therapeutic agents, represents a promising strategy for treating TGF-β-driven cancers. Ongoing and future research into the molecular underpinnings and clinical implications of *TWSG1* will pave the way for innovative cancer therapies and personalised treatment approaches.

Author Contribution Statement

Conceptualization: P.K.S.; J.M.N.; Data curation: P.K.S.; J.M.N.; Formal Analysis: P.K.S.; Investigation: P.K.S.; Methodology: P.K.S.; Writing – Original Draft: P.K.S.&A.P.; Writing – Review & editing: P.K.S.; J.M.N.; Visualization: P.K.S.; J.M.N.&A.P; Supervision: P.K.S. &A.P.

Acknowledgements

The authors would like to acknowledge the JSS Medical College and Hospital, JSS-AHER, Mysuru, for their valuable support.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable, as this study does not involve human participants, human data, or human tissue that would require ethical approval and consent to participate.

Conflict of interest

Authors declare that they do not have a conflict of interest

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