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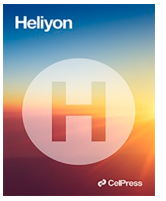

Review article

DACT2 modulates atrial fibrillation through TGF/β and Wnt signaling pathways

Bairu Luo [a,1], Rui Zheng [b,1], Chaoqun Shi [c], Deqing Chen [c], Xin Jin [c], Jian Hou [d], Guangtao Xu [c], Bo Hu [e,*]

[a] *Department of Clinical Pathology, Jiaxing University Master Degree Cultivation Base, Jiaxing Hospital of Traditional Chinese Medicine, Zhejiang Chinese Medical University, Jiaxing, 314001, ZJ, China*
[b] *Department of Clinical Pathology, The 3rd Clinical Medical College Affiliated to Zhejiang Chinese Medical University, Hangzhou, 310053, ZJ, China*
[c] *Department of Pathology, Institute of Forensic Science, Jiaxing University, Jiaxing, 314001, ZJ, China*
[d] *Department of Cardiology, The Affiliated Panyu Central Hospital of Guangzhou Medical University, Guangzhou, 510080, GD, China*
[e] *Department of Clinical Pathology, Jiaxing Hospital of Traditional Chinese Medicine, the 3rd Clinical Medical College Affiliated to Zhejiang Chinese Medical University, Jiaxing, 314001, ZJ, China*

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ABSTRACT

Atrial fibrillation (AF) is a common cardiac arrhythmia that seriously affects the quality of life of patients. Effective treatment and prevention are important to control the morbidity and mortality of AF. It has been found that cardiac fibrosis promotes the onset and progression of AF. It is now known that transforming growth factor β (TGF-β), an important fibrotic cytokine, plays an important role in cardiac fibrosis by inducing myofibroblast activation via the activation of classical (SMAD-based) and non-classical (non-SMAD-based) signaling pathways. In addition, specific activation of the Wnt/β-catenin pathway has been shown to promote the transformation of fibroblasts into myofibroblasts. In recent years, a new family of proteins, namely Disheveled-associated antagonist of beta-catenin (DACT) 2, can affect the Wnt/β-catenin and TGF-β signaling pathways by regulating the phosphorylation levels of these target proteins, which in turn affects the progression of fibrosis. The present study focuses on the effect of DACT2-guided β-catenin on atrial fibrosis. It is expected that the summarized information can be helpful in the treatment of AF.

1. Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia, with high morbidity and mortality. AF causes irregular, often abnormally fast contractions of the atrial cardiomyocytes, usually resulting in an irregular, rapid heart rate [1,2]. Atrial remodeling, including electrical and structural remodeling of the atrial tissue, is central to AF [3]. AF-induced atrial remodeling results in altered electrophysiological and ion channel characteristics and sustained structural damage in atrial cardiomyocytes, such as atrial enlargement and tissue fibrosis. Atrial fibrosis is the primary process by which atrial structure remodeling occurs and serves a key role in the development and persistence of AF [4]. Atrial fibrosis results in an increased population of fibroblasts/myofibroblasts in the

* Corresponding author.
E-mail address: hubo@zjxu.edu.cn (B. Hu).
[1] Bairu Luo and Rui Zheng were contributed equally in this study.

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fibrotic tissue and the increased deposition of extracellular matrix (ECM) proteins, such as collagen I and III [5].

In this regard, the conversion of cardiac fibroblasts to myofibroblasts is crucial and plays a vital role in the excessive accumulation of ECM components [6]. Cardiomyocytes can interact with cardiac fibroblasts (CFs) via ECM proteins and paracrine substrates, which may disrupt the myocardial architecture and promote a structural substrate that drives AF. In addition, under high-pressure and stress conditions, cardiomyocytes secrete reactive mediators to activate intracellular signaling pathways, such as the regulation of transforming growth factor β (TGF-β) and Wnt signaling pathways, accelerating fibrosis [7]. Eventually, atrial fibrosis causes heterogeneity in atrial conduction and reentry [8–10].

Dishevelled-associated antagonist of beta-catenin (DACT) family is a new family of proteins discovered recently that interact with dishevelled (DVL). The family consists of the three following members: DACT1, DACT2 and DACT3, among which DACT2 functions as a cytoplasmic attenuator that regulates both TGF-β/nodal and Wnt signaling pathways [11–18]. Recent studies have shown that DACT2 can regulate the electrical and structural remodeling of the atrium by regulating the expression of K^+/Na^+ channel proteins and collagen in atrial fibroblasts, which in turn participates in atrial fibrosis [19]. Previous studies have identified that the DACT2, TGF-β and Wnt signaling pathways are involved in the induction of the occurrence and development of AF; however, the correlation and causality among the three are still unclear. The present review provides an overview of the TGF-β and Wnt signaling pathways in the development of AF and subsequently explores the pathological mechanism of the DACT2 gene regulating the TGF-β and Wnt signaling pathways in the development of AF. Finally, it provides a theoretical basis for the prevention and treatment of AF that can be explored in future studies.

2. TGF-β signaling pathway

The TGF-β family consists of the TGF-β proteins, such as activin and nodal, bone morphogenetic proteins and growth and differentiation factors, which play pivotal roles in embryogenesis and tissue homeostasis [20,21]. TGF-β proteins have the three following phenotypes: TGF-β1, TGF-β2 and TGF-β3, functioning as pleiotropic cytokines that trigger cell-specific effects in a highly interdependent manner in various different tissues [22]. TGF-β is expressed in almost all tissues and cells, It can influence a variety of physiological processes, including angiogenesis, fibrosis, and immunosuppression by promoting the tumor microenvironment and thereby affecting multiple physiological processes [23,24], Overexpression of TGF-β can lead to metabolic disorders and dysfunctions in the body and can play an important role in cancer by regulating the cellular microenvironment with other effects of cytokines. In early stages, it can suppress tumors by inhibiting cell proliferation and inducing apoptosis. Many molecules targeting TGF-β or its receptor play an important role in blocking TGF-β signaling, but current information on the use of TGF-β to treat cancer, immune dysregulation fibrosis.TGF-β is associated with the progression of many types of cancer and acts as an indirect tumor suppressor by preventing inflammation through synergistic effects on different immune cells [22].And it can promote tumor progression and recurrence through immunosuppression as well as fibrosis, limiting the effectiveness of immunity [25].

There is growing evidence that members of the TGF-β family play important roles in cardiac pathophysiological processes, including fibrotic remodeling, fibroblast activation and extracellular matrix deposition [26–28]. TGF-β represents a key pro-fibrotic cytokine in cardiac fibrogenesis and inhibition of its action successfully reduces or prevents the development of fibrosis in a variety of animal models of heart disease [29,30]. TGF-β-SMAD signaling in CFs has been found to be associated with the development of myocardial fibrosis in pressure overload models. Fibroblast-specific deletion of SMAD3, but not of SMAD2, significantly reduced pressure overload-induced fibrosis and inhibited ECM protein synthesis [31]. The TGF-β protein is initially secreted and stored in the ECM as a latent complex, which is subsequently activated by proteins and enzymes and transformed into disulfide-linked dimers and homodimeric ligands. Following binding to the TGF-β receptor (TGFβR), TGF-β signaling is transmitted from the plasma membrane to the nucleus via a family of proteins known as the SMAD family, members of which are divided into the three following major classes: Receptor-regulated SMAD (including SMAD1, 2, 3, 5 and 8), co-mediator SMAD(SMAD4 only), and antagonistic or inhibitory SMAD (including SMAD6 and 7) [32,33]. The SMAD-dependent pathway (the typical response) or the SMAD-independent pathways (atypical response) activate different context-dependent transcription. The typical SMAD-dependent pathway is the predominant TGF-β pathway and is highly conserved across species [34]. Following binding of the TGF-β ligands to the heterodimeric receptors (TβR type I and II), TβRII phosphorylates and activates TβRI and initiates a signaling cascade mediated by the nuclear-translocated SMAD family to regulate the transcription of the relevant target genes. Among them, SMAD4 is a tumor suppressor that is mutated in many tumors (most commonly in gastrointestinal tumors), and survival analyses have shown that patients with positive SMAD4 signals live longer than those with negative signals. Typically, the TGF-β/SMAD4 pathway exerts tumor suppressor effects early in the tumor, inducing apoptosis and arrest of the cell cycle [35]. In the early stages of tumorigenesis and progression, TGF-βacts as a tumor suppressor by inhibiting proliferation and accelerating apoptosis; in the late stages of tumor progression, elevated levels of TGF-β promote tumor formation by facilitating migration, invasion, and evasion of the immune system [36]. Recent years, it has been found that TGF-β signaling is strongly activated after cancer chemotherapy and radiotherapy, which leads to the emergence of drug resistance. Cancer-associated fibroblasts (CAF), as a major component of the tumor microenvironment, are involved in cellular differentiation, and previous studies have found that TGF-β can exert multiple effects on CAF through autocrine and paracrine secretion, which makes it important in targeted therapy [37],however, current oncology treatment strategies consistently rely on their oncogenic properties, which sometimes fail to achieve the desired therapeutic effect [38]. Therefore, how to best utilize the role played by TGF-β in tumorigenesis in the design of oncology therapies requires in-depth research [39]. Second, the significance of TGF-β in fibrosis has been extensively studied in recent years; For example, downstream SMAD2 and SMAD3 are considered crucial mediators of TGF-β signaling in tissue fibrosis; the activation of TGF-β1 enhances the transcriptional activity of SMAD3, leading to increased expression of collagen I in cells [40]. By contrast, SMAD6 and SMAD7 are regarded as negative regulators to improve TGF-β-mediated fibrosis [41,

42].

In addition, the non-canonical SMAD-independent pathway functions via three different pathways, including the phosphatidylinositol 3-kinase/protein kinase B, the RhoA/Rho-associated protein kinases (RhoA-ROCK) axis, and the mitogen-activated protein kinases (MAPK) cascades [43].

TGF-β is an important pro-fibrotic cytokine involved in the development of AF which acts primarily via the SMAD2/3 axis leading to its upregulation, which is noted during cardiac hypertrophy, fibrotic remodeling, fibroblast activation and ECM deposition. Among them, SMAD3 can enhance transcription by directly binding to SMAD-binding proteins within gene promoters [44]. TGF-β-SMAD signaling in CFs has been found to be associated with the development of myocardial fibrosis in pressure overload models. Fibroblast-specific deletion of SMAD 3, but not of SMAD 2, significantly reduced pressure overload-induced fibrosis and inhibited ECM protein synthesis in TGF-β regulating the phenotypic conversion of CFs to myofibroblasts [45]. Myofibroblasts are an important intermediate mediator of atrial fibrosis and are derived from CFs proliferating and differentiating in response to fibrotic stimuli, including cytokines, such as α-smooth muscle actin (α-SMA), waveform protein, angiotensin II (Ang-II) and collagen, which are important drivers of the cardiac fibrotic response; these cytokines bind to the corresponding receptors thereby triggering the activation of downstream effector proteins, such as SMAD 3, and amplifying the fibrotic response (as shown in Fig. 1) [27,46,47]. SMAD7 inhibits protease expression in a TGF-β-independent manner and SMAD7 induction in myofibroblasts is a negative feedback mechanism induced by endogenous TGF-β [48,49]. Among other functions, the expression of SMA is an important feature of myofibroblast differentiation. Therefore, TGF-β1 can increase the myofibroblast contractility in tissue remodeling by stimulating the expression of SMA and incorporating stress fibers [50,51]. Moreover, it has been found that the inhibition of TGF-β1 leads to a decrease in the expressions of collagen I and α-SMA [52,53]. In addition, Ang-II was shown to induce CF differentiation into myofibroblasts and to produce ECM [54–56]. Ang-II also promotes fibrosis by mediating TGF-β and inducing atrial fibroblast differentiation [57–59]. These results suggest that TGF-β may mediate the development of AF by promoting atrial fibrosis via inducing the development of myofibroblasts.

3. Wnt signaling pathway

The Wnt signaling pathway is an important cellular signaling pathway involved in embryonic development, tissue homeostasis and various physiological processes [60,61]. The Wnt signaling can be categorized into the two following types: Canonical and non-canonical [60,62]. Wnt signaling promotes the activation and expansion of endocardium-derived fibroblasts during cardiac remodeling [63]. Wnt ligands are highly conserved secreted glycoproteins that are transcribed from 19 mammalian genes. Wnt1, 3A and 8A activates the canonical pathway, whereas Wnt5A and 11 activate the non-canonical pathway [64,65]. Canonical Wnt signaling is mediated through intracellular β-catenin, whereas non-canonical Wnt signaling functions through the planar cell polarity (PCP) pathway and calcium (Ca^{2+}) cascades. Both the canonical Wnt pathway and the non-canonical Wnt pathway can be regulated by the binding of Wnt ligands and a family of seven transmembrane receptors called Frizzled (FZD). Apart from the dominant FZD receptors, several co-receptors have been shown to be involved, such as low-density lipoprotein receptor-associated protein 5/6 (LRP5/6). The canonical Wnt/β-catenin pathway is activated with the binding of the Wnt ligands and the FZD and LRP5/6 receptors, causing the dissociation of the destruction complex and the accumulation of β-catenin in the nucleus by inhibiting glycogen synthetase kinase 3β (GSK3β)-dependent degradation complex. Furthermore, β-catenin binds to the T-cell factors/lymphoid enhancing factors (TCFs/LEFs) and activates the expression of the Wnt/β-catenin target genes. In addition, the non-canonical Wnt pathway signals independently of β-catenin and mainly functions via the Wnt/calcium and the PCP pathway. The Wnt/calcium pathway typically causes Ca^{2+} release and activates protein kinase C (PKC), calmodulin kinase II and calcineurin. The PCP pathway activates the Rho-family small GTPases through the DVL complex and subsequently triggers signaling via the activation of certain MAPKs (c-Jun N-terminal kinase, JNK and ERK1/2 kinases) and the RhoA-ROCK axis(As in Fig. 2).

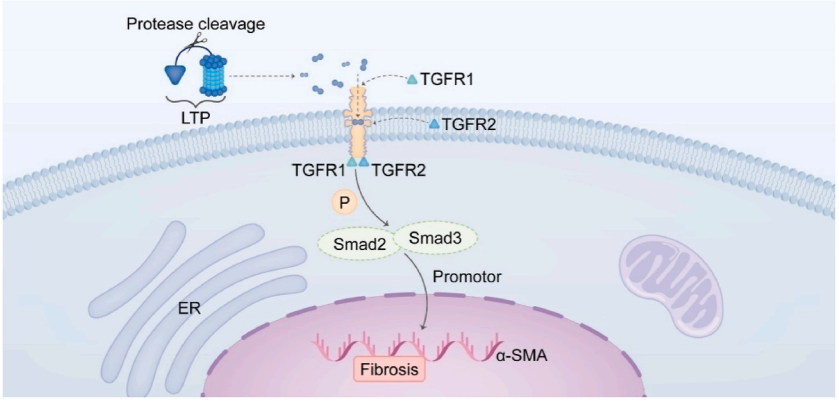

Fig. 1. The TGF-β ligand binds to heterodimeric receptors (TβRI type and II), phosphorylates and activates TβRI, initiates a signaling cascade mediated by the SMAD family of nuclear transporters (SMAD2 and 3) and raises the levels ofα-SMA thus promoting fibrosis. TGF-β, transforming growth factor β; TβR, TGF-β receptor.

The Wnt signaling pathway has become the focus of research on the activation of cell signaling pathways during adaptive cardiac remodeling [66,67]. In the context of myocardial fibrosis, at the cellular level, Wnt proteins are primarily involved in the activation of CFs. Wnt1 was shown to stimulate CF proliferation and cause an upregulation in the expression levels of the pro-fibrotic genes, including collagen I and endothelin-1 [68]. Wnt ligands are widely present in cardiomyocytes and endothelial cells [69]. Wnt ligands activate intracellular signaling by binding to receptors associated with the co-receptors LRP5/LRP6 (low density lipoprotein receptor family). Classical Wnt signaling inhibits the utilization of proteasomal β-linker proteins through the propagation of receptor activation. Moreover, it inhibits proteasomal β-cyclin utilization through the propagation of receptor activation, leading to translocation of β-cyclin to the nucleus and induction of Wnt target gene expression [70]. A recent study has shown that in the canonical Wnt/β-catenin signaling pathway, Wnt3A carried by exosomes can functionally contribute to cardiac fibrosis by activating profibrotic Wnt pathways and inducing the expressions of Wnt/β-catenin responsive genes on CFs [71,72]. In contrast to these observations, the loss of β-catenin in CFs significantly preserves cardiac function and reduces interstitial fibrosis via reduced canonical Wnt/β-catenin signaling [73]. Connexin 43 (CX43) acts as the most abundant cardiovascular gap junction in both atrial and ventricular gap junctions. A recent study has illustrated an interaction between the Wnt/β-catenin signaling pathway and CX43 [74]. CX43 is an upstream negative regulator of the canonical Wnt/β-catenin signaling pathway. Overexpression of CX43 can inhibit the transcriptional activity of β-catenin, thereby inhibiting Wnt/β-catenin signaling associated with the acquisition of cardiac differentiation and function [2]. Moreover, CX43 is also a downstream positive effector of the canonical Wnt/β-catenin pathway. For example, Wnt1 functions as a specific and potent inducer of CX43 in cardiomyocytes, leading to enhanced accumulation of the CX43 protein and the formation of functional gap junction channels [2]. Snail1, a member of the Snail family, is a specific marker of the EMT (Epithelial-mesenchymal transition)process and plays an important role in tissue fibrosis. Evidence has shown that the elevated Snail1 expression in the atrial myocardium positively correlates with the degree of AF-dependent atrial fibrosis. Moreover, the levels of canonical Wnt1, 3A, and 8A members and the levels of the noncanonical Wnt5A and Wnt11 members were significantly higher in the AF tissue. These results collectively suggested that the canonical and non-canonical Wnt signaling pathways associated with the development of EMT may contribute to the increased Snail1 expression and the development of atrial fibrosis [75,76]. Taken together, these data support an important role for β-catenin by directly modulating the canonical Wnt/β-catenin pathway and by regulating the transcription of fibrosis-related genes [77].

Apart from the canonical Wnt pathway, experimental studies have shown that the non-canonical Wnt pathway is also associated with cardiac fibrosis. Myocardial Wnt5A promotes interleukin (IL)-6 and TIMP-1(Issue Inhibitor of Metalloproteinase 1) release via the extracellular-regulated kinase 1/2 (ERK1/2) signaling in human CFs, which are markers of inflammation and fibrosis. The upregulated levels of Wnt5A that are associated with the severity of AFsupport the role of Wnt5A in contributing to cardiac fibrosis via induction of non-canonical Wnt signaling [78]. In addition, Wnt5A signaling can induce non-canonical Wnt signaling by activating Ca^{2+} cascades and its downstream transcription factor nuclear factor of activated T-cells (NFAT). NFAT activation is central to cardiac remodeling, promoting cardiac hypertrophy and fibrosis in experimental models [67]. In recent years, it has been reported that mitogen-activated protein kinases (MAPKs) play an important role in cardiac fibrosis and that conventional MAPKs, including extracellular signal-regulated kinases 1 and 2 (Erk 1/2 or p44/42), c-Jun N-terminal kinase (JNK), and the p38 isoforms (α, β, γ, and δ), can transmit signals from the cell membrane to the nucleus and regulate their expression. In the classic Wnt signaling pathway, its binding to the receptor complex inhibits the GSK-3β-dependent degradation complex, thereby disrupting the continuous synthesis of β-catenin, which acts as a transcriptional co-binding factor and initiates transcription of the Wnt pathway together with T cell factor (TCF) and lymphoid enhancer factor (LEF) transcription factors [79].

4. Crosstalk between the TGF-β and Wnt signaling pathways

Recent studies have highlighted the extensive cross-talk between the TGF-β and Wnt pathways, which are responsible for the transcription of pro-fibrotic genes [46]. TGF-β is a major fibrogenic cytokine that plays an important role in cardiac fibrosis [80]. Myocardial fibrosis has been reported to be prevented by inhibition of TGF-β. TGF-β prevents the development of diastolic dysfunction by promoting the proliferation and differentiation of fibroblasts into collagen-secreting myofibroblasts [19,81]. In a stress model, the

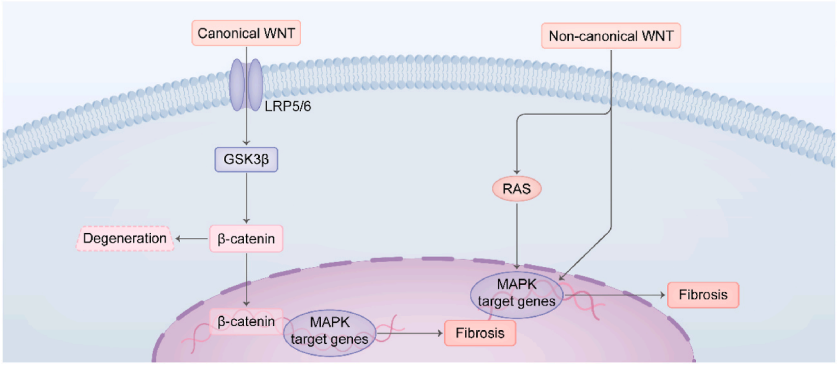

Fig. 2. It binds to LRP5/6 co-receptors to stabilizes β-catenin expression affecting fibrosis in the classical Wnt signaling pathway and to RAS/MAPK receptors in the non-classical Wnt signaling pathway. LRP, lipoprotein receptor-associated protein; MAPK, mitogen activated protein kinase.

anti-TGF-β antibody successfully inhibited fibrosis. TGF-β-SMAD signaling in CFs is also associated with the development of myocardial fibrosis. Fibroblast-specific TGF-β 1/2 or SMAD 3 deletion significantly reduced pressure overload-induced fibrosis and inhibited pressure overload-induced fibrosis [79].

Wnt signaling is an additional important signaling pathway. Non-classical Wnt5A inhibits GSK3β activity, activates ERK1/2 and JNK pathways and induces human CFs to produce pro-fibrotic IL-6, which in turn promotes fibrosis through the transcriptional activation of TGF-β [41]. Wnt5A has been associated with TGF-β-dependent fibrosis and EMT in a variety of organs and AF is closely associated with EMT and fibrotic processes[42,43,82].

To date, limited information has been reported regarding the effect of Wnt on TGF-β during fibrosis; however, experimental models have confirmed the potential negative regulation of TGF-β signaling by the classical Wnt pathway. Both TGF-β and Wnt signaling are responsible for regulating myofibroblast differentiation and cellular senescence [83]. Recent studies have shown that TGF-β controls the production of pro-fibrotic Wnt and IL-11 in CFs [39,45]. In addition, TGF-β stimulates the production and secretion of classical Wnt and activates β-catenin protein in CFs [35,46].IL-11 is a pleiotropic cytokine induced by several pro-tissue necrosis factors, including TGF-β; it is closely associated with fibroblast activation and cardiac fibrosis [47,48]. In TGF-β-activated fibroblasts, Wnt3A enhances IL-11 production and secretion. Neutralization of IL-11 activity by blocking IL-11 antibody effectively reduced the pro-fibrotic response of TGF-β and Wnt3A-activated CFs. Coactivation with nonclassical Wnt5A inhibited TGF-β-induced collagen I production compared with classical Wnt3A. In conclusion, Wnt/β-catenin signaling promoted TGF-β-mediated transformation of fibroblasts to myofibroblasts by enhancing IL-11 production [84]. It has been shown that the transformation of mouse CFs to myofibroblasts and the development of cardiac fibrosis are dependent on the delivery of IL-11 [45,85]. TGF-β can stimulate an increase in the cellular levels of IL-11 [86]. Wnt/β-catenin specifically controls TGF-β-dependent pro-fibrotic IL-11 during fibroblast transformation, thereby promoting fibroblast to myofibroblast transformation. In fibroblasts and cardiac inflammatory cells, TGF-β is involved in the production and secretion of Wnt proteins through a TAK1(Transforming Growth Factor-β-Activated Kinase 1)-dependent pathway; therefore, the classical Wnt signaling controls pro-fibrotic TGF-β responses. These data suggest that classical Wnt/β-catenin signaling plays an important role in TGF-β-mediated fibrosis [79].

5. DACT2 mediates TGF-β and Wnt/β-catenin signaling in AF

A canine model of AF has been established and it has been experimentally shown that DACT2 is both an antagonist of TGF-β signaling and an epigenetic regulator of Wnt signaling [16,17,41]; these functions play a crucial role in cardiac disease. It has been previously shown that overexpression of DACT2 inhibits TGF-β and acts as a negative regulator of the TGF-β/Nodal signaling pathway [87]. TGF-β1 has been associated with the selective development of AF; individuals with elevated levels of its expression are

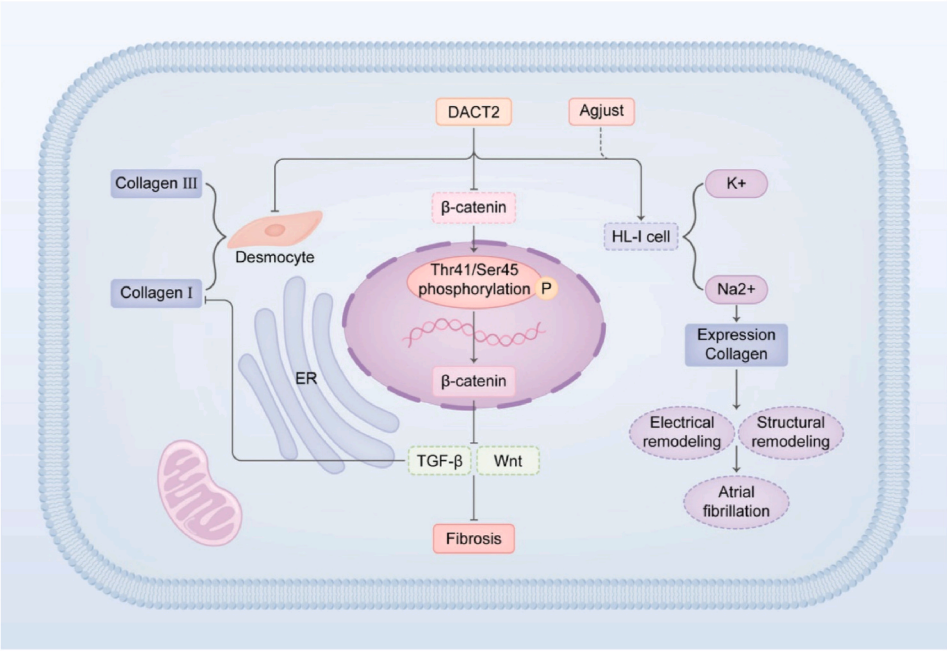

Fig. 3. DACT2 affects β-catenin accumulation by decreasing phosphorylation at Thr41/Ser45 and further inhibits the TGF-β signaling pathway in atrial fibroblasts. Moreover, DACT2 regulates collagen expression in atrial fibroblasts by modulating the levels of potassium and sodium channel proteins in HL-1 cells, which in turn regulates atrial electrical and structural remodeling. DACT2 also inhibits collagen I and III expressions and the TGF-β pathway in primary rat atrial fibroblasts, thereby inhibiting fibrosis. DACT2, Disheveled-associated antagonist of beta-catenin; TGF-β, transforming growth factor β.

susceptible to increased progression of AF [42,43]. Activation of Wnt signaling leads to myocardial hypertrophy and has been associated with left ventricular dilatation and decreased ejection fraction [44]. Moreover, DACT2 affects β-catenin accumulation by decreasing phosphorylation at Thr41/Ser45 and further inhibits the TGF-β signaling pathway in atrial fibroblasts; these experimental data suggest that the cell-specific regulations may play a role in AF. Moreover, DACT2 regulates collagen expression in atrial fibroblasts by modulating the levels of potassium and sodium channel proteins in HL-1 cells, thereby modulating atrial electrical and structural remodeling. DACT2 also inhibits fibrosis by suppressing the expression levels of collagen I and III as well as the TGF-β pathway in primary rat atrial fibroblasts(As in Fig. 3) [12,45,88].

DACT2 inhibits TGF-β and Wnt signaling pathways by suppressing the phosphorylation of β-catenin on Thr41/Ser45 in HL-1 cells, thereby attenuating the levels of fibrosis. The process of DACT2 modulation on the TGF-β and Wnt signaling pathways may reduce the occurrence of AF to a certain extent; however, the cause and effect of fibrosis and DACT2 in influencing AF and the effect of fibrosis on atrial electrical or structural remodeling remain unclear.

6. Conclusion

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and up to now, although there are more mature treatment methods, the medical expenditure is relatively high as well as the treatment modalities are relatively few. It will continue to have high morbidity and mortality in the coming years. Therefore, understanding the pathogenesis of atrial fibrillation and its developmental process is of great significance for the subsequent clinical treatment of atrial fibrillation.As described in the present study, decreased levels of DACT 2 expression are associated with AF and correlate with the severity of fibrosis in patients with heart valve disease. Atrial remodeling is an important part of the onset and progression of AF and DACT 2 can regulate electrical and structural remodeling by modulating the expression of potassium channel proteins, sodium channel proteins and atrial fibroblast collagen in atrial myocytes. The current data demonstrated the key role of Wnt and TGF-β signaling pathways in the process of cardiac fibrosis and DACT2 was demonstrated to be another important signal-regulating protein in the process of AF, which indirectly reduces atrial fibrosis by inhibiting the TGF-β and Wnt signaling pathways via inhibition of the phosphorylation of β-catenin on Thr41/Ser45 in HL-1 cells. To a certain extent, it may reduce the occurrence of AF.

In conclusion, this study summarized the effect of the DACT protein family on AF, but the roles of fibrosis and DACT2 in the development of AF remain unclear. The results of the current study are still in their infancy and may not reflect new developments and trends in a timely manner, which is a problem for the rapidly changing cardiovascular field. The results are still in their infancy, and the exploration and discovery of the causal relationship between DACT and AF is very important for the subsequent prevention and treatment of AF.

Data availability statement

Data will be made available on request.

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CRediT authorship contribution statement

Bairu Luo: Writing – original draft. **Rui Zheng:** Data curation. **Chaoqun Shi:** Methodology. **Deqing Chen:** Investigation. **Xin Jin:** Data curation. **Jian Hou:** Resources. **Guangtao Xu:** Resources. **Bo Hu:** Methodology, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A. Goette, et al., Presenting pattern of atrial fibrillation and outcomes of early rhythm control therapy, J. Am. Coll. Cardiol. 80 (4) (2022) 283–295.
[2] Z. Ai, et al., Wnt-1 regulation of connexin43 in cardiac myocytes, J. Clin. Invest. 105 (2) (2000) 161–171.
[3] M. Sagris, et al., Atrial fibrillation: pathogenesis, predisposing factors, and genetics, Int. J. Mol. Sci. 23 (1) (2021).
[4] R.S. Wijesurendra, B. Casadei, Mechanisms of atrial fibrillation, Heart 105 (24) (2019) 1860–1867.
[5] Q. Wang, et al., The crucial role of activin A/ALK4 pathway in the pathogenesis of Ang-II-induced atrial fibrosis and vulnerability to atrial fibrillation, Basic Res. Cardiol. 112 (4) (2017) 47.
[6] F. Yousefi, et al., TGF-β and WNT signaling pathways in cardiac fibrosis: non-coding RNAs come into focus, Cell Commun. Signal. 18 (1) (2020) 87.
[7] J.C. Lin, et al., Enhancement of beta-catenin in cardiomyocytes suppresses survival protein expression but promotes apoptosis and fibrosis, Cardiol. J. 24 (2) (2017) 195–205.
[8] J. Xu, et al., Atrial extracellular matrix remodeling and the maintenance of atrial fibrillation, Circulation 109 (3) (2004) 363–368.
[9] C. Knackstedt, et al., Association of echocardiographic atrial size and atrial fibrosis in a sequential model of congestive heart failure and atrial fibrillation, Cardiovasc. Pathol. 17 (5) (2008) 318–324.

[10] Y. Nakatani, et al., Tranilast prevents atrial remodeling and development of atrial fibrillation in a canine model of atrial tachycardia and left ventricular dysfunction, J. Am. Coll. Cardiol. 61 (5) (2013) 582–588.
[11] L. Zhang, et al., Dapper 1 antagonizes Wnt signaling by promoting dishevelled degradation, J. Biol. Chem. 281 (13) (2006) 8607–8612.
[12] Y. Su, et al., The evolutionally conserved activity of Dapper2 in antagonizing TGF-beta signaling, Faseb. J. 21 (3) (2007) 682–690.
[13] J. Hou, et al., DACT2 is a candidate tumor suppressor and prognostic marker in esophageal squamous cell carcinoma, Cancer Prev. Res. 6 (8) (2013) 791–800.
[14] T. Lan, et al., Diagnostic value of DACT-2 methylation in serum of prostate cancer patients, Ann. Palliat. Med. 10 (3) (2021) 2421–2428.
[15] Y.Z. Yu, et al., DACT2 is frequently methylated in human gastric cancer and methylation of DACT2 activated Wnt signaling, Am. J. Cancer Res. 4 (6) (2014) 710–724.
[16] D.H. Kim, et al., Dact2 is involved in the regulation of epithelial-mesenchymal transition, Biochem. Biophys. Res. Commun. 524 (1) (2020) 190–197.
[17] S. Wang, et al., DACT2 is a functional tumor suppressor through inhibiting Wnt/β-catenin pathway and associated with poor survival in colon cancer, Oncogene 34 (20) (2015) 2575–2585.
[18] M. Zhang, et al., Methylation of DACT2 accelerates esophageal cancer development by activating Wnt signaling, Oncotarget 7 (14) (2016) 17957–17969.
[19] J. Hou, et al., DACT2 regulates structural and electrical atrial remodeling in atrial fibrillation, J. Thorac. Dis. 12 (5) (2020) 2039–2048.
[20] J. Nickel, P. Ten Dijke, T.D. Mueller, TGF-β family co-receptor function and signaling, Acta Biochim. Biophys. Sin. 50 (1) (2018) 12–36.
[21] Y. Yang, et al., The role of TGF-β signaling pathways in cancer and its potential as a therapeutic target, Evid Based Complement Alternat Med 2021 (2021) 6675208.
[22] D. Peng, et al., Targeting TGF-β signal transduction for fibrosis and cancer therapy, Mol. Cancer 21 (1) (2022) 104.
[23] C. Larson, et al., TGF-beta: a master immune regulator, Expert Opin. Ther. Targets 24 (5) (2020) 427–438.
[24] J.B. Pawlak, G.C. Blobe, TGF-β superfamily co-receptors in cancer, Dev Dyn 251 (1) (2022) 137–163.
[25] J. Massagué, D. Sheppard, TGF-β signaling in health and disease, Cell 186 (19) (2023) 4007–4037.
[26] N.G. Frangogiannis, Cardiac fibrosis, Cardiovasc. Res. 117 (6) (2021) 1450–1488.
[27] M. Morikawa, R. Derynck, K. Miyazono, TGF-B and the TGF-β family: context-dependent roles in cell and tissue physiology, Cold Spring Harbor Perspect. Biol. 8 (5) (2016).
[28] G. Vilahur, et al., Molecular and cellular mechanisms involved in cardiac remodeling after acute myocardial infarction, J. Mol. Cell. Cardiol. 50 (3) (2011) 522–533.
[29] S. Frantz, et al., Transforming growth factor beta inhibition increases mortality and left ventricular dilatation after myocardial infarction, Basic Res. Cardiol. 103 (5) (2008) 485–492.
[30] S. Saadat, et al., Pivotal role of TGF-β/smad signaling in cardiac fibrosis: non-coding RNAs as effectual players, Front Cardiovasc Med 7 (2020) 588347.
[31] H. Khalil, et al., Fibroblast-specific TGF-β-Smad2/3 signaling underlies cardiac fibrosis, J. Clin. Invest. 127 (10) (2017) 3770–3783.
[32] X. Liu, et al., Smad7 but not Smad6 cooperates with oncogenic ras to cause malignant conversion in a mouse model for squamous cell carcinoma, Cancer Res. 63 (22) (2003) 7760–7768.
[33] F. Mannino, et al., Anti-oxidant and anti-inflammatory effects of ellagic and punicic acid in an in vitro model of cardiac fibrosis, Biomed. Pharmacother. 162 (2023) 114666.
[34] S. Aashaq, et al., TGF-β signaling: a recap of SMAD-independent and SMAD-dependent pathways, J. Cell. Physiol. 237 (1) (2022) 59–85.
[35] M. Zhao, L. Mishra, C.X. Deng, The role of TGF-β/SMAD4 signaling in cancer, Int. J. Biol. Sci. 14 (2) (2018) 111–123.
[36] G. Yang, X. Yang, Smad4-mediated TGF-beta signaling in tumorigenesis, Int. J. Biol. Sci. 6 (1) (2010) 1–8.
[37] F. Wu, et al., Signaling pathways in cancer-associated fibroblasts and targeted therapy for cancer, Signal Transduct. Targeted Ther. 6 (1) (2021) 218.
[38] T. MaruYama, W. Chen, H. Shibata, TGF-B and cancer immunotherapy, Biol. Pharm. Bull. 45 (2) (2022) 155–161.
[39] X. Dai, D. Hua, X. Lu, Roles of TGF-β in cancer hallmarks and emerging onco-therapeutic design, Expet Rev. Mol. Med. 24 (2022) e42.
[40] S.C. Hubchak, et al., Rac1 promotes TGF-beta-stimulated mesangial cell type I collagen expression through a PI3K/Akt-dependent mechanism, Am. J. Physiol. Ren. Physiol. 297 (5) (2009) F1316–F1323.
[41] K. Luo, Signaling cross talk between TGF-β/smad and other signaling pathways, Cold Spring Harbor Perspect. Biol. 9 (1) (2017).
[42] X.R. Huang, et al., Smad3 mediates cardiac inflammation and fibrosis in angiotensin II-induced hypertensive cardiac remodeling, Hypertension 55 (5) (2010) 1165–1171.
[43] K. Tzavlaki, A. Moustakas, TGF-B signaling, Biomolecules 10 (3) (2020).
[44] X.M. Meng, D.J. Nikolic-Paterson, H.Y. Lan, TGF-β: the master regulator of fibrosis, Nat. Rev. Nephrol. 12 (6) (2016) 325–338.
[45] F. Kuwahara, et al., Transforming growth factor-beta function blocking prevents myocardial fibrosis and diastolic dysfunction in pressure-overloaded rats, Circulation 106 (1) (2002) 130–135.
[46] C. Rao, et al., [Crosstalk between canonical TGF-β/Smad and Wnt/β-catenin signaling pathway], Zhejiang Da Xue Xue Bao Yi Xue Ban 42 (5) (2013) 591–596.
[47] F. Yang, et al., Angiotensin II induces connective tissue growth factor and collagen I expression via transforming growth factor-beta-dependent and -independent Smad pathways: the role of Smad3, Hypertension 54 (4) (2009) 877–884.
[48] Z.G. Ma, et al., IRX2 regulates angiotensin II-induced cardiac fibrosis by transcriptionally activating EGR1 in male mice, Nat. Commun. 14 (1) (2023) 4967.
[49] C. Humeres, et al., Smad7 effects on TGF-β and ErbB2 restrain myofibroblast activation and protect from postinfarction heart failure, J. Clin. Invest. 132 (3) (2022).
[50] Y.J. Lai, et al., miR-181b targets semaphorin 3A to mediate TGF-β-induced endothelial-mesenchymal transition related to atrial fibrillation, J. Clin. Invest. 132 (13) (2022).
[51] R. Feng, et al., Angiotensin-receptor blocker losartan alleviates atrial fibrillation in rats by downregulating frizzled 8 and inhibiting the activation of WNT-5A pathway, Clin. Exp. Pharmacol. Physiol. 50 (1) (2023) 19–27.
[52] C. Chen, et al., Ganoderma lucidum polysaccharide inhibits HSC activation and liver fibrosis via targeting inflammation, apoptosis, cell cycle, and ECM-receptor interaction mediated by TGF-β/Smad signaling, Phytomedicine 110 (2023) 154626.
[53] T. Li, et al., Neuroepithelial cell-transforming 1 promotes cardiac fibrosis via the Wnt/β-catenin signaling pathway, iScience 26 (10) (2023) 107888.
[54] T. Wei, et al., Fibroblast-to-cardiomyocyte lactate shuttle modulates hypertensive cardiac remodelling, Cell Biosci. 13 (1) (2023) 151.
[55] Y. Wu, et al., Irisin attenuates angiotensin II-induced atrial fibrillation and atrial fibrosis via LOXL2 and TGFβ1/Smad2/3 signaling pathways, Iran J Basic Med Sci 26 (6) (2023) 717–724.
[56] J. Rodríguez-Vita, et al., Angiotensin II activates the Smad pathway in vascular smooth muscle cells by a transforming growth factor-beta-independent mechanism, Circulation 111 (19) (2005) 2509–2517.
[57] F. Cao, et al., LncRNA PVT1 regulates atrial fibrosis via miR-128-3p-SP1-TGF-β1-Smad axis in atrial fibrillation, Mol Med 25 (1) (2019) 7.
[58] S. Ye, et al., Macrophage Dectin-1 mediates Ang II renal injury through neutrophil migration and TGF-β1 secretion, Cell. Mol. Life Sci. 80 (7) (2023) 184.
[59] J.C. Li, et al., Angiotensin II mediates hypertensive cardiac fibrosis via an Erbb4-IR-dependent mechanism, Mol. Ther. Nucleic Acids 33 (2023) 180–190.
[60] R. Nusse, H. Clevers, Wnt/β-Catenin signaling, disease, and emerging therapeutic modalities, Cell 169 (6) (2017) 985–999.
[61] Y. Guo, et al., Wnt/beta-catenin signaling: a promising new target for fibrosis diseases, Physiol. Res. 61 (4) (2012) 337–346.
[62] J. Liu, et al., Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities, Signal Transduct. Targeted Ther. 7 (1) (2022) 3.
[63] M. Han, et al., Dual genetic tracing reveals a unique fibroblast subpopulation modulating cardiac fibrosis, Nat. Genet. 55 (4) (2023) 665–678.
[64] C. Wolke, E. Antileo, U. Lendeckel, WNT signaling in atrial fibrillation, Exp Biol Med (Maywood) 246 (9) (2021) 1112–1120.
[65] R.J. Garriock, et al., Census of vertebrate Wnt genes: isolation and developmental expression of Xenopus Wnt2, Wnt3, Wnt9a, Wnt9b, Wnt10a, and Wnt16, Dev Dyn 236 (5) (2007) 1249–1258.
[66] J.J. Edwards, et al., Noncanonical WNT activation in human right ventricular heart failure, Front Cardiovasc Med 7 (2020) 582407.
[67] A. Abraityte, et al., Wnt5a is associated with right ventricular dysfunction and adverse outcome in dilated cardiomyopathy, Sci. Rep. 7 (1) (2017) 3490.
[68] J. Duan, et al., Wnt1/βcatenin injury response activates the epicardium and cardiac fibroblasts to promote cardiac repair, Embo j 31 (2) (2012) 429–442.

[69] I. Akoumianakis, et al., Adipose tissue-derived WNT5A regulates vascular redox signaling in obesity via USP17/RAC1-mediated activation of NADPH oxidases, Sci. Transl. Med. 11 (510) (2019).
[70] M. Waluś-Miarka, A. Polus, B. Idzior-Waluś, Aortic valve and arterial calcification in patients with familial hypercholesterolemia, Kardiol. Pol. 82 (2) (2024) 144–155.
[71] E. Działo, et al., WNT3a and WNT5a transported by exosomes activate WNT signaling pathways in human cardiac fibroblasts, Int. J. Mol. Sci. 20 (6) (2019).
[72] Z. Azadian, et al., Computational and in vitro validation of cardiogenic induction of quercetin on adipose-derived mesenchymal stromal cells through the inhibition of Wnt and non-Smad-dependent TGF-β pathways, J. Cell. Biochem. 123 (2) (2022) 450–468.
[73] F.L. Xiang, M. Fang, K.E. Yutzey, Loss of β-catenin in resident cardiac fibroblasts attenuates fibrosis induced by pressure overload in mice, Nat. Commun. 8 (1) (2017) 712.
[74] S.F. Fostok, et al., Gap junctions and Wnt signaling in the mammary gland: a cross-talk? J. Mammary Gland Biol. Neoplasia 24 (1) (2019) 17–38.
[75] F. Guo, et al., Snail1 is positively correlated with atrial fibrosis in patients with atrial fibrillation and rheumatic heart disease, Exp. Ther. Med. 14 (5) (2017) 4231–4237.
[76] S.R. Nayakanti, et al., Targeting wnt-ß-catenin-FOSL signaling ameliorates right ventricular remodeling, Circ. Res. 132 (11) (2023) 1468–1485.
[77] S. Al-Aidarous, et al., Management of arrhythmogenic right ventricular cardiomyopathy, Heart 110 (3) (2024) 156–162.
[78] A. Abraityte, et al., Wnt5a is elevated in heart failure and affects cardiac fibroblast function, J. Mol. Med. (Berl.) 95 (7) (2017) 767–777.
[79] E. Działo, K. Tkacz, P. Błyszczuk, Crosstalk between the TGF-β and WNT signalling pathways during cardiac fibrogenesis, Acta Biochim. Pol. 65 (3) (2018) 341–349.
[80] A. Leask, Getting to the heart of the matter: new insights into cardiac fibrosis, Circ. Res. 116 (7) (2015) 1269–1276.
[81] L. Meng, et al., NPRC deletion attenuates cardiac fibrosis in diabetic mice by activating PKA/PKG and inhibiting TGF-β1/Smad pathways, Sci. Adv. 9 (31) (2023) eadd4222.
[82] Q. Lv, et al., Pirfenidone alleviates pulmonary fibrosis in vitro and in vivo through regulating Wnt/GSK-3β/β-catenin and TGF-β1/Smad2/3 signaling pathways, Mol Med 26 (1) (2020) 49.
[83] T. Kadota, et al., Human bronchial epithelial cell-derived extracellular vesicle therapy for pulmonary fibrosis via inhibition of TGF-β-WNT crosstalk, J. Extracell. Vesicles 10 (10) (2021) e12124.
[84] E. Działo, et al., WNT/β-Catenin signaling promotes TGF-β-mediated activation of human cardiac fibroblasts by enhancing IL-11 production, Int. J. Mol. Sci. 22 (18) (2021).
[85] J.S. Waxman, et al., Zebrafish Dapper1 and Dapper2 play distinct roles in Wnt-mediated developmental processes, Development 131 (23) (2004) 5909–5921.
[86] L.F. Jiang, et al., The effect of hepatic stellate cell derived-IL-11 on hepatocyte injury in hepatic fibrosis, Life Sci. 330 (2023) 121974.
[87] Y. Su, et al., The evolutionally conserved activity of Dapper2 in antagonizing TGF-beta signaling, Faseb j 21 (3) (2007) 682–690.
[88] S. Huang, et al., Mechanism of dact2 gene inhibiting the occurrence and development of liver fibrosis, Cell Mol Biol (Noisy-le-grand) 67 (6) (2022) 33–39.