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Adiponectin Therapeutics for Fibrotic Diseases: Current Knowledge and Future Perspectives

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Review

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Abstract

Background: Fibrosis is characterised by the pathological accumulation of extracellular matrix components and represents both a driver and consequence of chronic tissue injury across multiple organs and is a major contributor to global morbidity and mortality. Despite this substantial clinical burden, approved antifibrotic therapies remain limited. Adiponectin, an adipokine secreted predominantly by adipocytes, is an endogenous antifibrotic mediator with potential therapeutic applications.

Methods: This review examines the pathobiology of fibrosis, the molecular mechanisms underlying adiponectin-mediated antifibrotic effects, and current advances in adiponectin-based therapeutic development. Evidence from preclinical studies across multiple organ system is discussed, with a focus on adiponectin signaling pathways and receptor agonists.

Results: Adiponectin actsprimarily through its cognate receptors AdipoR1 and AdipoR2, adiponectin suppresses key profibrotic signalling cascades, including TGF-β/Smad, NF-κB, Wnt/β-catenin, Notch and platelet-derived growth factor pathways, while simultaneously promoting anti-inflammatory, antioxidant and cytoprotective responses. Preclinical studies demonstrate that adiponectin deficiency exacerbates fibrotic remodelling in the liver, lungs, heart, kidneys, skeletal muscle and skin, whereas genetic or pharmacological augmentation of adiponectin signalling attenuates fibrosis progression. Two adiponectin receptor agonists, the small molecule AdipoRON and the peptide mimetic ALY688, have shown promising antifibrotic efficacy across multiple disease models.

Conclusions: Adiponectin signaling represents a promising therapeutic strategy for the prevention and treatment across multiple organs. Further investigation is needed to address current challenges and establish the safety, efficacy, and translational potential of adiponectin-based therapies in clinical settings.

Introduction

Fibrosis is a multifactorial pathological process characterised by excessive extracellular matrix (ECM) deposition and tissue scarring that can ultimately lead to organ dysfunction and failure (Ref. 1). Although fibrosis initially serves as a protective wound-healing response following tissue injury, persistent inflammation, repeated injury and metabolic stress cause fibroblasts to continuously differentiate into myofibroblasts that can drive maladaptive fibrotic remodelling by depositing excessive ECM in the tissue (Refs 2, 3). This process affects virtually every organ system, including the liver, lungs, heart, kidneys, skin and skeletal muscle, and collectively accounts for a substantial proportion of global morbidity and mortality (Ref. 1).

Many organs share common pathogenic mechanisms of fibrosis that contribute to disease progression. Transforming growth factor-beta (TGF-β) is widely recognised as a central regulator of fibrogenesis, promoting fibroblast activation, myofibroblast differentiation and excessive ECM deposition through both canonical Smad-dependent and non-canonical signalling pathways (Refs 4–11). Persistent inflammatory signalling further amplifies fibrotic responses through increases in cytokines and chemokines including TNF-α, IL-1β, IL-6, IL-13, IL-4 and CCL2, which promote immune cell recruitment and sustain fibroblast activation (Refs 12, 13, 14). Additional pathways including platelet-derived growth factor (PDGF), Wnt/β-catenin, Notch signalling, oxidative stress and hypoxia-inducible factor (HIF)-mediated responses contribute to fibroblast proliferation, epithelial-to-mesenchymal transition (EMT) and pathological ECM remodelling (Refs 15–22). Extensive crosstalk among these pathways establishes self-reinforcing profibrotic networks that ultimately drive tissue stiffening, architectural disruption and progressive organ dysfunction (Ref. 9). Despite this mechanistic clarity, approved antifibrotic pharmacotherapy remains confined to a few agents, including nintedanib and pirfenidone for lung fibrosis and resmetirom for liver fibrosis, none of which halt or reverse fibrotic progression, and no approved effective anti-fibrotic therapy exists for cardiac, renal, skeletal muscle or dermal fibrosis (Refs 23, 24, 25).

Among the endogenous regulators of fibrotic remodelling, adiponectin has emerged as a promising antifibrotic mediator. Adiponectin is a 244-amino acid peptide hormone originally

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characterised as an adipocyte-derived secretory factor (Ref. 26). Structurally, adiponectin contains an N-terminal signal sequence, a variable region, a collagenous domain and a C-terminal globular domain (Ref. 27). The protein circulates in distinct oligomeric isoforms: low molecular weight (LMW) trimers, medium molecular weight (MMW) hexamers and high molecular weight (HMW) multimers (Ref. 27). The trimeric form represents the basic structural unit, which assembles into hexameric MMW isoforms, and further oligomerisation of MMW adiponectin yields HMW complexes, which are considered the most biologically active form (Ref. 28).

Adiponectin confers its biological effects through two cognate receptors, adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2), as well as the glycosylphosphatidylinositol-anchored protein T-cadherin (Ref. 29). AdipoR1 and AdipoR2 are seven-transmembrane domain proteins that are structurally and functionally distinct from canonical G-protein-coupled receptors (GPCRs), with an intracellular N-terminus and extracellular C-terminus (Ref. 30). Both receptors are expressed in a variety of tissues at varying levels; AdipoR1 is most highly expressed in skeletal muscle and heart, whereas AdipoR2 is predominantly expressed in the liver (Ref. 31). Upon receptor engagement, adiponectin activates distinct but overlapping signalling pathways. AdipoR1 primarily stimulates AMP-activated protein kinase (AMPK) and AdipoR2 preferentially activates peroxisome proliferator–activated receptor alpha (PPAR-α) (Ref. 31).

AMPK activation by adiponectin antagonises TGF-β/Smad, Wnt/β-catenin and PDGF signalling simultaneously, thereby downregulating transcription of profibrotic target genes and curtailing myofibroblast activation and ECM accumulation, providing broad-spectrum antifibrotic coverage (Refs 32, 33, 34). Complementing its direct suppression of profibrotic signalling adiponectin also attenuates the inflammatory responses, including nuclear factor kappa B (NF-κB), leading to reduced expression of cytokines such as TNF-α and IL-6 that amplify fibrogenesis, while simultaneously promoting anti-inflammatory mediators such as IL-10 (Ref. 35). At the cytoprotective level, adiponectin guards against apoptosis and necroptosis in parenchymal cells, thereby limiting the damage signals that initiate and sustain wound-healing cascades. This is mechanistically linked to adiponectin's capacity to activate autophagy and mitophagy, which remove dysfunctional organelles and damaged proteins, preserving cellular homeostasis and reducing the pro-inflammatory cell death that feeds fibrotic signalling (Ref. 36). Beyond these intracellular mechanisms, adiponectin also operates through intercellular communication, and emerging evidence highlights its role in modulating extracellular vesicle-mediated cell-to-cell crosstalk, with adiponectin signalling influencing its cargo (Ref. 37). This multifaceted antifibrotic profile positions adiponectin and its mimetics as an attractive therapeutic target across fibrosis-related pathologies. Although the antifibrotic actions of adiponectin have been discussed previously, an updated synthesis integrating its effects across multiple fibrotic diseases with recent advances in adiponectin-targeted therapeutic development is lacking. This review addresses this gap by providing a cross-organ perspective on the conserved and tissue-specific mechanisms through which adiponectin modulates fibrosis in the liver, lung, heart, kidney, skin and skeletal muscle, while also considering age-associated fibrosis. In addition, we evaluate recent progress in adiponectin-based therapeutic strategies, with particular emphasis on adiponectin receptor agonists, including AdipoRON and ALY688 and critically discuss the translational challenges that may influence their clinical development, including interindividual variability in adiponectin signalling, biomarker development, the adiponectin paradox and clinical trial design. By integrating mechanistic, preclinical and emerging translational evidence, this review aims to provide an updated framework for understanding the therapeutic potential of targeting adiponectin signalling across fibrotic diseases. The common cellular and molecular mechanisms through which adiponectin attenuates fibrosis across multiple organs are summarised in Figure 1.

Adiponectin's role in mitigating fibrosis across various organ systems

Hepatic fibrosis

Pathogenesis of hepatic fibrosis

Fibrosis is a conserved wound-healing and tissue repair response that occurs across multiple organ systems. However, when injury is chronic or repair mechanisms become dysregulated, fibrosis can become pathological and lead to progressive organ dysfunction. In the liver, hepatic fibrosis commonly arises from chronic insults such as viral hepatitis, alcohol use or metabolic dysfunction-associated steatotic liver disease (MASLD), leading to excessive ECM accumulation that disrupts hepatic architecture and impedes blood and bile flow (Ref. 38). Prolonged hepatic fibrosis culminates in cirrhosis, which ranks as the eleventh leading cause of death globally (Ref. 39). Hepatic stellate cells (HSCs) occupy a central role in liver fibrogenesis: quiescent HSCs reside in the Space of Disse and store retinyl esters, but upon activation by reactive oxygen species, inflammatory cytokines or TGF-β, they transdifferentiate into myofibroblasts that secrete excessive collagen and ECM proteins, thereby driving fibrotic remodelling (Ref. 40).

Role of adiponectin in hepatic fibrosis

Numerous studies have demonstrated that low circulating adiponectin levels are associated with the development and progression of Nonalcoholic fatty liver diseases (NAFLD) and Nonalcoholic steatohepatitis (NASH) (Refs 41, 42, 43). Quantification of serum adiponectin in patients with different degrees of NAFLD concluded that lower levels were associated with early fibrosis and worse inflammation (Ref. 44). These clinical findings have been corroborated in animal models: adiponectin-deficient mice fed a high-fat diet are more susceptible to developing hepatic steatosis and metabolic dysfunction compared to wild-type controls (Ref. 45). A recent study generated HSC-specific adiponectin overexpression and null mouse models, demonstrating that HSC-specific adiponectin overexpression reduces liver fibrosis, whereas HSC-specific adiponectin elimination accelerates fibrosis progression, identifying a local adiponectin-PPARγ axis in HSCs that operates independently of circulating adiponectin (Ref. 46).

Mechanistically, adiponectin reduces TGF-β action in activated HSCs via AMPK-dependent signalling (Ref. 47). HSCs treated with adiponectin exhibit lower degrees of activation, and adiponectin-activated AMPK signalling in HSCs antagonises TGF-β signalling, ultimately suppressing fibrogenesis (Refs 48, 49). Additionally, adiponectin inhibits the TLR-4 signalling pathway in Kupffer cells, the resident macrophages of the liver, thereby preventing HSC proliferation and migration (Ref. 50). Studies using adiponectin knockout mice demonstrated that adiponectin deficiency enhanced NF-κB signalling in Kupffer cells and increased the secretion of pro-inflammatory cytokines, including TNF-α and IL-6, whereas adiponectin treatment suppressed inflammatory signalling and exerted anti-inflammatory effects in these cells (Refs 51–54). Together, these findings demonstrate that adiponectin suppresses

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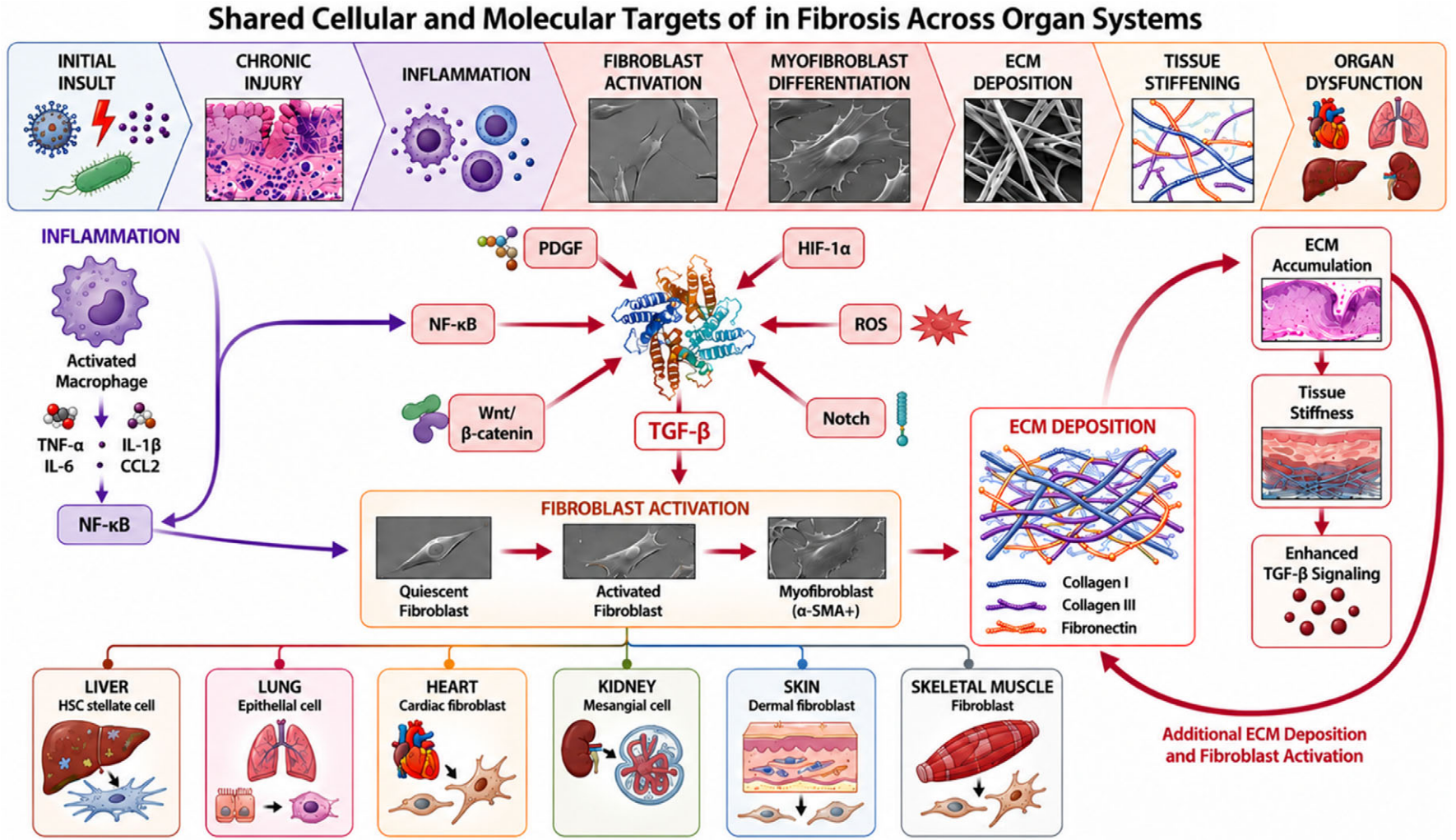


Figure 1. Schematic illustration of the conserved cellular and molecular mechanisms that drive fibrosis across multiple organ systems. Following chronic tissue injury, persistent inflammation promotes fibroblast activation and differentiation into α-smooth muscle actin (α-SMA)-positive myofibroblasts, resulting in excessive extracellular matrix (ECM) deposition, tissue stiffening and progressive organ dysfunction. Central profibrotic pathways include transforming growth factor-β (TGF-β), nuclear factor kappa B (NF-κB), platelet-derived growth factor (PDGF), Wnt/β-catenin, Notch signalling, hypoxia-inducible factor-1α (HIF-1α) and oxidative stress mediated by reactive oxygen species (ROS). Collectively, these interconnected pathways represent the major molecular and cellular processes implicated in fibrosis and constitute key therapeutic targets of adiponectin and adiponectin receptor agonists across the liver, lung, heart, kidney, skin and skeletal muscle. This schematic was generated using FigureLab AI (https://chat.figurelabs.ai/) in July 2026 based on author-developed prompts describing the biological mechanisms of fibrosis. The generated illustration was subsequently reviewed, edited and scientifically validated by the authors prior to publication.

pro-inflammatory and profibrotic signalling in both HSCs and Kupffer cells, positioning it as a key protective factor against hepatic fibrosis.

Pulmonary fibrosis

Pathogenesis of pulmonary fibrosis

Similar to hepatic fibrosis, pulmonary fibrosis is characterised by excessive ECM accumulation and progressive tissue remodelling (Ref. 55). In the lung, fibrotic changes primarily affect the alveolar walls, leading to thickening and stiffening of the pulmonary interstitium, disruption of normal alveolar architecture and impaired gas exchange (Refs 56, 57). As fibrosis progresses, reduced pulmonary compliance and impaired alveolar ventilation compromise oxygen uptake and carbon dioxide elimination, ultimately resulting in respiratory insufficiency (Ref. 56). Idiopathic pulmonary fibrosis (IPF), the most extensively studied fibrotic lung disease, exemplifies these pathological changes and is associated with a poor prognosis, with a median survival of only 3–5 years following diagnosis (Ref. 58).

Role of adiponectin in pulmonary fibrosis

Circulating adiponectin levels are reduced in patients with IPF and are inversely associated with the extent of pulmonary fibrosis, and adiponectin has been proposed as a potential prognostic biomarker for fibrotic interstitial lung diseases (Ref. 59). In chronic obstructive pulmonary disease (COPD), a mouse model established by tobacco smoke exposure demonstrated increased adiponectin production in bronchoalveolar lavage fluid and airway epithelial cells, an observation that, while initially paradoxical, likely reflects an adaptive compensatory response to counteract inflammation (Ref. 60).

Adiponectin exerts antifibrotic effects in the lungs through multiple mechanisms. Treatment with adiponectin inhibited EMT in alveolar epithelial cells, thereby preserving the epithelial phenotype and preventing transformation into collagen-secreting cells (Ref. 61). In a bleomycin-induced model of lung fibrosis, adiponectin treatment reduced α-SMA expression and type I collagen deposition. Further in vitro analyses demonstrated that adiponectin altered fibroblast signalling by shifting TGF-β pathways toward a less fibrogenic phenotype (Ref. 62). The study also showed that adiponectin inhibited NF-κB-mediated activation of lung fibroblasts, thereby attenuating inflammation-driven fibrotic responses. Collectively, these data support adiponectin as an endogenous antifibrotic mediator in the lungs that operates through suppression of EMT, myofibroblast differentiation and inflammatory signalling.

Cardiac fibrosis

Pathogenesis of cardiac fibrosis

In the heart, fibrosis contributes to both structural and functional remodelling of the myocardium (Ref. 63). Although cardiomyocytes account for the majority of myocardial volume, cardiac fibroblasts represent a substantial proportion of cardiac cells, comprising approximately 20%–60% of the total cardiac cell population by number, with their abundance increasing during development, ageing and disease (Ref. 64). As the primary resident mesenchymal cells of the myocardium, cardiac fibroblasts are responsible for maintaining ECM homeostasis, which provides structural support to cardiac tissue and regulates cellular communication, mechanical signalling and tissue integrity (Ref. 65). Consequently, alterations in ECM composition or turnover can adversely affect cardiac function by increasing myocardial stiffness and impairing contractile performance (Refs 66–69). Following cardiac injury, including mechanical stress, pressure overload associated with hypertension or ischaemic injury after myocardial infarction, cardiac fibroblasts become activated and differentiate into myofibroblasts (Refs 70–73). Initially, this response serves a reparative role by preserving structural integrity and facilitating wound healing. However, persistent injury leads to excessive ECM accumulation by myofibroblasts that promotes maladaptive interstitial and replacement fibrosis, ultimately contributing to adverse cardiac remodelling, impaired ventricular function, and heart failure (Ref. 74).

Role of adiponectin in cardiac fibrosis

Low levels of circulating adiponectin are consistently associated with increased cardiac fibrosis and adverse remodelling across multiple cardiovascular pathologies. In ischaemic heart disease, hypoadiponectinemia results in worsened inflammation and collagen accumulation, further compromising the function of the infarcted heart (Ref. 75). A prospective human study further found that hypoadiponectinemia itself is an independent risk factor for the development of hypertension (Ref. 76). In diabetic cardiomyopathy, characterised by metabolic dysfunction and low adiponectin levels, restoration of adiponectin signalling stabilises energy homeostasis and reduces cell death (Refs 77, 78). In heart failure, low adiponectin levels are associated with cardiac hypertrophy and increased fibrosis; in an aldosterone-induced model of heart failure, adiponectin transgenic mice had improved left ventricular function despite hypertrophy compared to wild-type mice (Ref. 79). In a murine model of angiotensin II-induced hypertensive heart disease, adiponectin knockout mice developed more severe cardiac fibrosis and inflammation than wild-type controls, accompanied by upregulation of collagen I, α-SMA, IL-1β and TNF-α (Ref. 36). They showed that adiponectin activated autophagy in macrophages and inhibited NFκB signalling and that it increased secretion of anti-inflammatory cytokines including IL-10 through the AMPK pathway, overall reducing the extent of cardiac fibrosis. Together, these studies suggest that adiponectin mitigates cardiac fibrosis through coordinated regulation of inflammatory, metabolic and profibrotic signalling pathways.

Renal fibrosis

Pathogenesis of renal fibrosis

Renal fibrosis is a hallmark feature of chronic kidney disease (CKD) and represents the final common pathway leading to progressive loss of kidney function and ultimately end-stage renal disease (ESRD) (Ref. 80). Despite the diverse etiologies of CKD, including diabetic nephropathy, glomerulonephritis and obstructive nephropathy, these conditions converge on shared fibrogenic mechanisms characterised by persistent inflammation, activation of fibroblasts and myofibroblasts and excessive deposition of ECM proteins (Ref. 81). In addition, renal mesangial cells, specialised structural cells within the glomerulus, contribute significantly to disease progression. Following kidney injury, particularly in conditions such as diabetes and lupus nephritis, mesangial cells become activated and undergo excessive proliferation, leading to increased production of ECM proteins and pro-inflammatory cytokines that promote glomerulosclerosis and fibrotic remodelling (Ref. 82). The resulting tubulointerstitial fibrosis and glomerulosclerosis disrupt normal renal architecture, impair nephron function and contribute to the irreversible decline in kidney function (Ref. 83).

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Role of adiponectin in renal fibrosis

Reduced adiponectin levels have been associated with increased renal fibrosis and loss of kidney function in both CKD and diabetic nephropathy. In diabetic nephropathy, hypoadiponectinaemia causes increased mesangial cell expansion and ECM accumulation within glomeruli (Ref. 84). In a mouse model of kidney disease, adiponectin deficiency resulted in worsened glomerular hypertrophy, fibrosis and overall kidney function, with elevated levels of TNFα, TGF-β and collagen. Restoration of adiponectin via adenoviral delivery improved overall kidney function and decreased inflammatory and fibrotic markers (Ref. 85). Adiponectin can also inhibit synthesis of ECM components in mesangial cells, slowing the progression of renal fibrosis (Ref. 32).

Adiponectin modulates renal fibrotic pathways through several complementary mechanisms. It suppresses TGF-β signalling and EMT in renal epithelial cells, thereby preventing renal fibrosis in hypertensive mice (Ref. 86). In glomerular tissue, adiponectin mitigates mesangial cell expansion via AMPK signalling; using human mesangial cells, it was shown that adiponectin prevented PDGF-induced mesangial cell expansion through an AMPK–mTOR pathway (Ref. 34). By curtailing TGF-β signalling, inhibiting mesangial cell expansion and stabilising epithelial cells, adiponectin modulates the fibrotic remodelling that characterises CKD and diabetic nephropathy.

Skeletal muscle fibrosis

Pathogenesis of skeletal muscle fibrosis

In skeletal muscle, fibrosis is a prominent pathological feature of disorders such as Duchenne muscular dystrophy (DMD) (Ref. 87). Excessive deposition of ECM components, particularly collagen, progressively replaces functional muscle tissue, disrupting normal muscle architecture and reducing tissue elasticity (Ref. 88). This pathological accumulation of ECM impairs force transmission, limits muscle regeneration by creating a hostile microenvironment for satellite cells and restricts nutrient and oxygen diffusion (Ref. 89). Consequently, skeletal muscle fibrosis contributes directly to muscle weakness, loss of contractile function and progressive functional decline observed in DMD and other chronic muscle disorders (Ref. 87).

Role of adiponectin in skeletal muscle fibrosis

Emerging evidence suggests that low adiponectin levels may contribute to the progression of skeletal muscle fibrosis and exacerbate the dystrophic phenotype in DMD (Ref. 90). In the *mdx* mouse model of DMD, adiponectin deficiency was associated with decreased muscle strength, increased muscle damage and heightened inflammatory responses (Ref. 90). Conversely, adiponectin administration attenuated disease severity by reducing the expression of pro-inflammatory mediators and suppressing NF-κB activity, while simultaneously promoting the expression of myogenic markers involved in muscle repair and regeneration (Ref. 91). Similarly, studies using the *D2.mdx* mouse model demonstrated that activation of adiponectin signalling mitigated early diaphragm fibrosis through the AMPK–PGC-1α pathway, leading to inhibition of both NF-κB-mediated inflammation and TGF-β-driven fibrotic signalling (Refs 92, 93). Given the central roles of chronic inflammation and excessive ECM deposition in DMD progression, these findings highlight adiponectin as a key regulator of muscle homeostasis and suggest that adiponectin-based therapies may represent a promising strategy for limiting fibrosis and preserving muscle function, particularly during the early stages of disease development.

Skin fibrosis

Pathogenesis of skin fibrosis in systemic sclerosis

Fibrosis also plays a central role in autoimmune conditions such as systemic sclerosis (scleroderma; SSc), a chronic multisystem autoimmune disease. The pathogenesis of SSc is complex and involves an interplay between vascular injury, inflammation and fibrotic remodelling (Ref. 94). Early endothelial cell damage triggers activation of both innate and adaptive immune responses, leading to the production of cytokines, chemokines and autoantibodies that promote fibroblast activation (Refs 95, 96). Activated fibroblasts subsequently differentiate into myofibroblasts, which secrete excessive amounts of collagen and other ECM components, resulting in progressive thickening, stiffening and loss of elasticity of the skin and connective tissues (Ref. 97). Although cutaneous fibrosis is a defining feature of SSc, fibrotic remodelling frequently extends to internal organs, including the lungs, heart, kidneys and gastrointestinal tract, where it contributes significantly to disease morbidity and mortality (Ref. 98).

Role of adiponectin in skin fibrosis

In SSc, circulating adiponectin levels are frequently reduced and exhibit an inverse correlation with the severity of skin fibrosis in affected patients (Ref. 99). Experimental studies have demonstrated that adiponectin-deficient mice develop an exaggerated dermal fibrotic response, whereas transgenic mice with constitutively elevated adiponectin levels are protected against both skin and peritoneal fibrosis and exhibit expansion of dermal white adipose tissue (Ref. 100). Using a murine model of SSc, it was shown that the adiponectin signalling improved dermal fibrosis via attenuated fibroblast activation and inhibition of EMT (Ref. 101). Furthermore, in vitro studies revealed that adiponectin counteracted the profibrotic effects of TGF-β in cultured fibroblasts and reduced fibrotic responses in three-dimensional human skin equivalents, partly through inhibition of focal adhesion kinase (FAK) signalling, a cytoplasmic tyrosine kinase that acts as a central hub linking extracellular matrix-derived mechanical signals to intracellular profibrotic pathways (Ref. 101). Collectively, these findings identify dysregulated adiponectin signalling as an important contributor to skin fibrosis and highlight the therapeutic potential of restoring adiponectin activity as a novel strategy for the treatment of SSc.

Age-related fibrosis

Fibrosis as a hallmark of ageing

Beyond organ-specific and autoimmune disorders, fibrosis is increasingly recognised as an important feature of biological ageing and a common contributor to age-related organ dysfunction. In recent years, the term ‘fibroageing’ has been proposed to describe the increased propensity for fibrosis associated with ageing (Ref. 102). Central to this concept is the ECM, which undergoes age-related modifications including glycation, crosslinking and accumulation, resulting in increased matrix stiffness (Ref. 103). These alterations not only disrupt normal tissue architecture and function but also reinforce profibrotic signalling through positive feedback mechanisms, further promoting ECM deposition. Furthermore, increased matrix stiffness has been implicated in several hallmarks of ageing, including cellular senescence and mitochondrial dysfunction, suggesting that ECM remodelling may represent a key mechanistic link between ageing, fibrosis and age-associated tissue decline (Ref. 102).

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Role of adiponectin in age-associated fibrosis

Given its role in mitigating fibrosis, adiponectin has garnered considerable interest as a therapeutic target for age-related diseases. In a mouse model of ageing combined with high-fat diet feeding, adiponectin knockout mice displayed accelerated ageing, worse glucose and lipid metabolism and shorter lifespan on both chow and high-fat diet. In contrast, adiponectin transgenic mice had improved metabolism, less age-related inflammation and fibrosis and enhanced lifespan (Ref. 104). In geriatric *mdx* mice (14 months of age), AdipoRon treatment reversed cardiac fibrosis, hypertrophy and oxidative stress through activation of the AdipoR1/CaMKK2/AMPK signalling axis (Ref. 105). Similarly, chronic AdipoRon administration in aged wild-type mice improved skeletal muscle function and enhanced mitochondrial capacity via AMPK/PGC-1α activation (Ref. 106). Collectively, these findings demonstrate that pharmacological activation of adiponectin receptors may help preserve tissue homeostasis, prevent age-related fibrosis and improve overall healthspan and lifespan.

Collectively, the evidence reviewed across hepatic, pulmonary, cardiac, renal, cutaneous, skeletal muscle and age-associated fibrosis indicates that adiponectin exerts broadly conserved antifibrotic effects despite the diverse cellular and molecular mechanisms underlying fibrosis in different tissues. Across organ systems, adiponectin consistently suppresses fibroblast and myofibroblast activation, attenuates TGF-β-mediated profibrotic signalling, reduces inflammation and oxidative stress and limits pathological ECM deposition. These findings support the concept that adiponectin functions as a key endogenous regulator of tissue remodelling and fibrosis. The consistent protective effects observed in both experimental and preclinical models highlight the therapeutic potential of targeting adiponectin signalling pathways, providing a strong rationale for the development of adiponectin-based interventions for the treatment of fibrotic diseases. The major antifibrotic actions of adiponectin across different organ systems are summarised in Figure 2.

Adiponectin-based therapeutic development

Pharmacological and lifestyle strategies to elevate adiponectin

Given the broad antifibrotic effects of adiponectin across multiple organ systems, considerable interest has focused on therapeutic strategies aimed at enhancing adiponectin signalling. Several

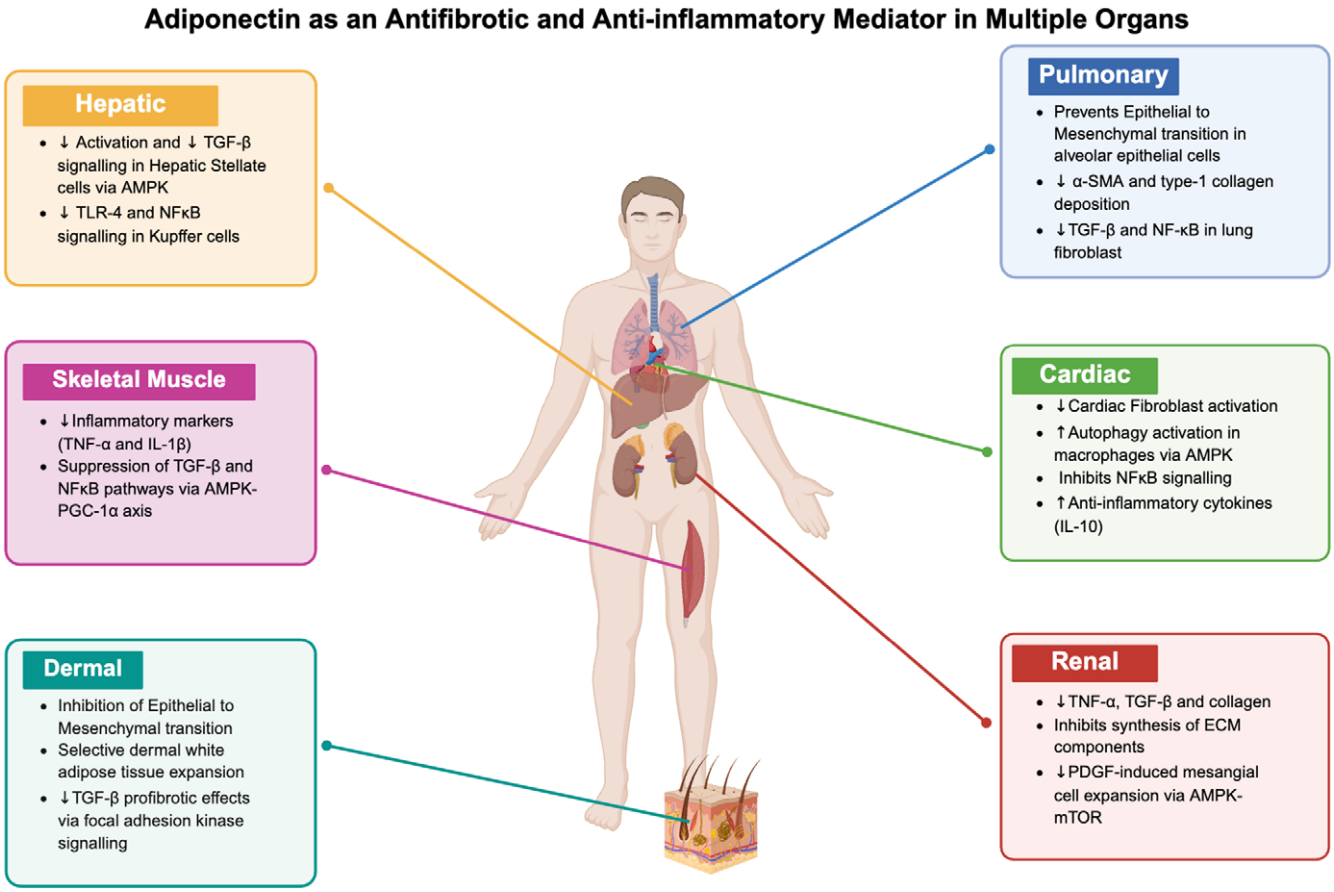


Figure 2. Summary of the conserved antifibrotic and anti-inflammatory actions of adiponectin across major fibrotic diseases. In the liver, adiponectin suppresses hepatic stellate cell activation through AMP-activated protein kinase (AMPK) signalling and inhibits Toll-like receptor 4 (TLR4)- and NF-κB-mediated inflammatory responses in Kupffer cells. In the lung, adiponectin inhibits epithelial-to-mesenchymal transition (EMT), reduces α-smooth muscle actin (α-SMA) expression and collagen deposition and suppresses TGF-β and NF-κB signalling. In the heart, adiponectin attenuates cardiac fibroblast activation, promotes macrophage autophagy via AMPK, suppresses NF-κB signalling and enhances anti-inflammatory cytokine production. In the kidney, adiponectin inhibits TGF-β signalling, reduces extracellular matrix synthesis and limits platelet-derived growth factor (PDGF)-induced mesangial cell proliferation through AMPK–mTOR signalling. In skeletal muscle, adiponectin suppresses inflammatory cytokine production and inhibits NF-κB signalling through activation of the AMPK–PGC-1α pathway. In the skin, adiponectin inhibits epithelial-to-mesenchymal transition, attenuates fibroblast activation, promotes dermal white adipose tissue expansion and suppresses focal adhesion kinase (FAK)-dependent profibrotic signalling. Collectively, these actions position adiponectin as a conserved endogenous regulator of fibrosis across diverse tissues. Created in BioRender.

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pharmacological agents have been shown to increase circulating adiponectin levels. Among these, PPAR agonists, including thiazolidinediones, have been consistently shown to elevate adiponectin levels in humans (Ref. 107). Similarly, metformin, a first-line therapy for type 2 diabetes, has been reported to increase adiponectin levels, which may partly underlie its pleiotropic metabolic and anti-inflammatory effects (Ref. 108). In addition to pharmacological approaches, lifestyle interventions have also been shown to modulate adiponectin signalling. Aerobic exercise has been associated with increased circulating adiponectin levels in prediabetic and diabetic individuals, whereas resistance training alone appears to have less consistent effects (Ref. 109). Likewise, adherence to a Mediterranean diet has been linked to enhanced adiponectin concentrations and improved metabolic health (Ref. 110). While strategies that increase circulating adiponectin levels have shown promise, the therapeutic efficacy may depend more on enhancing adiponectin receptor expression and downstream signalling than on increasing circulating adiponectin concentrations alone (Ref. 111).

Adiponectin receptor agonists

Increasing attention has focused on the development of therapies that directly target adiponectin receptor signalling. As mentioned earlier, AdipoR1 and AdipoR2 are the principal mediators of adiponectin activity that regulate key pathways involved in metabolism, inflammation, oxidative stress and fibrosis, including AMPK, PGC-1α and PPARα signalling. Pharmacological activation of these receptors has therefore emerged as an attractive strategy for harnessing the protective effects of adiponectin while overcoming some of the challenges associated with adiponectin administration itself.

AdipoRON

AdipoRON is a synthetic small-molecule dual AdipoR1/AdipoR2 agonist identified through high-throughput screening of approximately 24,000 compounds against the intracellular ligand-binding cavity revealed by AdipoR crystal structural studies. Its discovery was validated in a study demonstrating improvements in glucose tolerance, insulin sensitivity and survival in genetically obese (db/db) mice fed a high-fat diet (Ref. 112). AdipoRON activates AMPK and PPARα signalling in skeletal muscle and liver, respectively, and has demonstrated antifibrotic activity across multiple experimental systems, establishing the therapeutic rationale for adiponectin receptor agonism as a promising treatment strategy (Ref. 112).

Evidence for the antifibrotic effects of AdipoRON has been reported in several organ systems. In cardiac fibrosis, treatment of aged (18-month-old) *mdx* mice, a model combining muscular dystrophy and ageing, reversed established cardiac fibrosis, reduced left ventricular hypertrophy and attenuated cardiac oxidative stress through activation of the AdipoR1/CaMKK2/AMPK signalling pathway (Ref. 105). Similarly, chronic AdipoRON administration in aged wild-type mice improved skeletal muscle contractile force and mitochondrial oxidative phosphorylation capacity while reducing indices of age-related sarcopenic remodelling and fibrotic replacement through activation of AMPK/PGC-1α signalling (Ref. 106). In a murine model of systemic sclerosis-associated dermal fibrosis, oral AdipoRON reduced dermal thickness, collagen deposition, myofibroblast accumulation and microvascular abnormalities, with mechanistic studies demonstrating suppression of TGF-β1/Smad3 and FAK signalling (Ref. 86). In hepatic fibrosis models, AdipoRON inhibited TGF-β/Smad signalling in activated HSCs, leading to reduced expression of collagen I and fibronectin and attenuation of profibrotic responses (Ref. 113).

Despite its broad preclinical antifibrotic profile, the clinical advancement of AdipoRON has been hindered by several pharmacokinetic limitations, including modest aqueous solubility and relatively rapid in vivo clearance, which make sustained therapeutic concentrations difficult to achieve (Ref. 114). To address these challenges, PEGylation-based formulation strategies have been developed, with PEGylated AdipoRON derivatives demonstrating improved plasma exposure and more durable metabolic benefits compared with the parent compound in animal models (Ref. 114). Although no human clinical trials have been initiated to date, AdipoRON remains an important proof-of-concept compound for investigating adiponectin receptor signalling and continues to inform the development of next-generation adiponectin receptor agonists with improved drug-like properties.

ALY688

ALY688 (formerly ADP355) is a first-in-class, 10-amino acid peptidomimetic adiponectin receptor agonist derived from the receptor-binding globular domain of human adiponectin. Through the incorporation of D-amino acids and non-natural amino acid modifications, ALY688 was engineered to improve protease resistance and prolong biological activity relative to the native globular adiponectin sequence (Ref. 93). ALY688 activates both AdipoR1 and AdipoR2, with preferential potency toward AdipoR1 and demonstrates low nanomolar activity in adiponectin receptor activation assays, exceeding that of native globular adiponectin in direct receptor signalling studies (Ref. 93). To date, ALY688 has generated one of the most comprehensive preclinical datasets among adiponectin receptor agonists, demonstrating antifibrotic efficacy across multiple organ systems and disease models.

In skeletal muscle fibrosis, ALY688 treatment for 8 weeks in the *mdx* mouse model of DMD significantly improved grip strength, treadmill performance and maximal running velocity compared with vehicle-treated controls. These functional improvements were accompanied by marked reductions in collagen I deposition, α-SMA-positive myofibroblast accumulation and hydroxyproline content in both gastrocnemius and diaphragm muscle tissue. Mechanistic studies identified activation of the AMPK/PGC-1α axis and suppression of both NF-κB and TGF-β1 signalling as key mediators of these effects (Ref. 93). Similar findings were observed in the more severe *D2.mdx* model, in which the sustained-release formulation ALY688-SR prevented diaphragm fibrosis and preserved diaphragm contractile function when administered during the early stages of disease progression (Ref. 92).

The antifibrotic activity of ALY688 extends beyond skeletal muscle. In a murine model of NASH, ALY688 significantly reduced the expression of profibrotic genes, including Col1a1, Acta2 and TGFb1, while simultaneously improving hepatic steatosis (Ref. 115). Transcriptomic analyses revealed broad suppression of inflammatory and fibrotic gene programmes through AMPK-dependent signalling pathways. It demonstrated significantly less liver fibrosis after 12 weeks of treatment.

In a transverse aortic constriction model of heart failure with reduced ejection fraction, ALY688 attenuated left ventricular fibrosis and hypertrophy while preserving systolic function. Metabolomic analyses further demonstrated improvements in myocardial fatty acid oxidation and insulin sensitivity, suggesting restoration of cardiometabolic homeostasis in addition to direct antifibrotic effects (Ref. 116).

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In a murine model of systemic sclerosis, ALY688 significantly reduced dermal fibrosis, collagen deposition and myofibroblast accumulation, while also reversing established fibrosis when treatment was initiated after disease onset. Mechanistically, ALY688 inhibited TGF-β-induced fibroblast activation through activation of AMPK and suppression of Smad2/3 and FAK signalling, supporting its potential as a therapeutic strategy for systemic sclerosis (Ref. 100). Collectively, the consistent antifibrotic activity of ALY688 across models of DMD, NASH, cardiac remodelling and systemic sclerosis, together with its enhanced stability, potent receptor activation and favourable pharmacokinetic profile, positions it as a promising adiponectin receptor agonists currently under development for the treatment of fibrotic diseases.

Challenges in clinical translation

A major challenge in translating adiponectin-based therapeutics into clinical practice is the considerable interindividual variability in adiponectin levels, partly attributed to genetic polymorphisms in the ADIPOQ gene (Ref. 117). Factors such as age, sex, metabolic status and genetic background can influence circulating adiponectin concentrations as well as adiponectin receptor expression, potentially affecting therapeutic responses (Ref. 118). For example, transcription of adiponectin and AdipoR2 was reduced in aged rats, whereas AdipoR1 expression was increased, suggesting that age-dependent alterations in adiponectin signalling may influence the efficacy of adiponectin-targeted therapies (Ref. 119). While such variability may complicate treatment optimisation, it may also provide opportunities for biomarker-guided patient stratification and personalised therapeutic approaches.

An important consideration for the clinical translation of adiponectin-based therapeutics is the identification of biomarkers that can guide patient selection and treatment monitoring. Emerging evidence suggests that circulating adiponectin levels alone may not fully reflect the functional status of adiponectin signalling, as elevated adiponectin concentrations observed in certain fibrotic diseases may represent compensatory responses to tissue injury rather than preserved receptor activity (Ref. 120). Consequently, a more comprehensive assessment of the adiponectin signalling axis may be required to accurately predict therapeutic responsiveness. Encouragingly, recent studies have demonstrated the feasibility of identifying pharmacodynamic biomarkers of adiponectin receptor activation. Treatment with the adiponectin receptor agonist ALY688 induced a distinct peripheral blood gene expression signature that could be detected both in vivo and ex vivo, suggesting that blood-based biomarkers may be useful for monitoring adiponectin signalling activity and therapeutic responses (Ref. 121). These findings support the development of biomarker-guided patient stratification strategies incorporating adiponectin isoform profiles, AdipoR1/AdipoR2 expression patterns and downstream signalling signatures to improve patient selection and facilitate personalised adiponectin-targeted therapies.

Regulatory challenges further complicate clinical translation, particularly because universally accepted surrogate endpoints for fibrosis have not yet been established across organ systems by regulatory agencies such as the FDA and EMA. Traditional histological scoring systems, including METAVIR and Ishak staging for hepatic fibrosis and the modified Rodnan skin score for systemic sclerosis, often require invasive tissue sampling and remain susceptible to sampling limitations and inter-observer variability (Ref. 122). Consequently, there is growing interest in the use of non-invasive imaging modalities as alternative measures of disease progression and therapeutic response. Techniques such as cardiac magnetic resonance imaging-derived extracellular volume fraction and magnetic resonance elastography may provide more clinically feasible approaches for assessing fibrosis across multiple tissues (Ref. 123). However, broader regulatory acceptance of these modalities as primary efficacy endpoints will require extensive prospective validation and early integration of regulatory guidance into clinical trial design.

Despite extensive evidence demonstrating the beneficial effects of adiponectin on metabolism, inflammation and tissue homeostasis, numerous clinical studies have reported a positive correlation between circulating adiponectin levels and mortality in various disease states (Ref. 124). This phenomenon, commonly referred to as the 'adiponectin paradox', remains incompletely understood. Proposed explanations include the development of adiponectin resistance in target tissues, compensatory hypersecretion in response to chronic disease, impaired adiponectin clearance and interactions with natriuretic peptides (Refs 125, 126).

The adiponectin paradox is particularly evident in liver disease. In NAFLD and viral hepatitis, circulating adiponectin levels increase as disease severity progresses, contrasting with early-stage disease where adiponectin concentrations are often reduced (Refs 44, 127, 128). One proposed explanation is impaired hepatic clearance, whereby the diseased liver loses its ability to efficiently metabolise adiponectin, leading to systemic accumulation (Ref. 129). Alternatively, chronic inflammation associated with advanced liver disease may trigger a compensatory increase in adiponectin secretion from adipose tissue in an attempt to counteract ongoing fibrotic and inflammatory signalling.

These observations highlight both the promise and complexity of adiponectin as a clinical biomarker. While the paradoxical nature of adiponectin complicates interpretation, particularly across different stages of disease progression, adiponectin may still provide valuable diagnostic and prognostic information when evaluated alongside established clinical markers. Indeed, adiponectin has been incorporated into biomarker panels for the assessment of NASH and fibrosis, suggesting that although it may not be sufficient as a standalone marker, it can meaningfully complement existing approaches for disease stratification and monitoring (Ref. 130).

Conclusion

Fibrosis is a common pathological outcome of chronic injury across multiple organ systems and remains a major contributor to global morbidity and mortality. Although the cellular and molecular drivers of fibrosis vary between tissues, persistent fibroblast activation, excessive ECM deposition, chronic inflammation and dysregulated TGF-β signalling represent shared mechanisms underlying disease progression. The evidence reviewed in this article highlights adiponectin as a key endogenous regulator of these processes. Through activation of AdipoR1- and AdipoR2-mediated signalling pathways, adiponectin suppresses profibrotic signalling, attenuates inflammation and oxidative stress and limits pathological tissue remodelling in the liver, lungs, heart, kidneys, skin, skeletal muscle and age-associated fibrotic conditions.

Growing preclinical evidence further supports the therapeutic potential of targeting adiponectin signalling in fibrotic diseases. Pharmacological approaches that increase adiponectin activity, including adiponectin receptor agonists such as AdipoRON and ALY688, have demonstrated encouraging antifibrotic effects across

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multiple experimental models. Nevertheless, challenges related to interindividual variability, biomarker development, the adiponectin paradox and clinical trial design remain to be addressed. Continued investigation into adiponectin biology and the development of next-generation adiponectin-targeted therapies may ultimately provide new opportunities for the treatment of fibrosis and its associated complications.

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