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Signalling pathways regulated by FSTL1 in inflammation and potential therapeutic applications (Review)

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Abstract. Follistatin-like protein 1 (FSTL1), a secreted glycoprotein, serves a key role in regulating various biological processes. The present review explores the molecular mechanisms through which FSTL1 influences inflammation, cellular senescence and tumour progression. As a multifunctional protein with both autocrine and paracrine properties, FSTL1 regulates cell survival, proliferation, differentiation and migration, while also modulating immune responses. Evidence indicates that FSTL1 exerts context-dependent regulatory effects on pathological conditions by modulating signalling pathways, such as TGF-β, NF-κB and MAPK. Furthermore, increased FSTL1 expression has been found in the inflammatory synovial tissues of patients with osteoarthritis and it contributes to nucleus pulposus cell inflammation. In conclusion, the distinctive structural features and widespread expression of FSTL1 position it as a key target for understanding the mechanisms underlying inflammation, senescence and tumourigenesis, providing potential options for novel diagnostic and therapeutic strategies for these conditions.

Contents

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1. Introduction

Follistatin-like protein 1 (FSTL1) is a 315-amino acid secreted glycoprotein comprising an N-terminal signal peptide, a follistatin-like domain and a calcium-binding EF-hand domain (1,2). This structural configuration allows FSTL1 to engage with multiple proteins, thereby participating in intricate biological regulatory processes (3). FSTL1 is widely expressed in tissues such as the heart, lungs, skeletal muscle and synovial membranes (4-7). Under normal physiological conditions, FSTL1 maintains stable expression levels, supporting growth, development and cellular proliferation. However, its expression is notably upregulated in inflammatory states (8,9), and FSTL1 serves a role in inflammatory diseases, autoimmune responses and tumour progression by regulating various signalling pathways (10,11). Gene knockout models have highlighted the essential function of FSTL1 in multi-system development, with FSTL1-deficient mice exhibiting early mortality due to developmental defects (12,13). At the cellular level, FSTL1 primarily operates through paracrine and autocrine mechanisms, interacting with receptors such as activin and TGF-β receptors to regulate cellular processes (1,14). The differential expression of FSTL1 in different tissues is closely linked to its specific biological functions (15,16). As a novel inflammatory regulator, FSTL1 exhibits therapeutic potential in autoimmune diseases, cardiovascular disorders and tissue regeneration (7,17,18). Further investigations into its mechanisms of action may enhance understanding of the molecular regulatory network underlying inflammation (19,20), identify new targets for anti-inflammatory drug development (21), and improve diagnostic and prognostic approaches for diseases such as inflammatory diseases and fibrosis (4,22).

2. Role of FSTL1 in inflammatory regulation

FSTL1 is an extracellular matrix glycoprotein that serves a pivotal role in various inflammatory diseases. Research has demonstrated that FSTL1 modulates inflammatory responses through distinct signalling pathways (16,23), positioning it as a potential future therapeutic target for certain inflammatory conditions.

Role of FSTL1 in cell proliferation, differentiation and apoptosis. FSTL1 regulates cellular proliferation through complex mechanisms that vary across different cell types. This regulatory activity is particularly evident in tumour cell lines (24,25). For example, in MDA-MB-231 breast cancer cells, FSTL1 acts as a cell proliferation inhibitor, whereas in gastric cancer cells, it promotes cellular proliferation (26,27). This cell type-specific regulation highlights the functional diversity of FSTL1.

Regulatory mechanisms of FSTL1 in inflammatory responses. The role of FSTL1 in inflammatory responses is multifaceted, involving complex and precisely coordinated mechanisms (28,29). In terms of immune cell regulation, FSTL1 modulates immune cell infiltration and activation, maintaining immune system homeostasis by balancing pro-inflammatory and anti-inflammatory responses (27,30,31). By inhibiting hyperactivation of neutrophils and macrophages, FSTL1 helps prevent sustained inflammatory damage (31,32).

Inflammatory signal transduction is central to the regulatory functions of FSTL1. By modulating pathways such as NF-κB and MAPK, FSTL1 is involved in both the initiation and resolution of inflammation, serving a key role in innate and adaptive immune responses (33,34). Notably, FSTL1 interacts with the Toll-like receptor (TLR) system, particularly TLR4, to orchestrate inflammatory processes (Fig. 1). Through TLR4 engagement, FSTL1 activates the MyD88-dependent signalling cascade, triggering the downstream activation of NF-κB and MAPK pathways, which regulate the production of pro-inflammatory cytokines and chemokines across various cell types (2,35). The TLR4/MyD88/NF-κB axis represents a critical mechanism by which FSTL1 fine-tunes inflammatory responses in both physiological and pathological contexts. In certain scenarios, FSTL1 also exhibits anti-inflammatory properties by inhibiting TLR4-mediated inflammatory signalling, highlighting its context-dependent immunomodulatory functions. These unique regulatory mechanisms enable FSTL1 to orchestrate immune network interactions, serving an essential role in maintaining immune balance (30).

Regulation of articular cartilage by FSTL1 pathways. FSTL1 is a key regulator in cartilage biology, influencing chondrocyte behaviour and tissue homeostasis (7,36,37). In chondrocyte metabolism, FSTL1 promotes chondrocyte proliferation and differentiation, regulates cartilage matrix synthesis, and participates in complex cartilage tissue remodelling processes (38-40), all of which are essential for maintaining cartilage integrity and biomechanical function.

Emerging evidence has highlighted the specific pathological mechanisms of FSTL1 in joint disorders (41,42). In conditions such as osteoarthritis, FSTL1 contributes to disease onset and progression by modulating inflammatory responses, influencing chondrocyte apoptosis and survival, and regulating cartilage matrix protein expression through the TGF-β signalling pathway (2,43,44). Cartilage development and regeneration represent critical areas of FSTL1 research, given its potential in regulating cartilage-specific transcription factors, and promoting cartilage regeneration and repair (45,46).

3. Major signalling pathways and their mechanisms

FSTL1 modulates key signalling pathways that govern cellular homeostasis, inflammatory regulation and oncogenesis. The following chapter summarises the main signalling pathways involving FSTL1.

TGF-β and Raf/MEK/ERK signalling pathways. FSTL1 regulates TGF-β superfamily signalling through intricate molecular mechanisms, serving a central role in cellular biological processes (Fig. 1). The TGF-β pathway is essential for regulating cell proliferation, differentiation, migration and tissue development, with FSTL1 acting as a precise modulator in this context (47,48). Previous studies have established FSTL1 as a TGF-β-inducible gene encoding a secreted glycoprotein, creating a bidirectional regulatory relationship between FSTL1 and TGF-β signalling (44,49).

During mesenchymal cell development and tissue remodelling, FSTL1 influences TGF-β signal transduction through multiple mechanisms (39). One key mechanism involves the direct regulation of Smad protein phosphorylation, which impacts cell fate decisions (41). In 2025, research demonstrated that FSTL1 accelerates cellular apoptosis and extracellular matrix degeneration by activating the TGF-β/Smad2/3 pathway, promoting dose-dependent increases in phosphorylated (p)-Smad2/Smad2 and p-Smad3/Smad3 ratios, leading to nuclear translocation of these transcription factors (44). In processes such as cardiac regeneration, FSTL1 stimulates cardiomyocyte proliferation and differentiation via the TGF-β/Smad pathway, thereby facilitating tissue repair and functional recovery (44,50). FSTL1 enhances TGF-β non-Smad signalling by promoting phosphorylation-driven activation of the Raf/MEK/ERK cascade, thereby amplifying associated fibrogenic and proliferative effects (51). Moreover, exercise-induced FSTL1 has been shown to promote cardiac angiogenesis through the disco-interacting protein 2 homolog A (DIP2A)-Smad2/3 pathway following myocardial infarction, highlighting its therapeutic potential in cardiovascular regeneration (21,52-55).

FSTL1 regulates the TGF-β pathway at multiple molecular levels (56,57). In this context, FSTL1 modulates the phosphorylation levels of Smad2/3 proteins, alters their binding affinity with receptor complexes, and influences their nuclear translocation and transcriptional activity (40). A 2025 study confirmed the direct regulatory relationship between FSTL1 and TGF-β/Smad signalling, showing that TGF-β pathway inhibition using SB-431542 may reverse FSTL1-induced Smad2 and Smad3 phosphorylation (44). Additionally, FSTL1 regulates the spatial configuration of type I and II TGF-β receptors, affecting the stability of their interactions and modulating signal transduction efficiency (58).

In inflammatory microenvironments, FSTL1 expression is modulated by inflammatory cytokines such as TGF-β1, IL-1β and TNF-α (52,59). Its expression is subject to dose- and

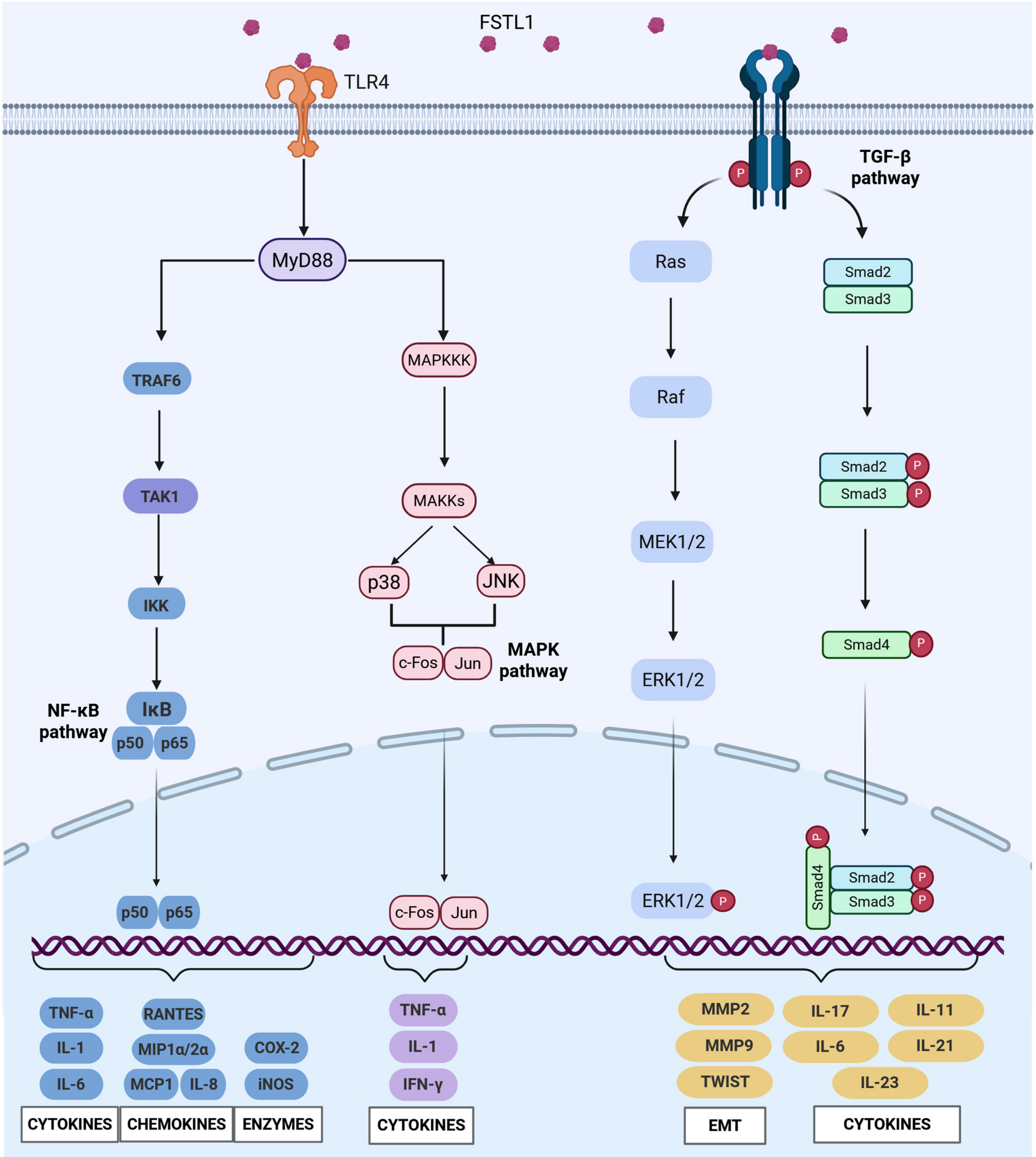

Figure 1. FSTL1-mediated crosstalk between TLR4 and TGF-β signalling pathways in inflammation and fibrosis. This schematic diagram illustrates the molecular mechanisms by which FSTL1 orchestrates crosstalk between TLR4 and TGF-β signalling pathways. Upon binding to cell surface receptors, FSTL1 simultaneously activates multiple downstream signalling cascades. TLR4 pathway activation: FSTL1 binding to TLR4 triggers MyD88-dependent signalling, leading to two major downstream branches: i) TRAF6-TAK1-IKK axis resulting in NF-κB pathway activation through IκB degradation and nuclear translocation of p50/p65 heterodimers; ii) MAPKKK-MAPKs cascade activating p38 and JNK, which converge on AP-1 (c-Fos/Jun) transcription factors. TGF-β pathway enhancement: FSTL1 promotes TGF-β receptor complex formation and enhances canonical Smad signalling through Smad2/3 phosphorylation and Smad4 nuclear translocation, while also activating non-canonical pathways, including the Ras-Raf-MEK-ERK cascade. Transcriptional outcomes: The convergence of these pathways results in coordinated transcriptional programs producing: i) Pro-inflammatory mediators, chemokines and enzymes; ii) fibrotic mediators including MMPs, pro-fibrotic cytokines and EMT-associated factors. Pathway interactions: Phosphorylated ERK1/2 and activated transcription factors (Smad2/3/4 complex, NF-κB, AP-1) coordinate nuclear gene expression programs that promote both inflammatory responses and tissue remodelling processes. The diagram demonstrates how FSTL1 serves as a critical hub protein integrating immune activation and fibrotic responses through simultaneous modulation of multiple signalling networks. Created with BioRender.com (Created in BioRender. Deng, Z. (2025) https://BioRender.com/3o0ydwz). EMT, epithelial-mesenchymal transition; FSTL1, follistatin-like protein 1; IKK, IκB kinase; iNOS, inducible nitric oxide synthase; MCP1, monocyte chemoattractant protein-1; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; TLR4, Toll-like receptor 4.

time-dependent regulation. Recent findings have suggested that plasma FSTL1 levels can serve as a non-invasive diagnostic biomarker for inflammatory and fibrotic diseases (60,61). By controlling the release of inflammatory mediators and modulating immune cell infiltration and activation, FSTL1 helps maintain inflammatory homeostasis (31,32).

FSTL1 and TGF-β signalling form a bidirectional regulatory network that is essential for tissue homeostasis and remodelling (52,62,63). FSTL1, as a TGF-β-inducible gene, is upregulated by TGF-β1 through Smad3-dependent transcriptional activation. In turn, secreted FSTL1 functions as a matricellular protein that facilitates TGF-β receptor complex formation and amplifies downstream signalling, creating a positive feedback loop. At the molecular level, FSTL1 directly regulates Smad2/3 phosphorylation, nuclear translocation and transcriptional activity, with TGF-β inhibitors reversing FSTL1-induced Smad phosphorylation (44,57,63). This TGF-β/Smad-FSTL1 axis orchestrates various physiological processes, including mesenchymal cell differentiation, extracellular matrix synthesis, cardiac regeneration and fibrotic responses (63,64). In inflammatory microenvironments, FSTL1 expression is modulated by cytokines such as TGF-β1, IL-1β and TNF-α (52,62,63). These multifaceted mechanisms position FSTL1 as a key amplifier in TGF-β-mediated signalling networks.

NF-κB signalling pathway. The NF-κB signalling pathway is a key regulator of cellular inflammation and immune responses (Fig. 1), with a critical role in inflammatory diseases, immune modulation and cell survival (65,66).

FSTL1 interacts with the NF-κB pathway in a bidirectional, context-dependent manner, with effects varying across tissue types and disease models. Recent studies have shown that in kidney inflammation, FSTL1 derived from renal tubular epithelial cells inhibits NF-κB activation, protecting against kidney fibrosis by reducing renal epithelial inflammation (67,68). Mechanistically, FSTL1 suppresses TNF-α-induced phosphorylation and nuclear translocation of NF-κB p65, thereby decreasing IL-1β, IL-6 and ICAM-1 expression, and limiting leukocyte infiltration (67,68). By contrast, in pulmonary fibrosis, FSTL1 promotes NF-κB activation, driving epithelial-mesenchymal transition and inflammation. FSTL1 expression is induced by TGF-β1, leading to NF-κB phosphorylation and establishing a pro-fibrotic feedback loop. Quercetin alleviates pulmonary fibrosis by downregulating FSTL1 expression and modulating NF-κB signalling (68).

FSTL1 is also essential for the initial activation of NF-κB signalling in specific disease contexts (31,35). By regulating the activity of the IκB kinase complex, FSTL1 directly affects the phosphorylation and degradation of NF-κB (31,35,69). In neuroinflammatory models, FSTL1 knockdown reduces microglial activation by suppressing NF-κB signalling, thereby protecting against neurological damage in Parkinson's disease models (70). In nucleus pulposus cells, FSTL1 accelerates cellular senescence and intervertebral disc degeneration (IVDD) through TLR4/NF-κB pathway activation (2). In macrophages and other immune cells, FSTL1 regulates NF-κB nuclear translocation and transcriptional activity, influencing the expression and release of inflammatory cytokines to maintain inflammatory homeostasis (35).

Oxidative stress is a key trigger for the activation of the NF-κB signalling pathway, with FSTL1 exerting complex regulatory effects on intracellular reactive oxygen species (ROS) production. In high glucose-induced oxidative stress models, FSTL1 exacerbates oxidative stress and cellular transdifferentiation injury in renal tubular epithelial cells, thereby promoting NF-κB activation and subsequent inflammatory responses (71).

Regulating inflammatory cytokine expression is a central mechanism through which FSTL1 modulates the NF-κB pathway (31,72). FSTL1 precisely controls the expression of inflammatory cytokines such as TNF-α, IL-6 and IL-1β, with its regulatory direction being tissue-specific: In renal epithelial cells, FSTL1 upregulation decreases TNF-α-induced secretion of IL-1β and IL-6 through NF-κB inhibition (67), whereas in pulmonary epithelial cells, FSTL1 enhances the secretion of these cytokines via NF-κB activation (2). Bioinformatics analyses have confirmed notable positive associations between FSTL1 and key NF-κB pathway components (RELA and NFKB1), as well as downstream cytokines, in patients with pulmonary fibrosis (68). In various inflammatory disease models, FSTL1 demonstrates marked anti-inflammatory effects by inhibiting NF-κB signalling, thereby reducing the intensity and duration of inflammatory responses (31,73).

Cell apoptosis and survival, central to NF-κB regulation, are also influenced by FSTL1, which impacts cell survival decisions through NF-κB-mediated modulation of apoptosis-related proteins and anti-apoptotic factors (74,75). In neurodegenerative disease models, particularly Parkinson's disease, inhibition of HOXA11-AS protects mice from neuroinflammation and neuronal apoptosis through the microRNA-124-3p-FSTL1-NF-κB axis, illustrating the therapeutic potential of targeting FSTL1-NF-κB signalling (70). In autoimmune disease models, FSTL1 has emerged as both a potential therapeutic target and a biomarker of inflammation, with its expression associated with disease activity in rheumatic diseases (74,76,77).

The regulation of the NF-κB pathway by FSTL1 is tissue- and disease-specific (27,78), with its regulatory patterns varying across cell types and disease models. In neuroinflammation, it may exert notable inhibitory effects, whereas in tumour microenvironments, the regulatory mechanisms are more complex (75,79). Specifically, in tumours, FSTL1 modulates tumour progression and metastasis by regulating the inflammatory polarisation of tumour-associated macrophages, offering potential targets for tumour immunotherapy (78,79).

MAPK signalling pathway. FSTL1 regulates a wide range of biological processes, including cellular stress responses, proliferation, survival and inflammation, primarily through the MAPK signalling pathway (Fig. 1) (17,80). Recent research has revealed that FSTL1 can function as both an activator and an antagonist of MAPK signalling, with its effects dependent on the cellular context (81).

Regulation of the MAPK pathway by FSTL1 is highly cell- and tissue-specific, and its mechanisms vary across different tumour cell types. In 2024, pioneering research demonstrated that FSTL1 acts as an antagonist of ERK1/2 phosphorylation during ciliogenesis and preadipocyte differentiation, revealing an inhibitory role in MAPK signalling that contrasts with its activating effects in other contexts (81). In the breast cancer cell line MDA-MB-231 and in cervical cancer cells, FSTL1 inhibits cell proliferation by regulating the phosphorylation and activity of MAPK family members, such as ERK, JNK and p38, thus influencing downstream gene expression and cell fate (82,83). In cervical cancer, FSTL1 upregulation markedly reduces cell proliferation, migration and invasion, while promoting apoptosis through downregulation of the insulin-like growth factor 1 receptor/PI3K/AKT pathway, which intersects with MAPK signalling.

FSTL1 serves a central role in regulating the inflammatory response, primarily mediating inflammatory cascades through the MAPK and NF-κB pathways. In cardiac fibrosis models, FSTL1 promotes profibrotic mechanisms by activating MAPK signalling via TGF-β1. FSTL1 upregulation enhances TGF-β signalling, leading to increased activation of ERK, JNK and p38 pathways. By contrast, depletion of FSTL1 reduces the levels of ERK, JNK and p38, while blocking JNK and p38 markedly impairs fibroblast proliferation, differentiation and migration (84). Furthermore, glycosylated FSTL1 specifically induces cardiac fibroblast proliferation through ERK1/2 activation, whereas non-glycosylated FSTL1 may exert distinct effects (85-87).

FSTL1-induced regulation of inflammation exhibits notable heterogeneity across different tissues (37). In nucleus pulposus cells and in IVDD, FSTL1 accelerates cell senescence and promotes inflammation via TLR4/NF-κB pathway activation, rather than directly through MAPK signalling. FSTL1 expression is upregulated in degenerative disc tissues, and FSTL1 small interfering RNA (siRNA) notably inhibits IVDD progression by reducing inflammatory responses (2,44,88).

Overall, FSTL1 serves diverse regulatory roles in cell proliferation and inflammatory responses through complex MAPK signalling pathways. Findings have revealed that FSTL1 can act as both an activator and an inhibitor of ERK1/2 phosphorylation, depending on the cellular differentiation state and tissue context. In cardiac tissue, FSTL1 activates MAPK pathways (ERK, JNK and p38) through TGF-β1-mediated mechanisms, promoting fibroblast activation and fibrosis. Conversely, during adipocyte differentiation and ciliogenesis, FSTL1 acts as an ERK1/2 antagonist, inhibiting MAPK signalling. These regulatory mechanisms exhibit marked cell- and tissue-specificity, offering potential novel strategies for tumour treatment and inflammatory disease research (33,89). Understanding the regulatory role of FSTL1 in signal transduction may facilitate the development of targeted therapies (17,58,71,90).

AKT/glycogen synthase kinase (GSK)-3β signalling pathway. The AKT/GSK-3β signalling pathway is crucial for regulating cell survival, proliferation, differentiation and apoptosis (17,91). FSTL1 modulates this pathway through various molecular mechanisms (41,92). At the cellular level, FSTL1 primarily influences signal transduction by modulating AKT protein phosphorylation and activity (Fig. 2), a process involving intricate protein interactions and conformational changes (93,94).

FSTL1 signalling facilitates the conversion of PIP_2 to PIP_3 at the plasma membrane, a critical step indicative of PI3K activation. FSTL1 activates the PI3K/AKT signalling pathway to regulate cell survival and proliferation (41,94). In different disease models, FSTL1 modulates the AKT/GSK-3β pathway in a tissue- and disease-specific manner. In tumour cells, FSTL1 enhances cell proliferation, migration and invasion by promoting AKT pathway activation, whereas in neuroprotective contexts, it exhibits inhibitory and protective effects (91,95).

GSK-3β, a key downstream target of AKT, is also regulated by FSTL1. In neurodegenerative and inflammatory disease models, FSTL1 inhibits GSK-3β activity by regulating its phosphorylation, thereby reducing cellular inflammation and oxidative stress damage (95). This mechanism serves a critical role in neuroprotection and inflammatory regulation, suggesting potential therapeutic applications.

Oxidative stress is a major pathological mechanism in various diseases. FSTL1 exerts potent antioxidant effects through the AKT/GSK-3β signalling pathway. In models of oxidative stress induced by high glucose and inflammation, FSTL1 activates the AKT pathway, inhibiting GSK-3β activity and effectively reducing cellular oxidative damage (96). This mechanism is critical for preventing and treating diabetic complications and neurodegenerative diseases. In multiple disease models, FSTL1 exhibits finely tuned regulatory functions through this pathway, highlighting its essential role in maintaining cellular homeostasis (92,96).

NLR family pyrin domain-containing 3 (NLRP3) inflammasome signalling pathway. FSTL1 serves a pivotal role in regulating the NLRP3 inflammasome signalling pathway, with its complex molecular mechanisms being critical for the development and progression of inflammatory diseases, such as acute pancreatitis, gout and neuroinflammatory disorders (19,69,97). As a key inflammatory regulatory complex in the innate immune system, the activation of the NLRP3 inflammasome is tightly controlled at multiple levels by FSTL1 (69,98,99).

During the initiation of inflammation, FSTL1 regulates the release of inflammatory mediators by modulating NLRP3 protein conformational changes and aggregation (Fig. 2) (19,69,100). In immune cells, such as macrophages and dendritic cells, FSTL1 inhibits excessive activation of the NLRP3 inflammasome, thereby modulating the intensity and duration of inflammatory responses and helping to maintain immune homeostasis (37,100,101).Oxidative stress is a key trigger for NLRP3 inflammasome activation, and FSTL1 serves an essential regulatory role in this process (101). By regulating the production and clearance of ROS within cells, FSTL1 directly influences the activation threshold of the NLRP3 inflammasome (19,98). In models of oxidative stress induced by high glucose and inflammation, FSTL1 mitigates aberrant NLRP3 inflammasome activation by inhibiting excessive ROS production, thereby reducing inflammatory damage (102,103).

Cellular apoptosis, a critical mechanism in NLRP3 inflammasome regulation, is influenced by FSTL1 through its modulation of caspase-1 activity and apoptotic pathways (97). In models of neurodegenerative and autoimmune diseases, FSTL1 effectively reduces cellular inflammatory damage (17,69,100).

Notably, FSTL1-induced regulation of the NLRP3 inflammasome signalling pathway exhibits notable tissue and disease specificity. Its regulatory mechanisms are complex and variable across different cell types and disease models, offering novel research perspectives for a deeper understanding of the role of FSTL1 in inflammatory regulation (19,37).

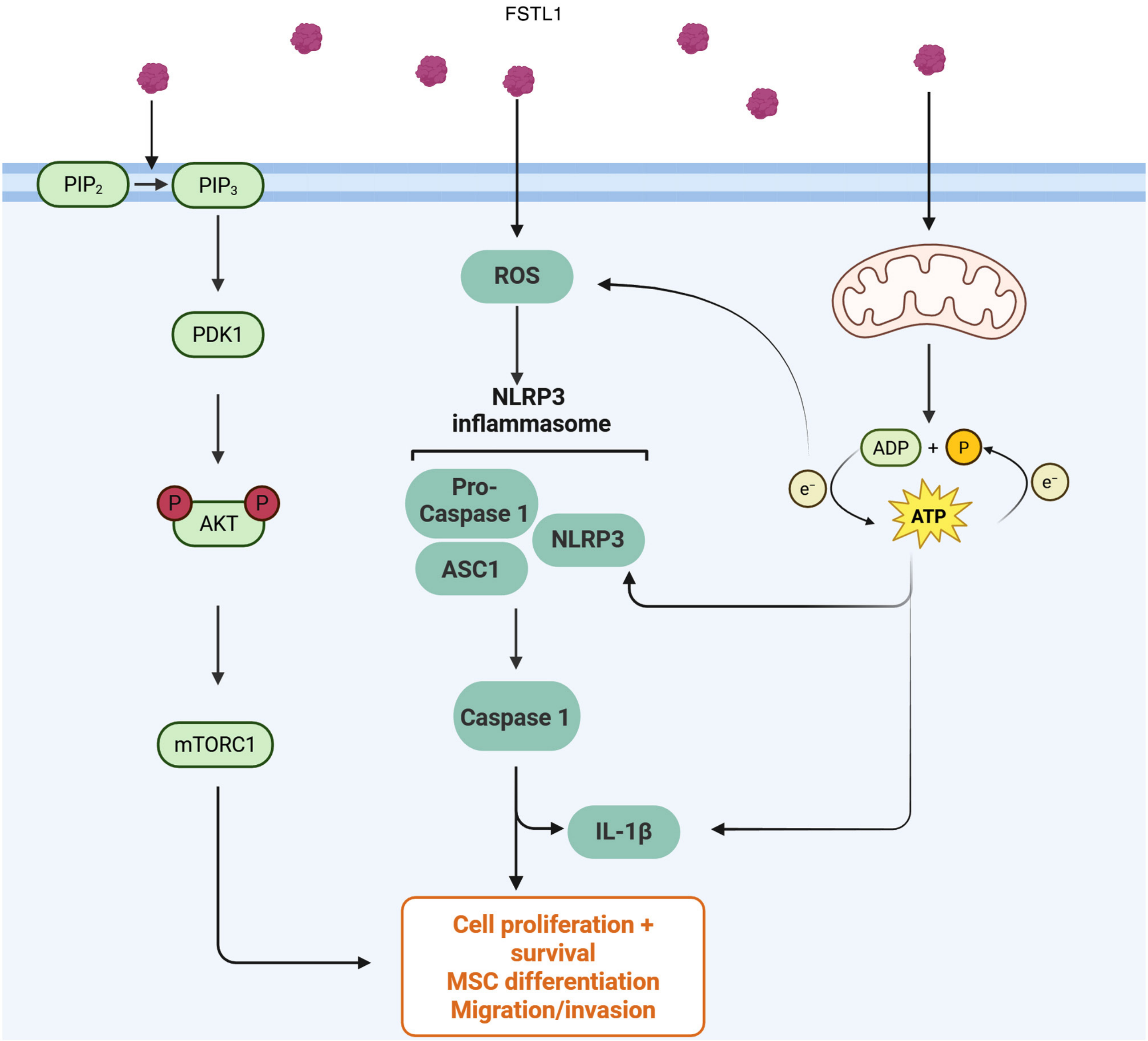

Figure 2. FSTL1 integrates metabolic, inflammatory and differentiation signalling through the PI3K/AKT/mTOR and NLRP3 inflammasome pathways. This diagram delineates the intracellular signalling mechanisms by which FSTL1 regulates cellular metabolism, inflammatory responses and cell fate decisions. PI3K/AKT/mTORC1 Axis: FSTL1 signalling facilitates PIP_2 to PIP_3 at the plasma membrane, a critical step indicative of PI3K activation. PIP_3 recruits and activates PDK1, which in turn phosphorylates and fully activates AKT. Activated AKT (phosphorylated-AKT) serves as a central signalling hub, driving the activation of the mTORC1 pathway, a master regulator of anabolic processes. NLRP3 inflammasome activation: Concurrently, FSTL1 stimulation induces the generation of ROS. Both FSTL1 and ROS contribute to the assembly and activation of the NLRP3 inflammasome complex. This multi-protein complex, consisting of NLRP3, the adaptor protein ASC and pro-caspase-1, leads to the cleavage and activation of caspase-1. Active caspase-1 then catalyses the maturation and secretion of the potent pro-inflammatory cytokine IL-1β. FSTL1 enhances electron transport chain activity, which promotes NLRP3 inflammasome activation and IL-1β secretion. Integrated functional outcomes: The convergence of these FSTL1-initiated signals orchestrates key cellular responses: Cell proliferation and survival, MSC differentiation and migration/invasion. Solid arrows indicate direct activation or conversion processes; tapered lines represent contributory pathways or functional outcomes. Created with BioRender.com (Created in BioRender. Deng, Z. (2025) https://BioRender.com/w34o3gm). ASC, apoptosis-associated speck-like protein containing a CARD; FSTL1, follistatin-like protein 1; MSC, mesenchymal stem cell; NLRP3, NLR family pyrin domain-containing 3; ROS, reactive oxygen species.

Other signalling pathways

FSTL1-mitochondria interactions. FSTL1 regulates inflammatory responses through its direct localisation to the mitochondria and involvement in mitochondrial quality control (MQC). By localising to macrophage mitochondria, FSTL1 enhances electron transport chain activity, which promotes NLRP3 inflammasome activation and IL-1β secretion (Fig. 2) (19,23). Mitochondrial dysfunction triggers inflammatory cascades through various mechanisms. Mitochondrial ROS (mtROS) generated by reverse electron transport activate NLRP3 inflammasomes (104), while the release of mitochondrial DNA (mtDNA) activates cGAS-STING pathways, driving interferon responses and contributing to cardiovascular inflammation (105,106). In ischemic cardiomyopathy, impaired MQC results in excessive mitochondrial fission, compromised mitophagy, and the release of damage-associated molecular patterns, which activate inflammatory pathways (107). FSTL1 preserves mitochondrial integrity by regulating dynamics and calcium homeostasis. During myocardial ischemia-reperfusion injury, FSTL1 may counteract nuclear receptor subfamily 4 group A member 1-mediated fission and promote FUN14 domain-containing 1-mediated mitophagy, helping to maintain mitochondrial networks (108). FSTL1 also modulates mitochondrial calcium homeostasis through interactions between transmembrane BAX inhibitor motif-containing 6 (TMBIM6) and voltage-dependent anion channel 1 (VDAC1), reducing calcium overload-induced necroptosis (109). Mitochondrial-induced vascular endothelial injury is another critical pathway linking mitochondrial dysfunction with cardiovascular inflammation (110). Pharmacological interventions have shown therapeutic potential: Quercetin preserves DNA-dependent protein kinase catalytic subunit-sirtuin 5-mediated MQC to inhibit necroptosis (111), while ginsenoside Rb1 ameliorates heart failure through mitochondrial and inflammatory regulation (112). FSTL1 further influences macrophage polarisation to promote liver fibrosis (31) and mitigates acute pancreatitis by regulating NLRP3-mediated pyroptosis (98). Targeting the FSTL1-mitochondria-inflammation axis offers a promising therapeutic strategy.

Endothelial nitric oxide synthase (eNOS) signalling pathway regulation. FSTL1 is crucial for endothelial cell function and promotes revascularisation of ischemic tissue by regulating the eNOS signalling pathway (16,41). Its mechanisms primarily involve modulating eNOS activity and expression, enhancing endothelial cell migration and tubule formation, which are vital for tissue repair and vascular regeneration (113). In cardiovascular and ischemic diseases, FSTL1 represents a potential therapeutic target by inhibiting endothelial cell inflammatory cytokine expression and reducing endothelial cell inflammatory responses (21,90).

AMPK signalling pathway regulation. As a cellular energy sensor, AMPK regulates cellular metabolism, proliferation and survival (94,114). FSTL1 influences mitochondrial biogenesis, fatty acid oxidation and glucose metabolism through the activation of the AMPK signalling pathway (16,115). In metabolic diseases and tumour progression, FSTL1 regulates cellular energy metabolism via the AMPK pathway, impacting cellular survival and proliferation (116,117).

Specificity of regulatory mechanisms. The roles of FSTL1 in eNOS and AMPK signalling exhibit notable tissue and cell specificity (16,118). Its regulatory patterns vary under different physiological and pathological conditions, highlighting FSTL1 as a unique multifunctional signalling molecule the activity of which is tightly controlled by multiple factors (119). Overall, FSTL1 regulates endothelial cell function and energy metabolism through eNOS and AMPK signalling pathways, showcasing its versatility in diverse biological processes (113,120,121).

Conclusion. FSTL1 regulates cell functions and inflammatory responses through multiple pathways, including the TGF-β, NF-κB, MAPK and AKT/GSK-3β signalling pathways, the NLRP3 inflammasome and mitochondria (17,33,91). These pathways are critical in inflammation, tissue development and tumour progression, positioning FSTL1 as a key target for studying inflammation, and cellular proliferation and development (57,92). A deeper understanding of the mechanisms of FSTL1 in physiological and pathological processes will provide valuable insights into its complex role in disease development and progression, paving the way for new therapeutic strategies.

4. Advances in FSTL1-associated therapeutic strategies

FSTL1, a central regulator of inflammation and fibrosis, has emerged as a potential therapeutic target across various diseases (63,64,122). Extensive research into the molecular functions and signalling pathways of FSTL1 has led to the development of several FSTL1-targeted therapeutic strategies, showing notable potential in multiple inflammatory disease models such as osteoarthritis and rheumatoid arthritis (8,36,123).

FSTL1 exhibits pleiotropic biological effects in inflammatory microenvironments (123,124). Notably, FSTL1 expression is markedly elevated in the synovial tissues and serum of patients with rheumatoid arthritis and osteoarthritis, and it is positively associated with disease severity (123,125,126). FSTL1 forms a key signalling axis with TGF-β, regulating Smad3 phosphorylation and SOX9 transcription factor activity, and directly influences chondrocyte differentiation and function (36,44). In osteoarthritis models, FSTL1 enhances inflammation through TLR4/MyD88/NF-κB and MAPK pathways, increasing the production of inflammatory cytokines such as IL-6, IL-8 and monocyte chemoattractant protein-1 (37,123,127). Additionally, FSTL1 exerts dual regulatory effects on extracellular matrix metabolism; moderate levels of FSTL1 promote cartilage matrix synthesis, whereas higher concentrations drive cartilage degradation by upregulating metalloproteinase expression (36,37). These molecular mechanisms provide a theoretical foundation for the development of FSTL1-targeted therapeutic strategies.

Monoclonal neutralising antibodies against FSTL1 are among the most extensively studied therapeutic strategies (63,122). In collagen-induced arthritis models, FSTL1-neutralising antibodies can markedly reduce joint swelling, synovial inflammation and bone erosion (8,63,128). In fibrotic disease models, such as pulmonary fibrosis and skin scar hyperplasia, these antibodies alleviate tissue fibrosis by inhibiting fibroblast activation and extracellular matrix deposition (63,99,122). Notably, FSTL1-neutralising antibodies exhibit synergistic effects when combined with traditional antirheumatic drugs, potentially enhancing efficacy while minimising adverse reactions (63).

siRNA and gene silencing technologies offer an alternative strategy for precise FSTL1-targeted therapy (2,129,130). Using nanoparticle delivery systems, such as liposomes, optimally designed siRNAs can reduce FSTL1 expression by >90% with high specificity (129,130). In IVDD models, FSTL1 siRNA-treated mesenchymal stem cells (MSCs) can improve disc tissue structure and function. MRI and histological examinations have confirmed a reduction in nucleus pulposus cell apoptosis and improved extracellular matrix homeostasis in response to FSTL1 siRNA (2,131).

The MSC-FSTL1 interaction presents an innovative therapeutic direction (36,37,132). FSTL1 demonstrates concentration-dependent effects: Low concentrations enhance the chondrogenic and osteogenic differentiation abilities of MSCs, increasing the expression of markers such as SOX9, collagen type II α1 chain and aggrecan (133), whereas high concentrations may inhibit cartilage formation and trigger inflammatory responses (37). FSTL1 also influences the immunomodulatory properties of MSCs by regulating their paracrine functions (30,134). In osteoarthritis models, MSCs with low FSTL1 expression exhibit stronger anti-inflammatory and cartilage-protective effects (135).

In disease-specific applications, FSTL1 displays microenvironment-dependent functions (37,136). In osteoarthritis, early-stage FSTL1 protects chondrocytes through TGF-β signalling, whereas at later stages, elevated FSTL1 concentrations accelerate cartilage degradation (137). FSTL1 regulates disease progression through cross-talk between the TGF-β/Smad, bone morphogenetic protein and Wnt/β-catenin pathways (127,137,138). In rheumatoid arthritis, high FSTL1 expression in synovial tissues and serum provides key insights into disease progression (6,126), and targeted inhibition of FSTL1 markedly alleviates joint inflammation and tissue damage (28,63). In fibrosis-related diseases, neutralising antibodies have shown efficacy in alleviating lung and skin fibrosis induced by bleomycin or TGF-β1, presenting a promising strategy for treating progressive organ fibrosis (122,139). Collectively, FSTL1-targeted therapies, as key modulators of inflammation and fibrosis, have broad therapeutic potential.

In the future, FSTL1 therapeutic strategies may evolve toward multi-target inhibition and precision medicine (128,140). Researchers are investigating the combined use of FSTL1 inhibitors with different mechanisms of action, such as pairing neutralising antibodies with siRNA technology (140) or combining FSTL1 targeting with traditional antirheumatic drugs for synergistic effects (17,141). Personalised treatment approaches based on the FSTL1 expression profiles and microenvironment characteristics of patients are also being developed. Assessing FSTL1 levels, and related signalling molecules in serum and tissues, may help identify the most effective interventions (123). The development of nanodelivery systems, including liposomes and polymer nanoparticles targeting cartilage or synovium, is progressing rapidly (142,143). These systems can markedly enhance drug accumulation in target tissues while minimising systemic side effects (123). Integrating genomics, proteomics and metabolomics will provide a comprehensive understanding of the dynamic and functional networks of FSTL1 across disease stages, laying the groundwork for precise interventions (17).

Despite the potential of FSTL1-targeted therapies, their clinical translation faces several challenges. First, since FSTL1 serves a role in various physiological processes, long-term inhibition may carry potential risks, particularly in the cardiovascular system, where FSTL1 has protective effects. Systemic inhibition could potentially affect cardiac function (16,87). Second, the concentration-dependent bidirectional regulatory effects of FSTL1 and its microenvironment-dependent functions add complexity to targeted therapy. Achieving precise control over FSTL1 concentration and activity in target tissues will be a key challenge (115,119,144). Moreover, to enable precision treatment, predictive biomarkers related to FSTL1 need to be developed to screen suitable patient populations and assess treatment efficacy (27,145,146). Finally, while FSTL1 inhibition has shown positive results in animal models, large-scale human clinical trial data are still lacking; multi-centre, randomised controlled trials will be crucial to evaluate the efficacy and safety of FSTL1-targeted drugs (52).

In conclusion, FSTL1 is a critical regulator in inflammatory and fibrotic diseases, and represents a highly promising therapeutic target (17,63). Through diverse strategies, such as monoclonal antibodies, siRNA-induced gene silencing and MSC modulation, FSTL1-targeted therapy offers novel, precise treatment options for chronic inflammatory diseases such as osteoarthritis and rheumatoid arthritis (6,8,30,92). This multi-faceted, multi-level research approach has suggested broad prospects for the application of FSTL1 in treating inflammatory diseases (147). As basic research deepens and translational medicine advances, FSTL1-targeted therapy is poised for clinical application in the near future, offering more effective and personalised treatment options for patients.

5. Conclusion and discussion

Multifaceted regulatory roles of FSTL1 in disease pathophysiology. FSTL1 has emerged as a multifunctional glycoprotein that orchestrates a wide range of biological processes in both physiological and pathological contexts. Its widespread expression in the heart, lungs, skeletal muscle and joint synovium highlights its critical role in regulating cellular proliferation, differentiation and apoptosis (4-7,17,118). The structural composition of FSTL1, consisting of an N-terminal signal peptide, a follistatin-like domain and a calcium-binding EF-hand domain, enables complex protein-protein interactions that mediate its diverse functions (1-3). Studies have revealed the dual roles of FSTL1 in disease progression, demonstrating both protective and pathogenic effects depending on tissue context, disease stage and microenvironmental factors (17,62,87,118).

In osteoarthritis, the upregulation of FSTL1 in synovial fluid accelerates chondrocyte apoptosis and mitophagy through activation of the TGF-β/Smad2/3 signalling pathways, thus driving disease progression (8,39,44,96). By contrast, in cardiovascular contexts, FSTL1 exhibits cardioprotective properties by promoting angiogenesis following myocardial infarction, acting as a cardiokine that aids cardiac regeneration (2,50,52-55,96).

Molecular mechanisms and signalling networks. FSTL1 exerts its diverse biological functions through the intricate regulation of multiple interconnected signalling pathways. The TGF-β/Smad signalling axis is a cornerstone of FSTL1 function, where it serves as both a TGF-β-inducible gene and a modulator of TGF-β receptor complex formation (56-58). Previous mechanistic studies have shown that FSTL1 directly regulates Smad2/3 phosphorylation in a dose-dependent manner, with TGF-β pathway inhibitors effectively reversing FSTL1-induced Smad activation (44,49,148). This bidirectional regulatory network creates a positive feedback loop that amplifies TGF-β-mediated responses in processes ranging from cardiac regeneration to fibrotic pathology.

The NF-κB signalling pathway is regulated in a tissue-specific manner by FSTL1 (27,78), exhibiting context-dependent pro-inflammatory and anti-inflammatory effects. In renal tubular epithelial cells, FSTL1 inhibits NF-κB activation by reducing TNF-α-induced p65 phosphorylation and nuclear translocation, offering protection against kidney fibrosis (67,68). By contrast, in pulmonary and intervertebral disc tissues, FSTL1 positively regulates NF-κB signalling through TLR4/MyD88-dependent pathways, driving inflammatory cytokine production and promoting tissue degeneration (2,68).

The regulation of MAPK signalling by FSTL1 has been refined by recent research, which has demonstrated that FSTL1 functions as an ERK1/2 antagonist during ciliogenesis and preadipocyte differentiation (81), in contrast to its activating role in cardiac fibrosis, where it promotes ERK, JNK and p38 pathway activation via TGF-β1-mediated mechanisms (85-87). This functional plasticity highlights the critical role of cellular differentiation states in determining the signalling outcomes of FSTL1.

The AKT/GSK-3β pathway is another key regulatory node where FSTL1 exerts context-dependent effects on cell survival and stress responses (17,91,149). FSTL1 activates PI3K/AKT signalling, modulating downstream GSK-3β activity through phosphorylation-dependent mechanisms (94). This axis exhibits bidirectional functions: It promotes cell proliferation and invasion in tumour contexts, while providing neuroprotection and antioxidant effects in neurodegenerative and metabolic diseases by inhibiting GSK-3β activity (91,95).

FSTL1 orchestrates innate immune responses by directly regulating the NLRP3 inflammasome (69,98). It modulates NLRP3 protein oligomerisation and controls the release of inflammatory mediators in immune cells. This regulatory mechanism exhibits notable tissue and disease specificity, providing protective effects in inflammatory and autoimmune conditions (100,102,103).

FSTL1 also regulates inflammatory responses through its direct localisation to mitochondria and modulation of MQC. By enhancing electron transport chain activity, FSTL1 promotes NLRP3 inflammasome activation (19,23), while mtROS and released mtDNA trigger inflammatory cascades via the NLRP3 and cGAS-STING pathways (105,106). On the other hand, FSTL1 maintains mitochondrial integrity by regulating mitochondrial dynamics, promoting mitophagy and modulating calcium homeostasis through TMBIM6-VDAC1 interactions, preventing necroptosis (109). This dual regulatory effect highlights the complex roles of the mitochondrial-inflammatory axis.

FSTL1 coordinates vascular and metabolic homeostasis through the integrated regulation of the eNOS and AMPK pathways (16). It activates the AKT-eNOS axis to enhance nitric oxide-mediated angiogenesis and endothelial function in ischemic tissues, while stimulating AMPK signalling to promote glucose uptake, mitochondrial biogenesis and fatty acid oxidation (16). These tissue-specific regulatory mechanisms link exercise-induced myokine secretion to systemic metabolic and cardiovascular benefits.

Therapeutic applications and clinical translation. The therapeutic landscape of FSTL1-targeted interventions includes monoclonal antibody strategies, RNA interference technologies and cell-based therapies. Monoclonal neutralising antibodies are the most clinically advanced approach, demonstrating efficacy in collagen-induced arthritis models by blocking FSTL1-receptor interactions and attenuating downstream signalling. In fibrotic disease models, FSTL1-neutralising antibodies markedly reduce tissue fibrosis by inhibiting fibroblast activation (63,64,122).

siRNA-mediated gene silencing offers precise temporal control of FSTL1 expression, with nanoparticle delivery systems achieving >90% suppression with high target specificity (130). In IVDD models, FSTL1 siRNA-treated MSCs markedly improve disc morphology and function while reducing nucleus pulposus cell apoptosis (2,44). Disease-specific applications have shown promising preclinical results, with recent 2025 investigations expanding the role of FSTL1 as a non-invasive diagnostic biomarker for advanced liver fibrosis (44,60). Plasma FSTL1 levels have demonstrated diagnostic utility in chronic liver diseases (60).

Challenges and future perspectives. Despite notable progress, the development of FSTL1-targeted therapeutics faces several challenges that must be addressed for successful clinical translation. The tissue-specific and context-dependent nature of FSTL1 regulation presents a fundamental complexity, as identical interventions may produce opposing outcomes depending on the cellular context and disease stage. The concentration-dependent bidirectional regulatory effects of FSTL1 highlight the need for precise dosing and pharmacokinetic control in target tissues. Developing controlled-release formulations, tissue-targeted nanodelivery systems and feedback-regulated expression platforms may help address these pharmacological challenges.

A major translational gap is the lack of validated biomarkers for patient stratification and treatment response monitoring. While plasma FSTL1 levels are associated with disease activity in several conditions, comprehensive biomarker panels that integrate FSTL1 with downstream pathway components are necessary to enable precision medicine approaches (27,60,145).

The absence of large-scale clinical trial data remains the most important barrier to the clinical application of FSTL1-targeted therapeutics. Current evidence largely stems from preclinical models and small-scale human biomarker studies, highlighting the need for rigorously designed clinical trials to establish safety and efficacy. Future research should focus on mechanistic investigations that elucidate tissue-specific regulatory mechanisms and identify context-dependent molecular switches controlling the pro-inflammatory roles of FSTL1 compared with its anti-inflammatory roles. The development of conditional knockout models and inducible expression systems will allow for precise temporal and spatial control, enabling the dissection of stage-specific roles in disease progression.

Concluding remarks. FSTL1 is a multifaceted molecular regulator at the core of inflammation, fibrosis and tissue remodelling processes. Its intricate regulation of pathways such as TGF-β, NF-κB, MAPK, AKT/GSK-3β and the NLRP3 inflammasome, alongside its novel role in MQC, positions FSTL1 as a master coordinator of cellular homeostasis and stress responses. Therapeutic strategies targeting FSTL1, including monoclonal antibodies, RNA interference and cell-based approaches, have shown promising efficacy in preclinical models of osteoarthritis, rheumatoid arthritis, fibrotic diseases and cardiovascular disorders. The emergence of FSTL1 as both a diagnostic and prognostic biomarker across various disease contexts further highlights its clinical relevance. However, successful clinical translation is dependent on overcoming key challenges, including the complexity of tissue-specific regulation, cardiovascular safety concerns and the development of reliable biomarkers. The integration of multi-omics technologies, precision medicine strategies and advanced drug delivery systems holds the potential to address these obstacles and unlock the therapeutic promise of FSTL1. As mechanistic understanding improves and translational research progresses, FSTL1-targeted therapies are poised to become transformative precision treatments for inflammatory and fibrotic diseases.

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Authors' contributions

All authors made substantial contributions to this work. CM and JLi were responsible for the core writing work of this review, including the integration and analysis of literature content, as well as the writing and organization of the full text. WJ, XC, JLiu and XT participated in the construction of the structural framework of this review, clarified the overall logic and chapter layout of the review, undertook the collection, collation and provision of relevant references, and completed the writing of the application section of the manuscript. WL, ZD and ZZ were responsible for the review and proofreading of this review, comprehensively examining the academic rigor, content accuracy, logical consistency and expression standardization of the review, and putting forward revision suggestions. CM and JL contributed equally to this article. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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