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POSTN(+) fibroblasts and SPP1(+) macrophages in scar formation: A review of mechanisms and therapeutic targets (Review)

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Abstract. Scar formation is a physiological process that occurs as a repair mechanism following tissue damage, often presenting as scar tissue at the site of injury. This process entails intricate biological responses that are intended to restore both the structure and function of the damaged tissue. Fibroblasts, the principal cells involved in scar tissue formation, are responsible for synthesizing collagen and various extracellular matrix components, all of which are vital for restoring tissue structure. During the inflammatory phase, macrophages fulfill a critical role through clearing dead cells and pathogens, and also by secreting cytokines that regulate fibroblast activity, thereby promoting the healing process. Recent studies have demonstrated that macrophages labeled with secreted phosphoprotein 1 (SPP1) and fibroblasts labeled with periostin (POSTN) are essential for scar formation, and their interaction may represent a crucial element in this process. Through performing literature searches, the aim of the present study was to further investigate the roles and mechanisms of SPP1(+) macrophages and POSTN(+) fibroblasts in scar formation, highlighting their potential synergistic crosstalk as a novel driver of fibrosis. Furthermore, the present study systematically analyzed their individual contributions, their interaction via signaling pathways and the molecular mechanisms underlying their pro-fibrotic effects, thereby filling a critical gap in current research by focusing on specific cellular subpopulations. Furthermore, the clinical implications of targeting these specific cell subsets are discussed and this discussion provides valuable insights into the pathophysiology of these conditions, thereby establishing a theoretical basis for the development of targeted therapies for abnormal scar formation.

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Key words: scar formation, secreted phosphoprotein 1, macrophages; periostin, fibroblasts, scar tissue, wound healing

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1. Introduction

Scar formation is a fundamental physiological process through which the body repairs tissue damage following injury (1-3). Although normal wound healing restores tissue integrity, aberrant repair mechanisms often lead to abnormal scarring, such as hypertrophic scars and keloids. Although scar formation represents a physiological outcome of tissue repair, excessive or dysregulated scarring can adversely affect the normal wound healing process. Pathological scars are characterized by persistent inflammation, excessive extracellular matrix (ECM) deposition and prolonged myofibroblast activation. These abnormalities disrupt the tightly regulated phases of wound healing, particularly the transition from inflammation to tissue remodeling, ultimately leading to abnormal tissue architecture and impaired tissue regeneration (3,4). These disruptions are closely associated with alterations in key signaling pathways that regulate wound healing. For example, sustained activation of the TGF-β/Smad pathway promotes persistent myofibroblast differentiation and excessive ECM deposition, thereby impairing the transition from the proliferative to the remodeling phase. In addition, prolonged inflammatory signaling, mediated by macrophage-derived cytokines such as IL-6 and platelet-derived growth factor (PDGF), delays inflammation resolution. Furthermore, an imbalance between matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) reduces ECM degradation, ultimately leading to abnormal tissue remodeling and pathological scar formation. These pathological scars, including hypertrophic scars and keloids, impose a significant physical and psychological burden on patients (3). These fibrotic conditions not only cause aesthetic disfigurement and hinder social reintegration, but they also lead to severe pruritus, pain and functional impairment, leading to a significant deterioration in the patients' quality of life (5). Despite the availability of various therapeutic modalities, including corticosteroid injections, laser therapy and surgical excision, current treatments remain largely symptomatic, and

are heavily limited by unpredictable efficacies and high recurrence rates (1). These difficulties highlight an urgent clinical need to elucidate the precise molecular mechanisms underlying scar pathogenesis, and also the need to identify novel, targeted therapeutic strategies.

At the cellular level, tissue repair is predominantly governed by the dynamic interplay between immune cells and structural cells. The process of scar formation typically occurs during wound healing when various tissues, such as skin, muscle or internal organs, are damaged (6-8). In response, the body activates a series of repair mechanisms, which result in new tissue generation at an injury site (6-8). Newly formed tissue is generally denser compared with the original tissue, and often lacks its normal functionality (6-8). Fibroblasts serve as the primary effector cells in the proliferative and remodeling phases, and have the role of synthesizing collagen and other ECM components to reconstruct the damaged tissue (9-12). On the other hand, macrophages orchestrate the inflammatory phase by clearing cellular debris and pathogens, at the same time secreting cytokines that subsequently modulate the wound microenvironment, thereby facilitating the healing process (13-15). Studies have identified specific cellular subpopulations that perform pivotal roles in these processes (16-23). Secreted phosphoprotein 1 (SPP1), a gene encoding the multifunctional matricellular protein osteopontin (OPN), serves as a crucial marker for a distinct, highly active macrophage subpopulation (16-19). SPP1(+) macrophages are deeply involved in immune modulation, local inflammation and the regulation of the tissue microenvironment during repair (20-23). Similarly, periostin (POSTN), a distinctive marker for fibroblasts, is a matricellular protein that is extensively expressed in the ECM during tissue remodeling and fibrosis (24-27). It acts as a key contributor to structural repair and pathological scarring through excessively secreting ECM components and driving fibrotic progression within both the wound healing and the tumor microenvironments (28-31).

Emerging evidence has emphasized that the intricate crosstalk between SPP1(+) macrophages and POSTN(+) fibroblasts critically dictates the trajectories of both tissue repair and scar formation (32-36). These two cellular subpopulations are engaged in complex signaling networks that drive key biological processes, including immune regulation and ECM remodeling (32); however, despite their recognized importance, to date, research in this area has predominantly focused on macrophages and fibroblasts as broad and heterogeneous cell populations, typically examining macrophage polarization states such as M1/M2 macrophages or describing fibroblasts as general ECM-producing stromal cells (3,37,38). Consequently, a significant knowledge gap remains regarding the precise molecular mechanisms and synergistic interactions that occur between distinct cellular subpopulations such as SPP1(+) macrophages and POSTN(+) fibroblasts. Through synthesizing recent findings on these specific cell types, the present study was designed to bridge this critical gap. The present study aimed to comprehensively clarify the specific roles, signaling pathways and interaction mechanisms of SPP1(+) macrophages and POSTN(+) fibroblasts during tissue scarring, with the goal of establishing a robust theoretical framework for the development of targeted, highly specific therapies for abnormal scar formation.

Several previous reviews have summarized the general mechanisms of wound healing and scar formation, particularly focusing on fibroblast activation, macrophage polarization and key fibrotic signaling pathways (39). However, most of these studies have primarily discussed macrophages and fibroblasts as broad and heterogeneous populations, without specifically addressing the functional roles of distinct cellular subpopulations (40). These previous studies have highlighted key pathways such as TGF-β/Smad signaling, inflammatory cytokine-mediated pathways (such as IL-6 and PDGF), and ECM remodeling regulated by MMPs and TIMPs, which collectively govern fibroblast activation, macrophage polarization and scar formation.

Advances in single-cell transcriptomics have revealed the presence of specialized macrophage and fibroblast subsets (35), such as SPP1(+) macrophages and POSTN(+) fibroblasts, which may play pivotal roles in fibrosis progression. Nevertheless, systematic reviews specifically examining the bidirectional crosstalk between SPP1(+) macrophages and POSTN(+) fibroblasts during scar formation are still lacking.

Therefore, the present review aimed to synthesize current evidence regarding the roles, signaling mechanisms and reciprocal interactions of SPP1(+) macrophages and POSTN(+) fibroblasts in scar formation. By emphasizing the crosstalk between these specific cellular subsets, it provides a more refined perspective on the cellular mechanisms of fibrosis and highlights potential therapeutic targets for abnormal scar formation.

2. Materials and methods

Literature search. To ensure a rigorous and comprehensive synthesis of the current literature regarding the distinct roles of SPP1(+) macrophages and POSTN(+) fibroblasts in scar formation, a systematic literature search was executed. The identification, screening and selection of relevant studies was carried out through searching primary biomedical and scientific databases, including the PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://clarivate.com/academia-government/scientific-and-academic-research/research-discovery-and-referencing/web-of-science/), Embase (https://www.embase.com/) and Scopus (https://www.elsevier.com/products/scopus). This comprehensive literature retrieval process included publications from database inception up to October 31, 2025. The search protocol utilized a strategic combination of Medical Subject Headings (MeSH) and free-text terms, linked by Boolean operators ('AND' and 'OR') to maximize both search sensitivity and specificity. The primary search terms, deployed both individually and in various combinations, included 'scar formation', 'hypertrophic scar', 'keloid', 'wound healing', 'SPP1', 'osteopontin', 'macrophage', 'POSTN', 'periostin', 'fibroblast', 'fibrosis' and 'single-cell sequencing'. Subsequent to the initial retrieval, strict inclusion criteria were applied to ensure high academic quality and relevance to the objectives of the present study.

Selected studies were required to be peer-reviewed original research articles, single-cell transcriptomic analyses, meta-analyses or comprehensive foundational reviews.

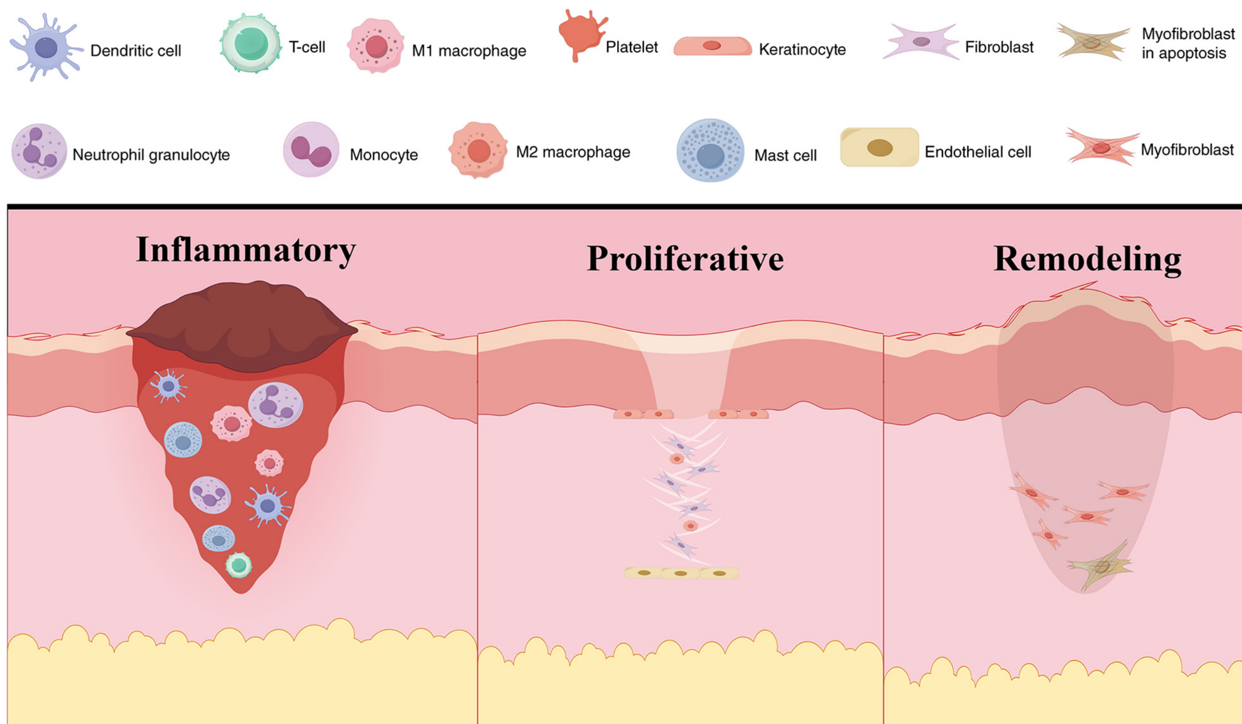

Figure 1. An overview of the scar formation process, using skin as an example. Following an injury, fibrin clots are formed as a result of platelet degranulation, contributing markedly to hemostasis. This process also results in elevated levels of TGF-β1 as well as PDGF, thereby triggering influx from various inflammatory cells, including dendritic cells, Langerhans cells, T cells, leukocytes and macrophages, along with mast cells. The cells secrete pro-inflammatory cytokines, whereas leukocytes, derived from monocytes as well as M1 macrophages, engage in phagocytosis, targeting harmful microorganisms along with cellular debris. Following this process, M1 macrophages are converted into M2 subtypes that release anti-inflammatory cytokines (for example, IL-1Ra, IL-10, VEGF, IGF-1, TGF-β1 and PDGF), thereby triggering the transition into the proliferative phase. Cytokines, as well as growth factors produced during this phase, promote movement among different cell types, including keratinocytes and endothelial cells, as well as fibroblasts. Keratinocytes contribute to re-epithelialization, endothelial cells assist with blood vessel reconstruction, and fibroblasts fulfill a key role in granulation tissue formation. Fibroblasts synthesize ECM components to support this process and, in collaboration with macrophages as well as newly developed blood vessels, they aid in granulation tissue development. Production of the ECM components is regulated through growth factors, especially TGF-β1 along with PDGF. As healing progresses, fibroblasts are transformed into myofibroblasts, which are essential in wound closure. These myofibroblasts subsequently undergo apoptosis after wound closure has occurred during a restructuring phase. At the same time, ECM synthesis persists, and its breakdown occurs through MMPs, which are controlled via TIMPs. The production of TIMPs occurs through MMPs, maintaining equilibrium in terms of ECM production vs. breakdown throughout the wound remodeling process. PDGF, platelet-derived growth factor; IL, interleukin; IGF, insulin-like growth factor; ECM, extracellular matrix; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of metalloproteinases.

Furthermore, eligible publications had to be written in English, and also had to be directly concerned with investigating the cellular mechanisms, molecular crosstalk or therapeutic targeting of the specific SPP1(+) and POSTN(+) cellular subpopulations within the context of tissue repair, fibrosis and scar pathogenesis.

To maintain a precise focus on the mechanisms of scar formation, systematic exclusion criteria were concurrently implemented. Publications were systematically excluded if: i) They were non-English articles; ii) the abstract was lacking in accessible full text; or iii) the study was devoid of specific mechanistic insights into scarring. Additionally, research articles that were primarily focused on unrelated oncological pathways or other diseases without a distinct fibrotic or wound-healing context were also omitted from this review, thereby ensuring that the synthesized data directly contributed to an understanding of abnormal scar formation.

3. Results and Discussion

Scar formation and its underlying mechanisms. Scar formation is a physiological necessity during tissue repair, culminating in the deposition of a collagen-rich ECM to restore structural integrity following injury (Fig. 1) (41-43). At the molecular level, macrophages regulate wound healing by sensing DAMPs/PAMPs via Toll-like receptors and releasing profibrotic mediators, including PDGF, IL-6, IL-11 and TGF-β1, which drive fibroblast activation. TGF-β1 is a key regulator that induces Smad2/3 phosphorylation, Smad4 complex formation and nuclear translocation, thereby promoting transcription of collagen and α-smooth muscle actin (α-SMA) and facilitating myofibroblast differentiation. In parallel, excessive ECM accumulation is reinforced by an imbalance between MMPs and TIMPs, leading to reduced matrix degradation. These processes are normally restricted by inhibitory Smads (Smad6/7) and ubiquitin-mediated degradation via Smurf1/2. However, sustained activation of these pathways results in persistent myofibroblast activity and pathological scar formation. Although the process of normal wound healing follows a highly coordinated spatiotemporal sequence that progresses through hemostasis, inflammation, proliferation and remodeling, aberrant repair mechanisms may cause a derailing of this progression (44-46). Consequently, this dysregulation leads to pathological scarring, including

the development of hypertrophic scars and keloids, which are characterized by excessive ECM accumulation and distinct clinical presentations (Table I) (4,47-49). Rather than functioning as homogeneous populations, recent evidence has demonstrated that specific cellular subsets orchestrate the transition from normal repair to pathological fibrosis. During the phases of normal scar formation, macrophages and fibroblasts exhibit highly coordinated crosstalk (Table II) (50-52). However, in pathological scarring, the prolonged activation of specific subsets, most notably SPP1(+) macrophages and POSTN(+) fibroblasts, creates a pro-fibrotic microenvironment. The continuous infiltration of these specialized macrophages, coupled with the hyperproliferation and impaired apoptosis of myofibroblasts, drives the unabated ECM deposition that is characteristic of hypertrophic scars and keloids (Fig. 2) (53-62).

The initiation of this aberrant fibrotic response is deeply rooted in prolonged innate immune activation. Damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) persistently activate inflammatory cells via Toll-like receptors (63-65). This sustained activation, in turn, triggers a cascade of pro-fibrotic cytokines, including PDGF, IL-6 and TGF-β1. Furthermore, the DAMP/PAMP-mediated stimulation of mast cells induces the secretion of histamine and proteases, which leads to a further amplification of the release of basic fibroblast growth factor and fibroblast growth factor 7 (52,64,65). Within this cytokine-rich milieu, PDGF, IL-6 and IL-11 act synergistically with TGF-β1 to forcefully drive the differentiation of fibroblasts into α-SMA-expressing myofibroblasts, which especially enriches the highly active POSTN(+) subpopulation (66). At the same time, elevated levels of TIMPs, such as the protease TIMP-1, suppress MMP activity, leading to the severe impairment of ECM degradation and ensuring massive matrix accumulation (12,38,67). Central to this pro-fibrotic signaling network is the TGF-β/Smad axis, heavily secreted by highly active macrophage subsets, including SPP1(+) macrophages (38,68,69).

Specifically, TGF-β signaling initiates downstream signal transduction by binding to type I and II TGF-β receptors on the cell membrane (70). TGF-β1 is the master regulator of the fibrotic response, binding to specific membrane receptors to phosphorylate receptor-regulated Smads (R-Smads), primarily Smad2 and Smad (71-73). Once complexed with Co-Smad (Smad4), this transcriptional complex is translocated to the nucleus, where it directly regulates gene expression and stimulates the synthesis of α-SMA and collagen (70-73).

This signaling pathway is crucial for the proper functioning of fibroblasts and myofibroblasts, especially in the context of fibrosis, where TGF-β signaling directly influences collagen synthesis and deposition (74-76). Moreover, the TGF-β signaling pathway is tightly regulated by feedback mechanisms. Inhibitory SMADs (I-Smads), for example, Smad6 and Smad7, negatively modulate the pathway by preventing the binding of R-Smads to the receptor, thereby reducing phosphorylation and shutting down TGF-β signaling (77).

In normal tissue remodeling, this intense signaling is strictly self-limiting, regulated by I-Smads such as Smad6 and Smad7, as well as precise ubiquitination mechanisms (78-81). Specifically, a number of E3 ubiquitin ligases, including Smad ubiquitin-associated factors 1 (Smurf1) and Smad ubiquitin-associated factors 2 (Smurf2), target R-Smads and the TGF-β type I receptor for proteasomal degradation, thereby effectively controlling the intensity and duration of TGF-β signaling (Fig. 3) (78). Smurf1 specifically binds to Smads 1, 5 and 8 within the cytoplasm, facilitating the ubiquitination of these proteins, whereas Smurf2 selectively targets phosphorylated Smad2 within the cell nucleus, leading to its degradation (81-84). Similarly, Smad3 ubiquitination is mediated by a ROC1-Skp1-cullin 1-F-box (SCF) E3 ubiquitin ligase complex via Fbw1a (84-86). Ultimately, the complex of Smurf together with Smad7 facilitates ubiquitination, as well as proteasomal degradation, targeting the TGF-β type I receptor, ultimately leading to the cessation of TGF-β/Smad signaling (87,88). Considered altogether, macrophages and fibroblasts fulfill an essential role in pathological scar formation, working in close association to facilitate a smooth progression from the inflammatory phase to tissue repair. Macrophages drive this process by regulating immune responses and releasing growth factors, whereas fibroblasts contribute to the process by synthesizing collagen and other ECM components, thereby forming new tissue and ensuring both wound closure and scar formation. Furthermore, the TGF-β signaling pathway is crucial for regulating collagen synthesis and fibrosis during tissue repair via Smad proteins, also ensuring that these processes are finely controlled through feedback mechanisms.

Role of POSTN(+) fibroblasts in scar formation: Mechanisms and contribution to fibrosis progression. The specific role and contribution of POSTN(+) fibroblasts in scar formation have garnered significant attention. During normal wound healing and pathological scarring, fibroblasts undergo activation and transition into myofibroblasts, a process that drives the massive secretion of collagen, and subsequent structural remodeling (12,13,26,36,54). Evidence has highlighted that distinct fibroblast subpopulations dictate the intensity of this fibrotic response (89-96). For example, in the study by Deng *et al* (89), the single-cell transcriptomic profiling of human keloid tissues revealed a marked increase in the expression of the *POSTN* gene in mesenchymal fibroblasts, strongly correlating with enhanced ECM deposition. This finding suggested that POSTN(+) fibroblasts possess a markedly amplified collagen-secreting capacity compared with POSTN(-) fibroblasts. Early foundational *in vivo* studies performed by Oka *et al* (90) further established this critical role. This research group also demonstrated that, within the first 10 days post-myocardial infarction, mice lacking the *POSTN* gene (*Postn*$^{-/-}$ mice) exhibited a markedly higher susceptibility to ventricular rupture; however, the surviving *Postn*$^{-/-}$ mice displayed markedly attenuated fibrosis, with the preservation of ventricular function. Furthermore, these knockout mice exhibited reduced levels of fibrotic remodeling and hypertrophy under chronic pressure overload conditions (90). In terms of the underlying mechanism, the *Postn*$^{-/-}$ murine models were shown to have profound molecular alterations as far as the fibroblast functional program was concerned. Fibroblasts isolated from these deficient hearts exhibited both severely compromised adhesion to cardiomyocytes and notable

Table I. A summary of the characteristics of various scar types (38-45).

Characteristic	Physiological scar	Hypertrophic scar	Keloid	Atrophic scar	(Refs.)
Clinical features	A smooth, light-colored skin patch	Red and rigid lesion	Red and rigid lesion	Sunken or pitted areas	(42,43)
	At the level of the surrounding skin	Rises above skin level	Rises above skin level	NA	(42,43)
	Firmer and less flexible than healthy tissue	Does not spread outside an original injury site	Typical projects beyond the original wound margins	NA	(42-44)
Timeframe	Scar remodeling can take several months, sometimes lasting as long as two years	4-8 weeks following injury	Developments over years	Weeks to months after the initial injury	(38,42)
		Rapid growth phase for up to 6 months	No spontaneous regression	NA	(42,43)
		Gradually regresses over years	NA	NA	(42)
Histology	Collagen fibers undergo realignment, cross-linking, as well as a transition from type III to type I collagen, offering greater tensile strength	Primarily type III collagen	Type I and III collagen	Loss of collagen, elastin, and other extracellular matrix components	(41,45)
	The collagen arranges itself in small parallel bundles, unlike the basket-weave structure found in uninjured dermis	Oriented parallel to the epidermal surface	Disorganized collagen bundles	Thinner dermis and epidermis	(41,45)
		Presence of parallel arrays of thick collagen bundles	Numerous fibroblasts appear organized in nodules scattered throughout the dermis	NA	(45)
		Inflammatory infiltrate comprising lymphocytes and macrophages	Absence in inflammatory infiltrate	NA	(40,43)
		NA	Altered ECM composition featuring elevated glycosaminoglycans	NA	(45)
Physiology/ Pathophysiology	Fibroblasts transdifferentiate into myofibroblasts	An exaggerated inflammatory response accompanied by an elevated release of cytokines as well as growth factors	Dysregulated fibroblast proliferation and collagen synthesis	A deficiency in collagen, often caused by impaired fibroblast activity	(38-40)
	The balance between ECM synthesis alongside degradation depends on the interaction between MMPs and TIMPs	Absence of myofibroblast apoptosis	Enhanced expression of pro-inflammatory cytokines	Enhanced degradation of the extracellular matrix	(41,45)

Table I. Continued.

Characteristic	Physiological scar	Hypertrophic scar	Keloid	Atrophic scar	(Refs.)
	Apoptosis in myofibroblasts, leading to a scar characterized by fewer cells	Excessive synthesis of collagen along with other ECM components	Genetic predisposition coupled with altered signaling pathways (such as MAPK, NF-κB)	Prolonged inflammation or infection can exacerbate tissue loss	(39,45)
		Imbalance between ECM synthesis and degradation	NA	NA	(45)

ECM, extracellular matrix; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of metalloproteinases; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NA, not applicable.

Table II. Characteristics of the stages of scar formation.

Phase of wound healing	Main effectors	Characteristic	(Refs.)
Hemostasis	Platelets Coagulation factors	Vasoconstriction • Platelet aggregation • Clot formation	(39-41)
Inflammation	Platelets Neutrophils Macrophages Lymphocytes Fibroblasts Myofibroblasts	Clot formation Neutrophils migrate into wound tissue Macrophages clear debris Lymphocytes infiltration ECM formation Deposition of collagen III	(46-48)
Proliferation	Vascular endothelial cells Fibroblasts	• Angiogenesis • Dissolution of clot • Wound contraction • Collagen I replaces collagen III	(39,40,46)
Remodeling	Fibroblasts Macrophages	Increased tensile strength of tissue MMPs break down collagen III	(39,40,46-48)

ECM, extracellular matrix; MMPs, matrix metalloproteinases.

transcriptional shifts, suggesting that the *Postn*$^{-/-}$ fibroblasts are incapable of secreting sufficient collagen to execute effective structural repair (90). Expanding on the origin of these highly active cells, Kanisicak *et al* (91) demonstrated that POSTN-expressing myofibroblasts in the fibrotic heart are derived from tissue-resident fibroblasts of the Tcf21 lineage, rather than from endothelial, myeloid or smooth muscle precursors. Collectively, these foundational studies have provided robust evidence that the POSTN(+) subpopulation is a primary driver of collagen biosynthesis and fibrotic progression, a paradigm that has been supported by extensive subsequent research studies across various fibrotic diseases (92-96).

Despite the clear phenotypic evidence, elucidating the precise intracellular mechanisms via which POSTN drives myofibroblast hyperactivation remains a central focus. Recent mechanotransduction studies have provided critical insights into this process (89,97-103). Xu *et al* (97) demonstrated that Piezo-type mechanosensitive ion channel component 1 (Piezo1) was highly expressed in POSTN(+) myofibroblasts within a pulmonary fibrosis model, serving as a pivotal node for mechanical activation. Subsequently, the conditional deletion of Piezo1 in POSTN(+) myofibroblasts led to a marked attenuation of pulmonary fibrosis by inhibiting cellular activation and proliferation (97). At the molecular level, the loss of Piezo1 both disrupted actin filament organization and blocked the nuclear localization of the Yes-associated protein 1 (YAP)/WW-domain-containing transcription regulator 1 (WWTR1, or TAZ) mechanotransducers (97). The inhibition of these processes effectively shifted the myofibroblasts from a highly proliferative state towards cellular stress and apoptosis (97,99) Crucially, fibroblast-specific deletion of YAP/TAZ replicated the protective phenotype observed in conditional Piezo1 knockout models, thereby firmly establishing the

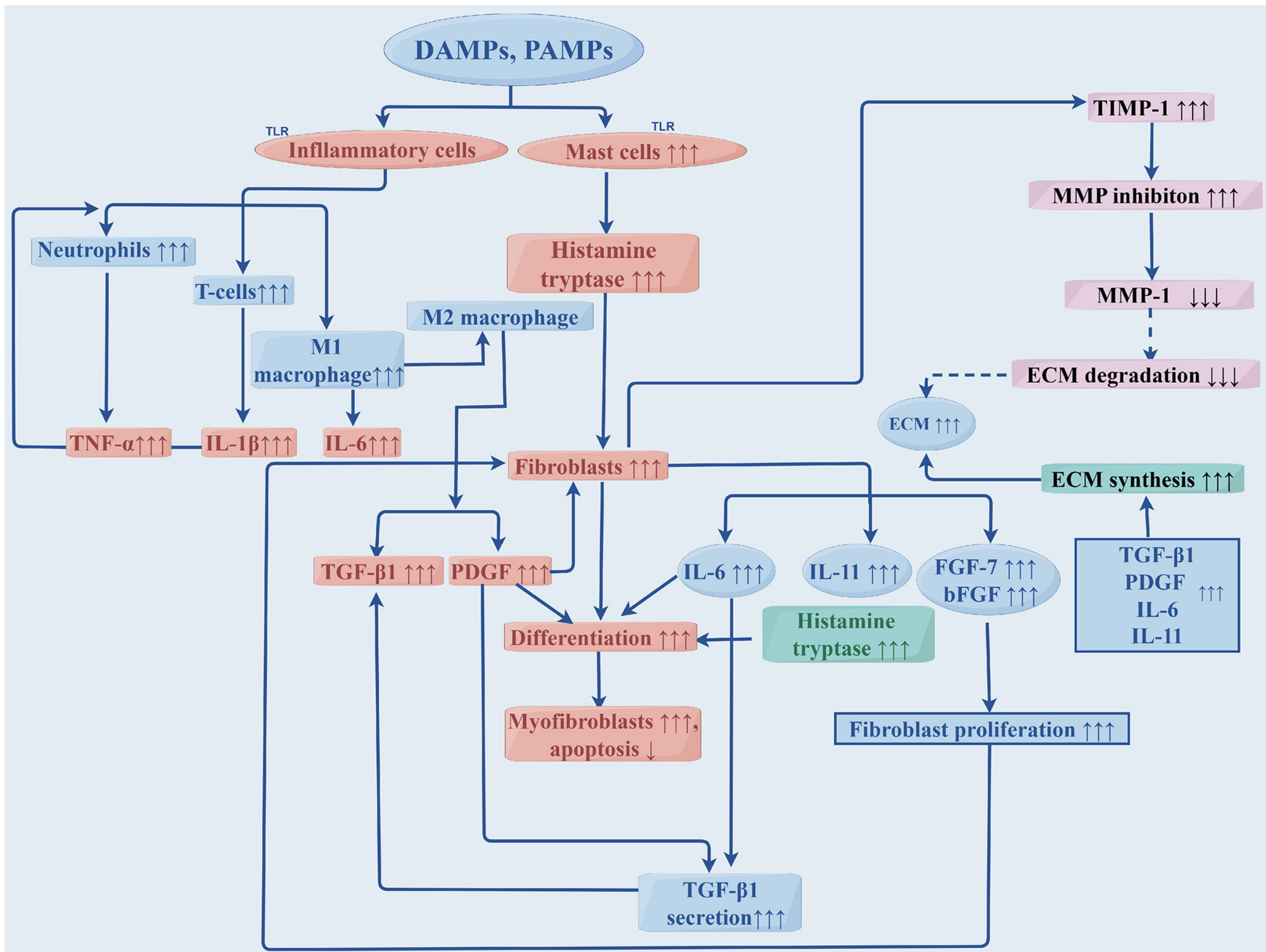

Figure 2. An overview of the biological mechanisms in hypertrophic scar, as well as keloid, formation. DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; TLR, Toll-like receptor; FGF-7, fibroblast growth factor 7; bFGF, basic fibroblast growth factor; IL-1β, interleukin-1β; PDGF, platelet-derived growth factor; TGF-β1, transforming growth factor-β1; TNF-α, tumor necrosis factor-α; M1, classically activated macrophages; M2, alternatively activated macrophages; TIMP-1, tissue inhibitor of metalloproteinase-1; MMP-1, matrix metalloproteinase-1; ECM, extracellular matrix.

Piezo1/YAP/TAZ axis as being indispensable for POSTN(+) fibroblast function (97,99).

Similar regulatory mechanisms have been identified in the pathological cutaneous scarring process. Akita *et al* (100) reported a positive association between the density of POSTN(+) fibroblasts and the expression of Piezo2 in human keloid tissues. Fibroblasts exhibiting elevated levels of Piezo2 were found to have increased levels of downstream signaling, leading in turn to increased ECM production, suggesting a functional reliance of POSTN(+) fibroblasts on Piezo2-mediated mechanotransduction, although further functional validation of these findings is required (100). Beyond mechanosensing, POSTN(+) fibroblasts are heavily regulated by complex fibrotic signaling cascades. Jiang *et al* (101) elucidated that POSTN performs a vital role in keloid inflammation and fibrosis through activating the JAK-STAT signaling pathway and dynamically modulating the IL-4/IL-13 feedback loop within the T helper 2 cell immune response. In this context, IL-4 actively upregulates POSTN expression in fibroblasts, creating a pathogenic positive feedback loop. Similarly, Maeda *et al* (102) confirmed that IL-4 induced POSTN secretion subsequently triggers TGF-β1 signaling via the RhoA/ROCK signaling pathway. The resulting elevation in TGF-β1 levels further stimulates POSTN synthesis, thereby trapping the local microenvironment in a continuous cycle of abnormal scar expansion (102).

Crucially, the pathogenic influence of POSTN(+) fibroblasts extends beyond autocrine collagen production to include profound paracrine effects on the broader wound microenvironment. For example, Zhang *et al* (103) discovered that POSTN(+) fibroblasts directly activate the extracellular-regulated kinase 1/2 (ERK1/2) and focal adhesion kinase (FAK) signaling pathways in adjacent endothelial cells. This paracrine cross-talk causes a marked enhancement of local angiogenesis, thereby supplying the metabolic demands of the expanding keloid lesion, and exacerbating the fibrotic pathology (103).

Considered altogether, during pathological wound healing, the highly active POSTN(+) fibroblast subpopulation emerges as a central orchestrator of scar formation. Through integrating profound mechanotransduction signals via Piezo channels and participating in relentless cytokine feedback loops, these cells not only drive massive autocrine collagen deposition, but also facilitate complex paracrine networks, including the process of angiogenesis, to sustain continuous and abnormal fibrosis.

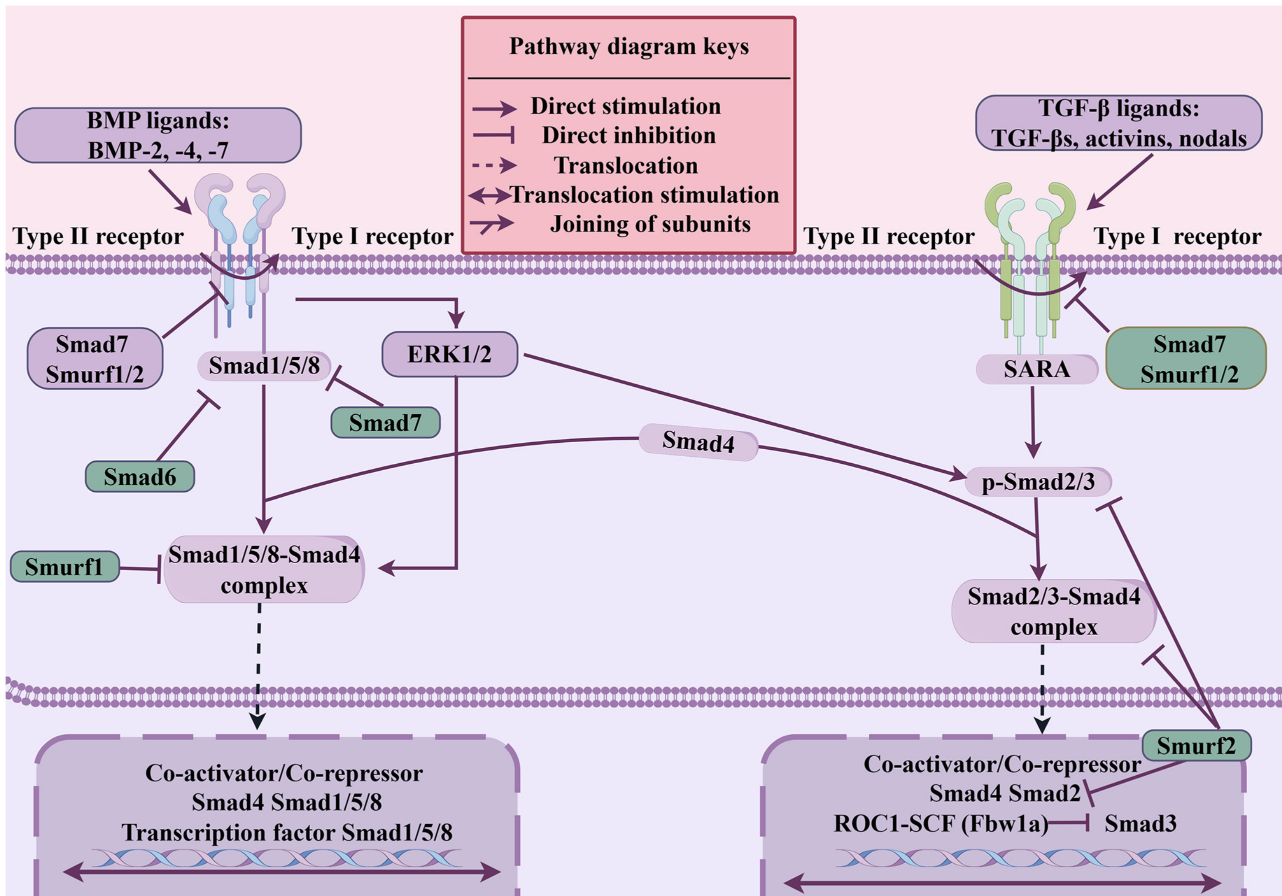

Figure 3. Smad-dependent pathway activated by TGF-β. The interaction between the ligand TGF-β and its receptor activates the type II receptor, which, in turn, initiates phosphorylation of the type I receptor. Upon phosphorylation, the type I receptor specifically identifies and phosphorylates R-Smad proteins, such as Smad2, as well as Smad3. This phosphorylation weakens their binding to the FYVE domain-containing protein SARA, while enhancing its binding to Smad4, commonly referred to as Co-Smad. Once Smad2 and Smad3 dissociate away from SARA, both bind to Smad4, forming a transcriptional complex. This complex is subsequently translocated into the nucleus, where it binds with gene-specific coactivators as well as corepressors, thereby regulating gene expression across multiple pathways. TGF-β, transforming growth factor-β; BMP, bone morphogenetic protein; Smad, small mothers against decapentaplegic homolog; Smurf, Smad ubiquitination regulatory factor; SARA, Smad anchor for receptor activation; ERK1/2, extracellular signal-regulated kinase 1/2; ROC1, regulator of cullins 1; SCF, Skp1-Cullin1-F-box; Fbw1a, F-box and WD repeat domain-containing 1A.

SPP1(+) macrophages: Their role in fibrosis formation. The recognition of SPP1(+) macrophages as central mediators of tissue repair dates back to the last century, where high levels of SPP1 expression and secretion were detected in macrophages that had infiltrated areas of the heart and brain that had sustained ischemic-reperfusion injuries (104,105). Although the exact functional significance of these cells has remained elusive since then, a landmark study by Bevan *et al* (106) in 2020 established that macrophage-derived SPP1 (also known as OPN) is indispensable for fibrotic healing in cardiac injury. Subsequent studies have transitioned from phenotypic observations to investigations aimed at elucidating the associated mechanisms, and these have characterized SPP1 as a critical paracrine regulator that modulates the surrounding cellular microenvironment to facilitate tissue repair and scar formation.

As a multifunctional secreted protein, SPP1 exerts its regulatory effects by binding to various cell surface receptors, thereby orchestrating diverse cellular responses across different tissues (18,35,106-108). Gliem *et al* (107) demonstrate that SPP1 produced by blood-derived macrophages induce astrocytes to extend their processes towards the infarct boundaries, a morphological shift that is essential for the structural repair of the ischemic neurovascular unit. Similarly, in another study by Rotem *et al* (108), macrophage-secreted SPP1 was found to directly stimulate the proliferation of myocardial cells, further supporting the repair of damaged cardiac tissue. Beyond these reparative functions, a growing body of evidence suggests that the primary contribution of the SPP1(+) macrophage subpopulation to pathological scarring lies in its ability to drive the transition of fibroblasts into myofibroblasts (Fig. 4) (35,109-113).

Recent advances in single-cell transcriptomics have further refined our understanding of the specific crosstalk between immune and mesenchymal subpopulations. A pivotal study by Hong *et al* (32) demonstrated that SPP1(+) macrophages may exacerbate pathological scar formation by establishing a specialized paracrine signaling axis with POSTN(+) fibroblasts. Even though these findings were primarily derived from computational bioinformatics analysis and necessitate further experimental validation *in vivo*, they nonetheless provide a compelling theoretical framework. This proposed interaction highlights SPP1(+) macrophages as critical upstream regulators that potentially dictate the fibrotic activity of POSTN(+) fibroblasts, thereby positioning this specific cellular axis as a key driver of aberrant tissue repair.

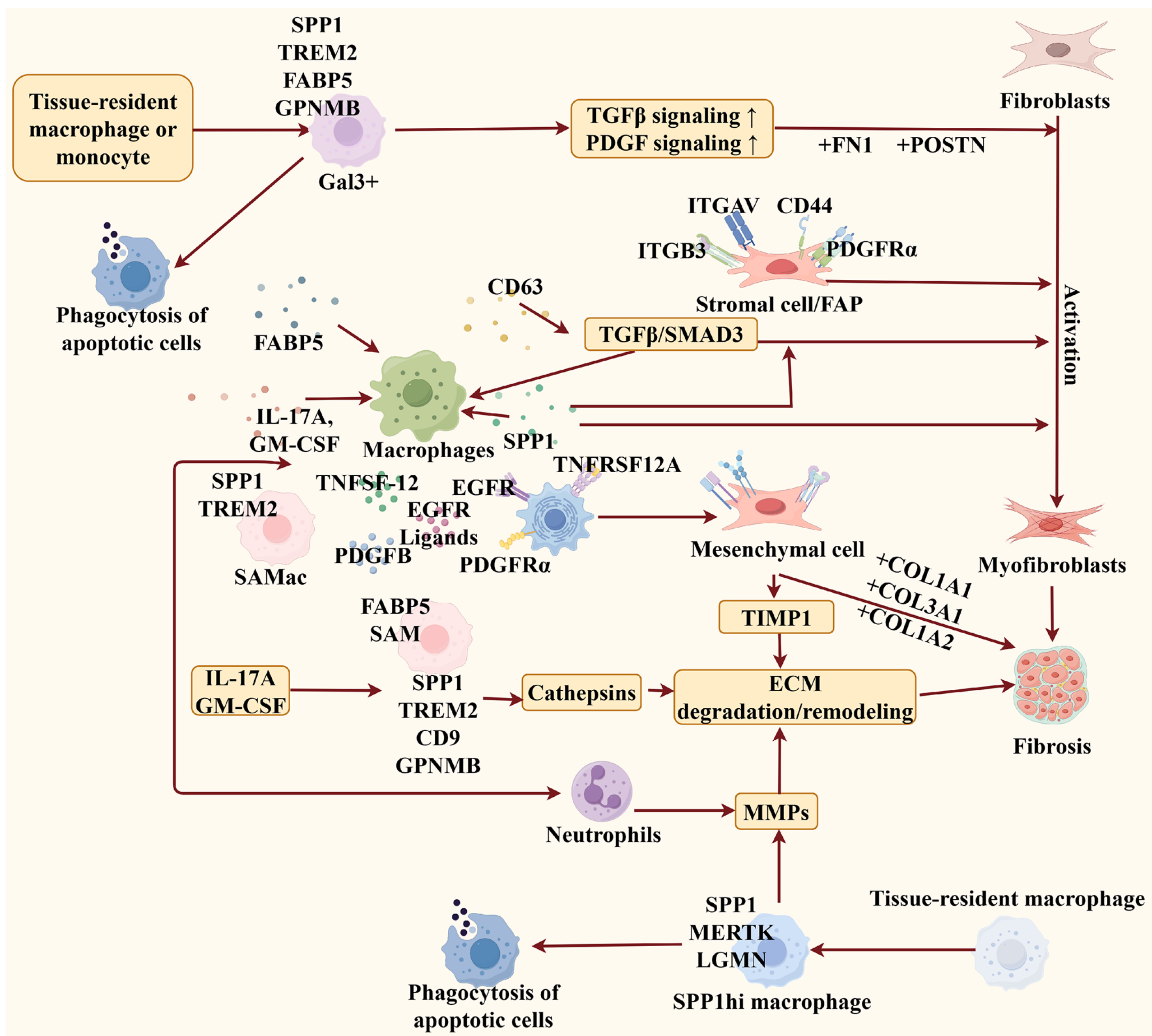

Figure 4. SPP1⁺ macrophages in fibrosis. Gal3+, galectin-3-positive; SPP1, secreted phosphoprotein 1; TREM2, triggering receptor expressed on myeloid cells 2; FABP5, fatty acid-binding protein 5; GPNMB, glycoprotein non-metastatic melanoma protein B; TGFβ, transforming growth factor-β; PDGF, platelet-derived growth factor; FN1, fibronectin 1; POSTN, periostin; ITGAV, integrin subunit αV; ITGB3, integrin subunit β3; CD44, cluster of differentiation 44; PDGFRα, platelet-derived growth factor receptor α; FAP, fibroblast activation protein; CD63, cluster of differentiation 63; IL-17A, interleukin-17A; GM-CSF, granulocyte-macrophage colony-stimulating factor; TNFSF-12, tumor necrosis factor superfamily member 12; EGFR, epidermal growth factor receptor; PDGFB, platelet-derived growth factor subunit B; TNFRSF12A, tumor necrosis factor receptor superfamily member 12A; SMAD3, SMAD family member 3; SAMac, scar-associated macrophage; SAM, scar-associated macrophage; TIMP1, tissue inhibitor of metalloproteinase 1; COL1A1, collagen type I α1 chain; ECM, extracellular matrix; MMPs, matrix metalloproteinases; MERTK, MER proto-oncogene, tyrosine kinase; LGMN, legumain.

Crosstalk between POSTN(+) fibroblasts and SPP1(+) macrophages in scar formation. Emerging evidence suggests that SPP1(+) macrophages and POSTN(+) fibroblasts may engage in functionally relevant interactions during fibrotic processes (114-116); however, direct experimental evidence of their crosstalk remains limited. To date, a direct interaction between these two specific cellular subpopulations has primarily been reported in a single-cell transcriptomic study of acne keloidalis (32), which identified ligand-receptor interactions indicative of active communication. Most of the current mechanistic understanding is derived from indirect evidence obtained from separate studies focusing on either macrophages or fibroblasts in different fibrotic contexts. For example, in pulmonary fibrosis and liver fibrosis models, macrophage-derived SPP1 has been shown to bind to receptors such as CD44 and integrins (such as αvβ3 and αvβ5) on fibroblasts, thereby activating intracellular signaling pathways including FAK and PI3K/AKT, which promote fibroblast activation and survival (117-121). In addition, SPP1 has been reported to facilitate the activation of latent TGF-β1, further enhancing fibroblast-to-myofibroblast differentiation and ECM production in fibrotic disease models (122,123). Conversely, studies investigating fibroblast biology have demonstrated that POSTN can modulate the local immune microenvironment in tumor and fibrotic settings, including breast cancer and lung cancer models, by interacting with integrins on macrophages, thereby promoting macrophage recruitment and retention (24,25,28,124). Furthermore, increased ECM stiffness

driven by POSTN-expressing fibroblasts has been shown, in mechanotransduction studies of fibrosis and tumor microenvironments, to influence macrophage phenotype and sustain a profibrotic state (97). Taken together, while these findings collectively support the existence of a potential bidirectional interaction between SPP1(+) macrophages and POSTN(+) fibroblasts, most evidence remains indirect and inferred from separate studies conducted in pulmonary fibrosis, liver fibrosis and tumor-associated models. Further experimental validation, particularly in disease-specific models of pathological scarring, is required to definitively establish the direct crosstalk between these two cellular subpopulations. Disrupting this specific, localized communication network therefore represents a crucial target in the development of definitive, targeted therapies against hypertrophic scars and keloids, moving beyond broad-spectrum, anti-inflammatory approaches.

Clinical implications and therapeutic perspectives. The complex interplay between POSTN(+) fibroblasts and SPP1(+) macrophages constitutes a core driving force in pathological scar formation. Consequently, disrupting this specific cellular crosstalk presents a highly promising therapeutic frontier for managing keloids and hypertrophic scars. Since these cellular subsets sustain the pro-fibrotic microenvironment through continuous cytokine secretion and molecular feedback loops, strategically targeting them could halt, or even reverse, the progression of severe fibrosis. For SPP1(+) macrophages, the primary pathogenic mechanism relies on the excessive local secretion of the SPP1 protein (123,125). A highly viable clinical intervention involves the deployment of engineered neutralizing antibodies designed to specifically block the interaction between SPP1 and both its own receptors and downstream receptors, including CD44 and various integrins (for example, $\alpha5\beta1$, $\alpha v\beta3$ and $\alpha4\beta1$) (18,108,119,123,125). Neutralizing antibodies targeting OPN (SPP1) have been investigated in several fibrotic and inflammatory disease models, including liver fibrosis, pulmonary fibrosis and tumor-associated fibrosis, where inhibition of SPP1 signaling attenuates fibroblast activation and ECM deposition (126-129). This targeted blockade directly severs the pro-fibrotic signaling cascade, thereby preventing the persistent activation of adjacent fibroblasts, and halting subsequent ECM deposition (79,80). Furthermore, the formation of immune complexes between these therapeutic antibodies and SPP1 has been shown to enhance Fc receptor-mediated phagocytosis by local macrophages (130). This process markedly accelerates the clearance of SPP1 from the fibrotic microenvironment, massively reducing its overall bioavailability. Even though the development of direct anti-SPP1 therapies for cutaneous scarring is currently in the preclinical stages, analogous SPP1-targeted monoclonal antibodies are undergoing rigorous clinical evaluation for other fibrotic and neoplastic conditions, providing a robust translational framework for future scar treatments.

Concurrently, directly targeting the POSTN(+) fibroblast subpopulation through genetic silencing affords an exceptionally precise therapeutic avenue. Precision medicine approaches utilizing RNA interference (RNAi) technologies, specifically those involving small interfering RNA (siRNA) and short hairpin RNA (shRNA), may be engineered to achieve the robust knockdown of POSTN expression (131,132). In terms of the underlying mechanism, these synthesized double-stranded RNA molecules are processed into single strands that are incorporated into the RNA-induced silencing complex, or RISC, within the fibroblast cytoplasm (133,134). This complex subsequently binds to the highly complementary POSTN mRNA sequence, inducing its precise enzymatic cleavage, and also preventing the translation of the POSTN protein (135). In addition to synthetic RNAi, endogenous microRNAs (miRNAs), such as miR-876 and miR-577, have emerged as potent post-transcriptional regulators (134).

Previous studies have demonstrated that these miRNAs can directly regulate POSTN-related signaling pathways. For example, miR-876 has been shown to suppress POSTN expression in hepatocellular carcinoma-associated liver fibrosis models, where it inhibits epithelial-mesenchymal transition by downregulating TGF-β signaling and reducing the expression of fibrosis-related markers such as α-SMA and collagen (132). Similarly, the miR-577/POSTN axis has been investigated in breast cancer models, where miR-577 regulates POSTN expression and downstream ILK/AKT/mTOR signaling, leading to reduced fibroblast proliferation and decreased ECM production, including collagen deposition (131). In addition to miRNA-mediated regulation, experimental strategies targeting POSTN have also been explored. For instance, in *in vitro* fibroblast systems, suppression of POSTN expression has been shown to reduce α-SMA expression, inhibit fibroblast activation and decrease collagen synthesis. *In vivo* studies using fibrotic disease models have further demonstrated that genetic or functional inhibition of POSTN attenuates fibrosis progression through modulation of TGF-β signaling pathways and ECM remodeling (90,92). However, direct evidence from siRNA/shRNA-based studies in fibrotic models remains limited. Despite these promising molecular targets and therapeutic strategies, however, several limitations must be acknowledged within both the current research landscape and the present study. However, most of these therapeutic strategies remain at the preclinical stage and clinical trials specifically targeting POSTN or SPP1 in scar formation are currently limited. At present, no registered clinical trials specifically targeting POSTN or SPP1 for pathological scar formation have been reported, and most available evidence remains limited to preclinical or early-phase studies in other fibrotic or neoplastic conditions (136,137). A primary limitation in the broader scientific field is that the majority of functional validations heavily rely on murine models. These models fundamentally lack the biological capacity to form true human keloids, thereby limiting the direct clinical translatability of the *in vivo* findings. Furthermore, although single-cell transcriptomics has proven to be useful in terms of precisely mapping the distinct presence of the SPP1(+) and POSTN(+) subpopulations, numerous studies have been only observational and descriptive in nature. More rigorous *in vivo* lineage tracing and cell-specific knockout experiments are urgently required to definitively prove direct causality in human tissue. Regarding the limitations of the present study, the literature synthesis deliberately focused on these two specific subpopulations and their immediate molecular interactions. This highly targeted scope inevitably omitted the potential contributions of other critical microenvironmental factors, including regulatory T cells, endothelial cell dysfunction and broader epigenetic

modifications that also dictate scar pathogenesis. Additionally, the rapid evolution of single-cell sequencing technologies should lead to the definitions of the transcriptomic markers for these cellular subsets being further subdivided or refined in the near future.

In conclusion, POSTN(+) fibroblasts and SPP1(+) macrophages are not merely passive participants in tissue repair, but also act as central orchestrators of aberrant fibrosis and scar formation. Through their continuous engagement in intricate autocrine and paracrine signaling loops, they sustain the inflammatory and proliferative phases indefinitely. Looking to the future, treatment approaches targeting POSTN(+) fibroblasts and SPP1(+) macrophages should offer new possibilities for treating keloids and hypertrophic scars. The development of neutralizing antibodies or other molecular strategies aimed at blocking the binding of POSTN or SPP1 to their respective receptors may help to slow, or even reverse, the scar formation process. Specifically, neutralizing antibodies against SPP1 have been shown to reduce fibroblast activation and collagen deposition, which, in turn, may mitigate the progression of fibrosis. Additionally, silencing POSTN expression in POSTN(+) fibroblasts prevents their excessive activation, thereby reducing both scar formation and fibrosis. Targeting the expression of these critical molecules through techniques that employ siRNAs, shRNAs and miRNAs is likely to provide effective strategies for managing abnormal scars. A primary limitation in the current body of literature is that numerous findings are derived from bioinformatics analyses and single-cell transcriptomic studies, which require further experimental validation. Although several studies have provided evidence from *in vitro* experiments and animal models, large-scale *in vivo* human clinical studies remain limited (136). Therefore, additional experimental and clinical investigations are needed to confirm the causal roles and therapeutic potential of these cellular subpopulations in scar formation.

Therefore, POSTN(+) fibroblasts and SPP1(+) macrophages serve not only as key regulators of scar formation, but also as promising targets for future therapies. As research into these cells and their molecular pathways continues to advance, it will enable the development of novel therapeutic strategies for treating a wide range of fibrotic diseases and improving scar formation.

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HW and XD designed the study and wrote the manuscript. Data authentication is not applicable. Both authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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