KALTPLASMA-THERAPIE (PLASMA CARE®) IN DER REGENERATIVEN WUNDMEDIZIN

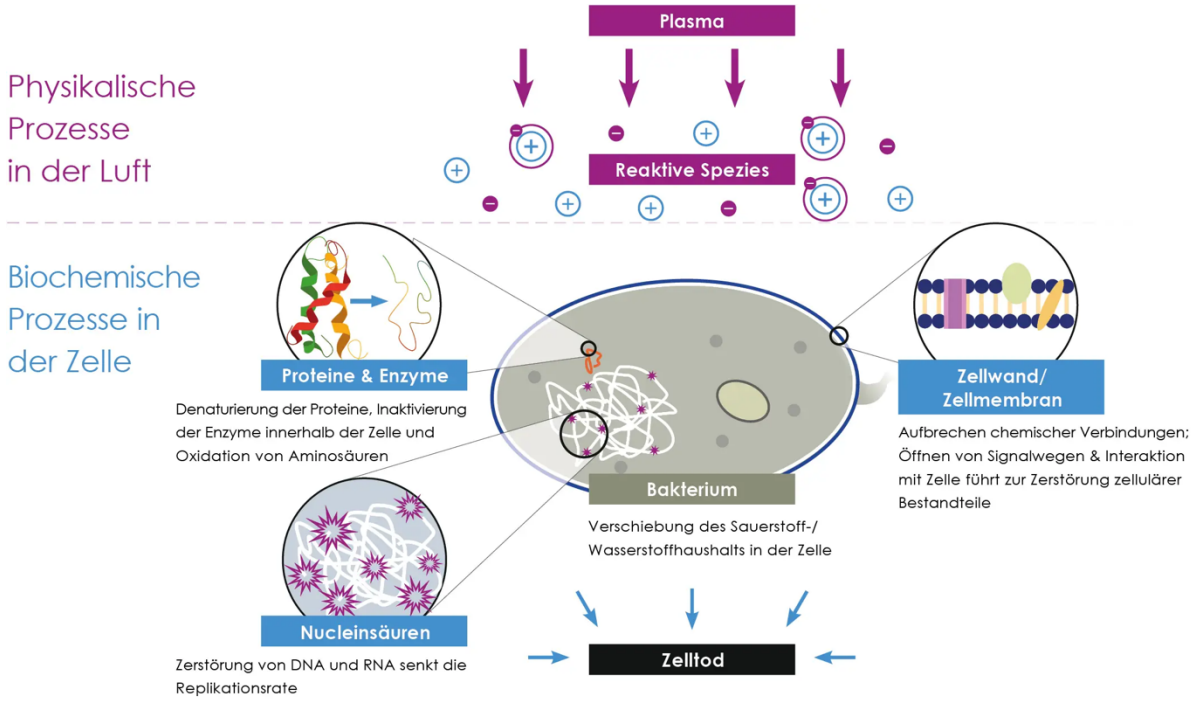
Das **Plasma Care®-System** stellt ein innovatives, medizinisch validiertes Therapieverfahren zur Behandlung infizierter und chronischer Wunden dar. Es basiert auf der Applikation von **kaltem atmosphärischem Plasma (KAP)** und ermöglicht eine effektive, nicht-invasive Dekontamination der Wundoberfläche bei gleichzeitig hoher Gewebeverträglichkeit.

PHYSIKALISCH-BIOLOGISCHES WIRKPRINZIP

Kaltes atmosphärisches Plasma ist ein partiell ionisiertes Gas, bestehend aus einem komplexen Gemisch aus:

- reaktiven Sauerstoff- und Stickstoffspezies (ROS/RNS)
- freien Elektronen
- Ionen
- UV-Photonen (im nicht-schädigenden Bereich)

Diese Komponenten wirken in synergistischer Weise auf mikrobiologische Strukturen. Das Plasma Care® nutzt eine **fortgeschrittene Dünnschichttechnologie** (basierend auf der *Surface Micro-Discharge Technology, SMD*), die eine kontrollierte Generierung von Plasma unter **Raumtemperatur und atmosphärischem Druck** erlaubt.



ANTIMIKROBIELLE UND ZELLBIOLOGISCHE EFFEKTE

Die therapeutische Wirkung beruht auf mehreren komplementären Mechanismen:

- **Disruption mikrobieller bakterieller Zellmembranen**
  Kurzzeitige Permeabilisierung („Nano-/Mikroporenbildung") führt zur Destabilisierung der Zellintegrität.
- **Induktion oxidativen Stresses**
  Reaktive Spezies führen zu strukturellen Schäden an Proteinen, Lipiden und Nukleinsäuren.
- **DNA-Schädigung und Inaktivierung von Mikroorganismen**
  Bakterien, Viren, Pilze
- **Biofilm-Reduktion**
  Plasma kann etablierte mikrobielle Biofilme aufbrechen

KLINISCH RELEVANTE EFFEKTE

- Signifikante Reduktion der mikrobiellen Last
- Antiinflammatorische Modulation im Wundmilieu
- Förderung eines regenerationsfördernden Mikromilieus
- Schmerzlinderung und Reduktion von Juckreiz
- Verbesserung von perilesionalen Dermatosen (z. B. irritative Ekzeme)

SICHERHEITSPROFIL UND ANWENDUNG

- Anwendung bei Raumtemperatur → keine thermische Gewebeschädigung
- Keine elektrische Stromleitung durch den Körper
- Keine ionisierende Strahlung
- Kein Einsatz von Edelgasen erforderlich
- Schmerzfreie Behandlung mit hoher Patientenakzeptanz

Die empfohlene Behandlungsdauer beträgt etwa 1 Minute pro 13 cm² Wundfläche, abhängig vom klinischen Befund.

Die Kaltplasma-Therapie stellt eine **hochwirksame Ergänzung zur kausalen und phasengerechten Wundbehandlung** dar. Sie ist insbesondere bei:

- infizierten oder kritisch kolonisierten Wunden
- therapieresistenten Wundverläufen
- Biofilm-assoziierten Heilungsstörungen

ein wertvoller Bestandteil eines **regenerativ ausgerichteten, ärztlich geführten Therapiekonzeptes**.

MIKROBIOLOGISCHE KONTROLLE –
DIE GRUNDLAGE FÜR REGENERATIVE HEILUNG.

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Review

Mechanisms of extracorporeal shock wave therapy in burn scar repair: Advances in immunoactivation-based scar remodeling research

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ABSTRACT

Extracorporeal Shock Wave Therapy (ESWT) plays a key role in burn scar treatment through its immunoregulatory effects, influencing inflammation, fibrosis remodeling, and angiogenesis. These mechanisms collectively mediate scar repair, highlighting the importance of ESWT in restoring tissue homeostasis. However, its clinical efficacy depends on precise optimization of parameters such as energy flux density, pulse frequency, and treatment duration. Without proper adjustments, its therapeutic potential may be limited. This review systematically explores ESWT-mediated immunoregulation in scar formation and repair, addressing its impact on inflammatory responses, tissue fibrosis, and abnormal angiogenesis. Furthermore, we discuss challenges in optimizing treatment parameters, developing personalized strategies, and enhancing clinical translation. By focusing on immunoactivation signaling pathways, this review provides mechanistic insights into ESWT's role in burn scar management and underscores its potential for precision therapy. Ultimately, it offers a theoretical foundation and practical guidance for advancing standardized clinical applications of ESWT.

1. Introduction

Burn Injuries, caused by heat, radiation, electricity, or chemicals, result in damage to the skin and other organic tissues [1–3]. Burn Injuries are the fourth most common type of trauma globally, with approximately 180,000 deaths annually, predominantly occurring in low- and middle-income countries with limited medical resources. Severe burns not only lead to high mortality rates but also impose long-term adverse effects on survivors, including reduced quality of life, psychological issues, chronic pain, and functional impairments [4–6]. Burn injuries are associated with multiple complications, including infections, sensory abnormalities (pain and itching), scar formation (hypertrophic scars and keloids), and functional disabilities such as joint contractures. Among these, pathological scars are one of the most common and challenging complications [7–9]. The impact of scars extends beyond cosmetic defects, causing severe sensory abnormalities, functional impairments, and emotional disturbances [10]. Increased scar thickness and reduced elasticity further exacerbate chronic pain and itching, significantly affecting daily quality of life [11,12]. Clinical practice often employs a combination of treatment approaches to manage scars and restore function. These include pressure garments, silicone dressings, scar massage, laser therapy, intralesional injections, and surgical excision [9]. However, these methods are typically limited to localized scars and are less effective in addressing extensive burn scar areas [13,14]. Therefore, there is an urgent need for a novel, non-invasive therapeutic strategy suitable for treating large-scale burn scars [15].

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In recent years, Extracorporeal Shock Wave Therapy (ESWT) has garnered significant attention as a potential therapeutic approach in the field of burn scar management [16]. ESWT is a non-invasive treatment modality that utilizes mechanical sound waves to stimulate tissues. Initially introduced in the 1980s for the treatment of kidney and gallbladder stones, ESWT has since been expanded to address a wide range of conditions, including musculoskeletal disorders, ischemic heart disease, neurological diseases, and dermatological conditions [17–19]. Its non-invasiveness, good patient tolerance, precise controllability of intensity and frequency, low incidence of complications, and suitability for outpatient settings make ESWT an ideal treatment option [20,21]. Additionally, its cost-effectiveness and potential application in the early inflammatory stages have established ESWT as a promising approach for preventing fibrosis and promoting tissue repair [22,23]. In burn scar treatment, Fioramonti et al. demonstrated that patients receiving ESWT exhibited significant improvements in scar appearance by the end of the study period, suggesting that ESWT is a feasible and cost-effective therapeutic option [24]. Moreover, Saggini et al. validated the efficacy of unfocused ESWT, either as a standalone treatment or combined with manual therapy, in improving scar contraction in hand scars. Their findings revealed statistically significant enhancements in scar appearance, pain reduction, and functional activity, with histopathological evidence of increased dermal fibroblasts and neovascularization [25]. Additionally, a one-year randomized controlled trial (RCT) conducted by Wang et al. compared ESWT with intralesional triamcinolone injection and found that ESWT led to substantial improvements in scar appearance, texture, and functional scores. These findings further underscore the potential of ESWT as a valuable therapeutic modality for scar management [26,27].

Although ESWT has demonstrated significant potential in the treatment of burn scars, its precise mechanisms of action remain incompletely understood, which limits the development of precision therapies. Burn scar formation is a complex pathological process involving multiple mechanisms, including inflammatory responses, fibroblast activation, extracellular matrix (ECM) remodeling, and angiogenesis [25]. Current studies suggest that ESWT may exert therapeutic effects by modulating fibroblast function, promoting neovascularization, and improving the elasticity and thickness of scar tissue. However, individual variations among patients often result in inconsistent therapeutic outcomes, and the underlying molecular mechanisms—particularly the role of immune regulation in scar remodeling—remain insufficiently investigated [10,28–31]. Immune responses play a pivotal role in scar formation, with the dynamic regulation of immune cells (e.g., macrophages and T cells) and inflammatory mediators during the inflammatory phase directly influencing scar characteristics [22]. ESWT is hypothesized to modulate immune responses by reducing inflammation or promoting the release of anti-inflammatory factors, thereby impacting the scar repair process. Nonetheless, these mechanisms require further validation, posing a critical challenge in optimizing treatment parameters and achieving precision therapy [32,33].

This study aims to review recent advances in immune regulation and scar remodeling to explore the molecular mechanisms of ESWT in burn scar treatment. By providing a theoretical basis for its clinical application, it seeks to pave the way for the development of precision therapeutic strategies. Such efforts not only have the potential to enhance the efficacy of ESWT but also contribute to a more comprehensive approach to burn scar management.

2. Mechanisms of burn scar formation: the role of immune activation in burn scar

To understand the mechanisms of ESWT in scar treatment, it is essential to first clarify the mechanisms underlying burn scar formation. Burn scar formation is a complex process of wound healing, typically divided into three phases: the inflammatory phase, the proliferative phase, and the maturation phase [34]. During the inflammatory phase, fibrin clots rapidly form at the site of injury, providing a scaffold for subsequent repair while releasing large amounts of cytokines and chemokines (e.g., TGF-β, PDGF, and EGF). These factors recruit neutrophils, monocytes, and macrophages to the wound area and simultaneously trigger the recruitment and activation of fibroblasts [25,35–37]. In the proliferative phase, fibroblasts migrate extensively to the wound area and, under the stimulation of TGF-β, proliferate and differentiate into myofibroblasts, which secrete ECM components such as hyaluronic acid, proteoglycans, and large amounts of collagen [38]. The maturation phase represents the final stage of scar formation, during which collagen fibers cross-link, type III collagen is replaced by type I collagen, and the ECM undergoes remodeling. However, burn scars often exhibit abnormal collagen cross-linking and dysregulated angiogenesis, resulting in increased stiffness and reduced elasticity [28,39–41] (Fig. 1).

Throughout this process, immune responses play a pivotal role in regulating the speed and severity of scar formation by modulating inflammation, fibroblast activity, collagen deposition, and angiogenesis. Understanding the mechanisms of burn scar formation—particularly those involving immune activation, abnormal inflammation, fibroblast activation, aberrant collagen deposition, and disrupted angiogenesis—is therefore crucial for unraveling the principles behind ESWT's therapeutic effects and optimizing its treatment strategies [9,35].

2.1. Immune-inflammatory response activation

The inflammatory response in burn scar formation begins with the activation of signals triggered by tissue damage. During the inflammatory phase, fibrin clots form in deep wounds, providing not only a structural scaffold for cell migration but also releasing a variety of cytokines and chemokines (e.g., PDGF, TGF-β, and EGF) to recruit repair cells such as mast cells and fibroblasts [34,42–44]. Additionally, damage-associated signal molecules, including transforming growth factor-beta (TGF-β), tumor necrosis factor-alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), and IL-8, further amplify the local inflammatory response [45]. These molecules promote the recruitment and activation of immune cells, initiating an inflammatory cascade essential for tissue repair [14].

These inflammatory factors attract immune cells such as neutrophils and monocytes to the wound site via chemotaxis, activating their functions. Neutrophils, the first immune cells to arrive at the injury site, clear necrotic tissue by releasing reactive oxygen species (ROS) and proteases [46,47]. Subsequently, monocytes are recruited to the wound in response to inflammatory chemokines and differentiate into macrophages [48,49]. Early in the inflammatory response, macrophages predominantly exhibit the M1 phenotype, releasing pro-inflammatory factors such as TNF-α and IL-6 to sustain inflammation, clear necrotic debris, and stimulate fibroblast activation. As the repair process progresses, macrophages transition to the M2 phenotype, secreting anti-inflammatory factors such as TGF-β and IL-10 to suppress inflammation. M2 macrophages further promote the deposition of ECM components,

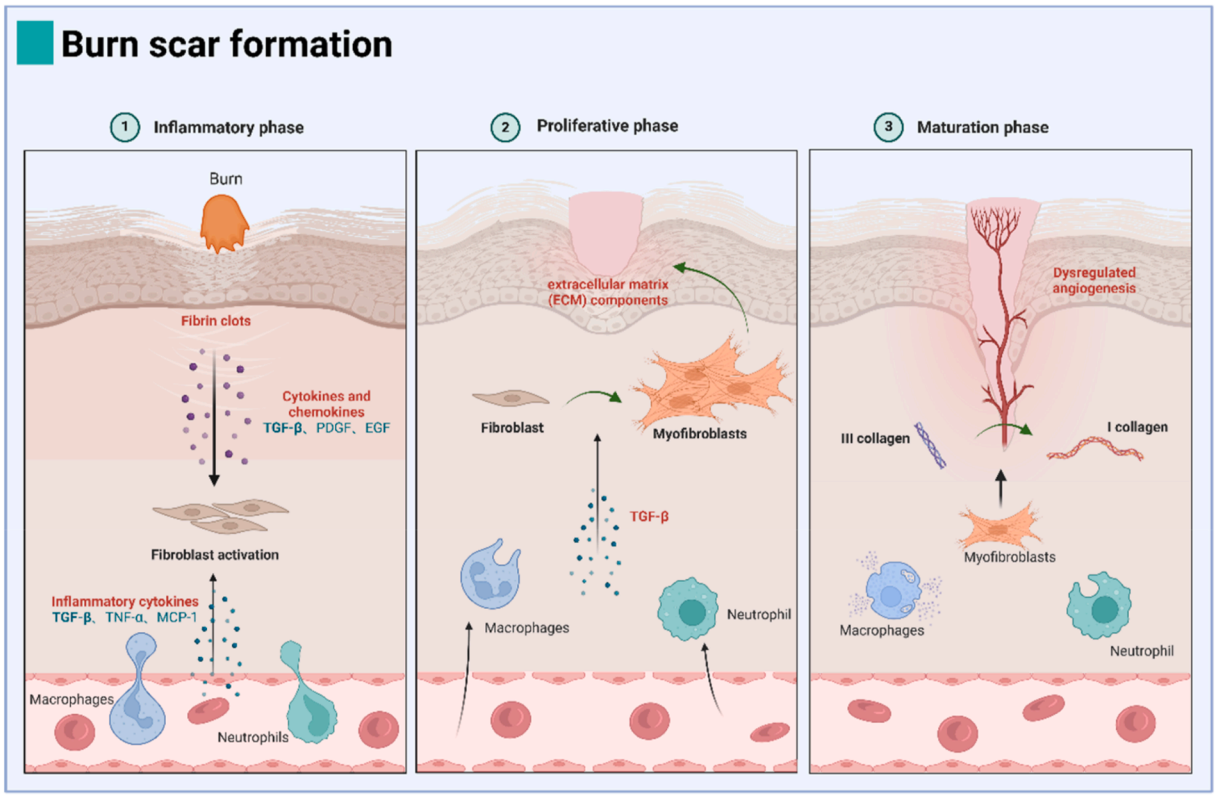

Fig. 1. Diagram of burn scar formation mechanisms.

including collagen, by fibroblasts, thereby driving scar formation [23,50–52].

2.2. Fibroblast activation and collagen deposition imbalance

The formation of burn scars is a complex pathological process driven by aberrant fibroblast activation and imbalanced collagen deposition, with immune responses playing a critical regulatory role in this process. Following dermal injury, fibroblasts are rapidly recruited to the wound site through inflammatory signaling and exhibit a highly activated state. This activation is accompanied by morphological changes, including expansion of the rough endoplasmic reticulum and the expression of specific surface markers, enhancing their capacity to produce ECM components. Fibroblasts secrete precursors of ECM, such as type I and III collagen, glycosaminoglycans, and glycoproteins, which contribute to tissue repair [38]. However, excessive fibroblast activation in burn scars leads to abnormal collagen deposition. In healthy skin, type I and III collagen account for 80 %–85 % and 10 %–15 % of total collagen, respectively, maintaining a stable ratio. During scar formation, type III collagen is rapidly deposited to initiate healing, but its subsequent replacement by type I collagen is often delayed or disrupted. This imbalance results in reduced elasticity and increased stiffness of scar tissue [39].

Immune responses play a crucial role in regulating fibroblast function during this process. For instance, macrophages in the inflammatory response secrete pro-inflammatory cytokines such as IL-6 and TNF-α, which directly activate fibroblasts. Simultaneously, these macrophages induce fibroblast differentiation into myofibroblasts via the TGF-β1 signaling pathway. Myofibroblasts are key contributors to wound contraction and excessive ECM deposition, further exacerbating scar formation [34,45,53]. Furthermore, immune-fibroblast interactions constitute another critical mechanism in burn scar formation. The polarization state of macrophages plays a pivotal role in this process: M1 macrophages drive fibroblast activation and accelerate type III collagen deposition during the early inflammatory phase by releasing TNF-α and IL-1β, whereas M2 macrophages promote scar maturation in later stages through the secretion of IL-10 and TGF-β1 [23,54]. Chronic inflammation following burns is often characterized by an imbalance in M1/M2 polarization, resulting in the persistent release of pro-inflammatory factors, excessive fibroblast activation, and further accumulation of ECM and fibrosis.

Signaling pathways such as TGF-β1/Smad, nuclear factor kappa B (NF-κB), and Wnt also play integral roles in regulating macrophage activity and scar fibrosis [23]. These pathways not only sustain fibroblast activation but may also inhibit the activity of matrix metalloproteinases (MMPs), thereby impairing ECM degradation. Additionally, the increased stiffness of scar tissue exacerbates hypoxic conditions, inducing the activation of hypoxia-inducible factor-1 alpha (HIF-1α), which stimulates TGF-β1 and other pro-fibrotic factors, creating a vicious cycle of fibrosis [52]. Therefore, immune responses, by mediating the regulation of inflammatory factors and signaling pathways, dictate the progression of scar fibrosis and the ultimate quality of tissue remodeling. Targeting key factors or pathways within the immune response may offer novel therapeutic strategies for the treatment of burn scars.

2.3. Dysregulated angiogenesis

Aberrant vascular regeneration plays a significant role in promoting scar formation, primarily through imbalances and dysfunction in angiogenesis. Following burns, hypoxic conditions

at the injury site activate HIF-1α, which upregulates the expression of vascular endothelial growth factor (VEGF), thereby stimulating endothelial cell proliferation and migration [55–57]. While angiogenesis is crucial for wound healing, excessive neovascularization leads to an abnormal increase in capillary density within scar tissue. This abnormal vascular structure not only supplies fibroblasts with additional oxygen and nutrients, further accelerating their activation and collagen deposition, but also sustains local chronic inflammation through the release of pro-inflammatory factors such as IL-6 and TNF-α [34,42,58]. Furthermore, dysregulated angiogenesis may cause localized blood flow disturbances, exacerbating oxidative stress and inflammatory responses, thus perpetuating a vicious cycle of fibrosis within the scar tissue [59]. Consequently, abnormal vascular regeneration significantly influences the scar microenvironment and fibroblast activity, playing a critical role in the formation and progression of burn scars.

In summary, the formation of burn scars is a complex process driven by mechanisms such as inflammatory responses, fibroblast activation with abnormal collagen deposition, and dysregulated angiogenesis. In the early stages following a burn, inflammatory responses mediated by pro-inflammatory factors (e.g., TNF-α, IL-1β) activate fibroblasts and induce their differentiation into myofibroblasts, leading to substantial type III collagen deposition. Subsequently, chronic inflammation and imbalances in macrophage polarization (M1/M2) further exacerbate the abnormal accumulation of ECM. Meanwhile, aberrant angiogenesis, mediated by signaling pathways involving HIF-1α and VEGF, not only intensifies local inflammation but also promotes excessive fibroblast activity by supplying nutrients and oxygen, thereby perpetuating a vicious cycle of scar fibrosis. Together, these mechanisms contribute to increased scar stiffness, reduced elasticity, and functional impairment.

These insights are highly informative for understanding the therapeutic mechanisms of ESWT. By potentially modulating inflammatory responses, suppressing excessive fibroblast activation, restoring collagen balance, and ameliorating abnormal angiogenesis, ESWT may interrupt this pathological cycle, providing a foundation for precision-based scar treatment.

3. Mechanisms of ESWT in burn scar repair based on immune activation

ESWT is a non-invasive therapeutic approach that uses high-energy sound waves propagating through tissues to induce repair and remodeling. Based on the intensity of energy flux density (EFD), ESWT can be categorized into high-energy (>0.12 mJ/mm^2) and low-energy (<0.12 mJ/mm^2) applications [60]. Shock waves, as mechanical perturbations with high propagation speeds, generate biological effects in tissues through dissipation, reflection, and kinetic energy absorption [61–63]. The therapeutic outcomes of ESWT are influenced by multiple physical parameters, including peak pressure, EFD, pulse number, and treatment intervals. However, many studies fail to comprehensively document these parameters, hindering the comparability of different experimental results [64].

Clinical studies have already highlighted the significant therapeutic value and promising potential of ESWT. For example, a prospective study by Taheri et al. demonstrated that ESWT effectively alleviates pain, itching, and scar appearance in PBPS patients [26,27]. Joo's research indicated that ESWT reduces collagen fiber accumulation by enhancing tissue microperfusion and upregulating matrix metalloproteinases (MMPs) [28]. Additionally, animal studies have shown that ESWT improves collagen alignment in hypertrophic scars, reduces scar proliferation indices, decreases fibroblast density, and modulates the proliferation and migration of keratinocytes and fibroblasts in scar tissue [31,65,66]. Despite these advancements, the precise molecular mechanisms underlying ESWT in PBPS treatment remain unclear, particularly regarding its regulatory effects on inflammatory responses, fibrosis, and angiogenesis. The lack of clarity in these mechanisms limits the optimization and precise application of ESWT in scar therapy.

ESWT exerts its therapeutic effects through mechanotransduction, converting physical stimuli into intracellular signals and inducing a cascade of cytoplasmic modifications and signal transduction pathways. This process regulates the expression of genes associated with cell proliferation, differentiation, and apoptosis, including Bax, Bcl2, ASK1, and Notch1 [11]. The therapeutic potential of ESWT in scar treatment is attributed to its ability to reduce inflammatory responses, modulate fibroblast activation, mitigate abnormal collagen deposition, and ameliorate dysregulated angiogenesis. These mechanisms involve the downregulation of TGF-β1, α-smooth muscle actin (α-SMA), and collagen type I expression [67–71]. Simultaneously, ESWT reduces inflammatory mediators and leukocyte infiltration levels while promoting neovascularization and dermal remodeling, ultimately improving the structural integrity of scar tissue [9]. A deeper understanding of these mechanisms will not only enhance our comprehension of the therapeutic effects of ESWT but also advance the development of precision treatments in clinical settings.

3.1. ESWT repairs scars by modulating immune-inflammatory responses

ESWT plays a pivotal role in scar formation and repair by regulating inflammatory responses. Hypertrophic scars (HTS), a comm on complication following burns, are primarily driven by excessive activation of inflammatory responses during wound healing. Activated T cells, macrophages, and Langerhans cells release excessive pro-inflammatory factors such as TNF-α and IL-1β, which disrupt normal tissue repair and lead to abnormal ECM accumulation [33,72]. ESWT modulates these inflammatory responses through mechanical stimulation, activating intracellular signaling pathways such as the ERK 1/2 pathway, which alters the expression of cytokines and growth factors [28,73]. Low-energy shock waves generated by ESWT can shift macrophages from a pro-inflammatory (M1) phenotype to an anti-inflammatory (M2) phenotype, a process critical for resolving inflammation and promoting scar repair [10]. Moreover, ESWT enhances the secretion of anti-inflammatory factors (e.g., IL-10) while reducing the levels of pro-inflammatory factors (e.g., TNF-α and IL-1β), thereby regulating the intensity of the inflammatory response and preventing the persistence of chronic inflammation. This dual regulatory mechanism facilitates the normal healing of scars [61,74,75]. While ESWT shows great potential as an effective therapeutic intervention, its precise mechanisms of action require further investigation and validation.

3.1.1. The role of ESWT in activating immune cells for inflammation modulation in scar formation

ESWT exerts a significant influence on multiple cell types, playing a crucial role in regulating inflammatory responses and scar formation, particularly through macrophage activation and phenotype switching. Under ESWT stimulation, macrophages can shift from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype [19,76]. This transformation is potentially mediated by the activation of key signaling pathways, including NF-κB nuclear translocation and TGF-β-induced ERK 1/2

activation [77–80]. Research by Holsapple et al. demonstrated that ESWT significantly reduces the expression of pro-inflammatory M1 macrophage markers (e.g., CD68 and HLA-DR) and decreases the secretion of pro-inflammatory cytokines such as TNF-α and IL-6, while simultaneously increasing the expression of anti-inflammatory M2 macrophage markers such as CD163 [19,81]. This shift toward an anti-inflammatory phenotype suppresses chronic inflammation and promotes tissue repair. Additionally, scar tissues treated with ESWT exhibit a higher overall macrophage count compared to untreated groups, with a marked increase in the proportion of M2 macrophages. ESWT further modulates inflammation by influencing macrophage secretion of cytokines and growth factors such as TNF, IL-1, TGF-β, and VEGF (9). Studies indicate that when ESWT pulses reach 150, levels of TNF, IL-1, PDGF, and TGF-β increase significantly, while increasing the pulse count to 300 primarily enhances TNF and TGF-β expression, with minimal changes observed in IL-6 and VEGF levels [19,82]. This suggests that ESWT can precisely regulate cytokine expression at specific doses (Fig. 2).

Furthermore, ESWT impacts lymphocytes, enhancing the expression of CD20 in B lymphocytes and CD3 in T lymphocytes, thereby amplifying the early inflammatory response critical for initiating tissue repair [83]. Natural killer (NK) cells also exhibit heightened activity under ESWT, which aids in the rapid clearance of damaged cells and inflammatory mediators, creating a favorable environment for scar repair [56]. Overall, ESWT modulates the activity and function of various cell types throughout different phases of the inflammatory response, with macrophage phenotype switching playing a central role in promoting scar repair and resolving inflammation [75,84].

3.1.2. ESWT dual-modulation of inflammatory responses for scar repair

ESWT exerts dual-modulatory effects on inflammatory responses by suppressing pro-inflammatory factors and enhancing anti-inflammatory mediators, thereby facilitating scar repair. In the context of pro-inflammatory responses, ESWT significantly reduces the secretion of pro-inflammatory cytokines such as TNF-α and IL-1β, effectively mitigating chronic inflammation and inhibiting M1 macrophage-driven inflammatory activity [10]. This regulation prevents excessive tissue damage and abnormal ECM accumulation. Simultaneously, ESWT enhances anti-inflammatory responses by upregulating IL-10 expression and increasing the proportion of M2 macrophages. This promotes the resolution of inflammation and accelerates tissue repair [19,85]. The dual-regulatory effects extend to the inhibition of fibroblast overactivation and the correction of abnormal collagen deposition. Specifically, ESWT reduces TGF-β1 levels, which leads to decreased α-SMA expression and suppresses excessive collagen type I synthesis, ultimately improving the structural and functional properties of scar tissue [28,31]. By modulating the intensity and duration of inflammation, ESWT promotes normal scar healing and improves scar appearance, providing a critical theoretical basis for the precise treatment of inflammation-associated scars.

3.1.3. The inflammatory modulation mechanism behind ESWT clinical applications

ESWT plays a pivotal role in modulating inflammatory responses through precisely designed physical parameters, significantly contributing to burn scar repair. These parameters, including EFD, pulse count, and frequency, directly influence the

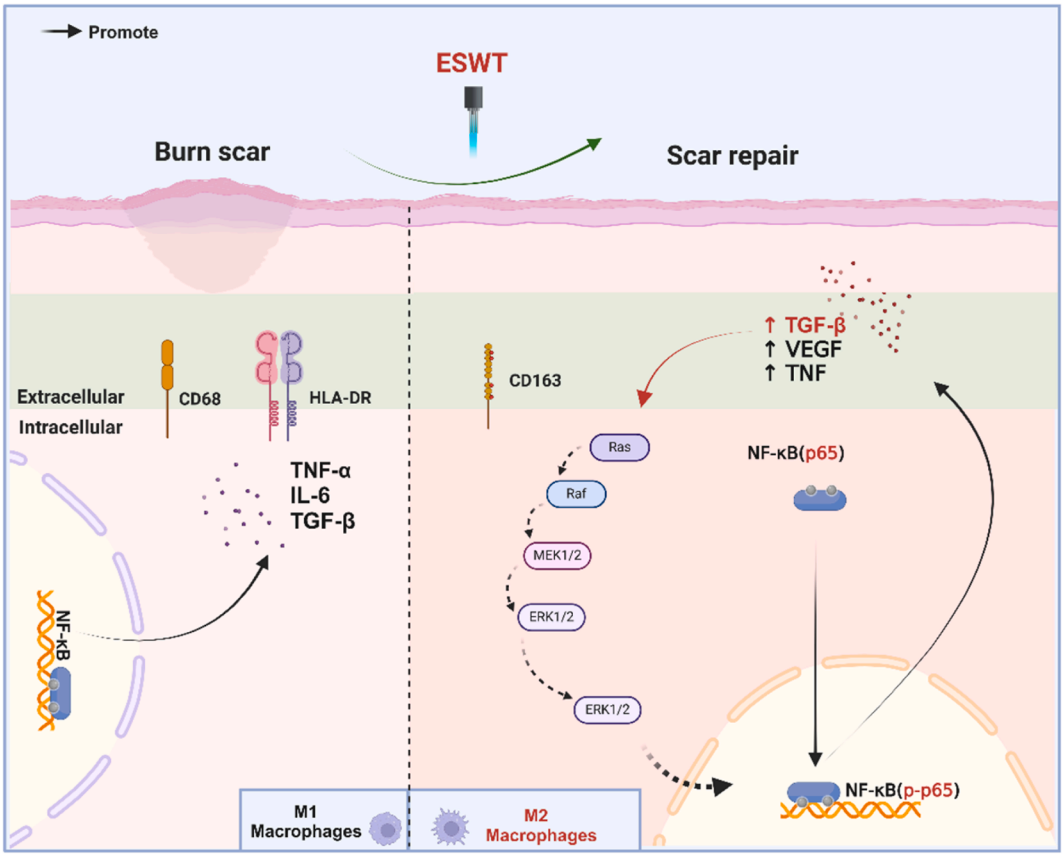

Fig. 2. ESWT regulates burn scar repair through macrophage modulation.

molecular regulatory mechanisms during the inflammatory phase. Studies have demonstrated that EFD levels ranging from 0.0024 to 0.30 mJ/mm^2 have profound effects on the expression of inflammatory factors. During the inflammatory phase, low EFD (0.0024–0.09 mJ/mm^2) combined with 200 pulses effectively upregulates chemokines such as CXCL1, CXCL12, and CXCL13, facilitating the recruitment of inflammatory cells and creating an essential cellular environment for wound repair [23,86]. Moderate EFD (0.11–0.14 mJ/mm^2) plays a crucial role in macrophage polarization, particularly in balancing the pro-inflammatory M1 phenotype and the anti-inflammatory M2 phenotype. This modulation significantly impacts the secretion of cytokines such as IL-1, IL-6, and TNF-α while enhancing VEGF expression to promote angiogenesis [87–90]. Higher EFD levels (0.18–0.30 mJ/mm^2) are closely associated with T-cell activation, as evidenced by the notable upregulation of IL-2 expression at 0.18 mJ/mm^2, indicating ESWT's capacity to influence cytokine secretion by T cells and its involvement in inflammatory responses [17]. Furthermore, EFDs ranging from 0.2 to 0.3 mJ/mm^2 regulate the expression of p21 and p27, which are critical for inflammatory modulation [29]. Interestingly, the effects of high EFD levels vary depending on cell type. For instance, fibroblasts treated with 0.30 mJ/mm^2 exhibit significant modulation of inflammatory mediators and cellular activity [87]. However, inconsistencies have been observed in Ki67 expression, as significant changes were only detected at 0.2 mJ/mm^2, suggesting that ESWT's inflammatory modulation effects are influenced by both cell type and parameter settings [91,92].

Overall, ESWT achieves inflammatory regulation through parameterized design, enabling both the promotion of inflammatory cell recruitment and early inflammatory responses with low-energy settings, and the modulation of inflammatory mediators and cell proliferation with moderate to high-energy settings. This dual approach allows ESWT to effectively control and repair inflammation (Table 1).

ESWT exerts multifaceted effects on scar repair through the bidirectional regulation of inflammatory responses. Its mechanisms involve reducing chronic pro-inflammatory factor levels and enhancing the secretion of anti-inflammatory cytokines to facilitate tissue repair. Additionally, ESWT modulates the expression of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, thereby mitigating the persistence of chronic inflammation. Through these combined mechanisms, ESWT significantly improves scar appearance and functionality, providing an important therapeutic approach for post-burn scar management. In the future, optimizing ESWT parameter settings and further elucidating its molecular mechanisms in inflammatory regulation will enhance its precision application and clinical efficacy in scar treatment.

3.2. ESWT repairs scars by modulating immune-fibrotic interactions

ESWT plays a pivotal role in alleviating scar formation by regulating key pathways of fibrogenesis through immune processes. Fibrosis is the central process in pathological scar formation, characterized by fibroblast activation, myofibroblast differentiation, and abnormal ECM accumulation. ESWT mitigates fibrogenesis through multiple mechanisms, including modulation of inflammatory responses, regulation of fibroblast activation, and promotion of collagen fiber remodeling [24,93]. Studies have demonstrated that ESWT significantly reduces the expression of inflammatory cytokines such as TGF-β1, α-SMA, and collagen type I, thereby inhibiting the transformation of fibroblasts into myofibroblasts. Simultaneously, it enhances the expression of E-cadherin, suggesting a potential role in suppressing epithelial-mesenchymal transition (EMT) during scar formation [29]. Furthermore, ESWT reduces the activity of the NF-κB signaling pathway, suppressing pro-inflammatory cytokine expression and subsequently diminishing ECM accumulation and associated fibrotic responses [20,94]. By regulating integrin α11 (ITGα11) expression, ESWT influences the migration and contractility of fibroblasts, further mitigating scar fibrosis [22]. In conclusion, ESWT alleviates the fibrotic process through multidimensional mechanisms, offering a promising therapeutic approach for burn scar management.

3.2.1. ESWT inhibits fibroblast activation to reduce burn scar formation

ESWT reduces scar formation by inhibiting fibroblast activation and associated molecular mechanisms, decreasing α-SMA expression and abnormal ECM accumulation. Fibroblasts are key cells in the fibrotic process, differentiating into myofibroblasts under pro-fibrotic stimuli, characterized by high expression of α-SMA and collagen type I, and contributing to ECM synthesis and remodeling [95]. For instance, scar-derived fibroblasts exhibit unchanged survival rates but significantly reduced migration ability following ESWT treatment, suggesting that ESWT reduces sustained stimulation to wound sites by impairing fibroblast migration. Additionally, ESWT significantly downregulates the expression of α-SMA, collagen type I, fibronectin, and twist-1 while enhancing E-cadherin expression, indicating its potential to interfere with the fibrotic process by blocking the EMT pathway [10]. By upregulating E-cadherin, ESWT restores intercellular adhesion and decreases the transition of fibroblasts into a fibrotic phenotype.

3.2.2. ESWT regulates ECM formation

In ECM formation, ESWT regulates fibrosis by breaking down collagen fibers and promoting their realignment. Studies have demonstrated that ESWT significantly reduces the accumulation of disorganized collagen fibers while activating fibroblasts to deposit thinner and more parallel collagen structures [25,96]. Furthermore, in vivo studies revealed that scar tissues treated with ESWT exhibit higher collagen content, along with thicker dermis and epidermis compared to normal skin, suggesting that ESWT supports scar repair through dermal remodeling and epithelial regeneration [97,98]. On the molecular level, ESWT decreases the

Table 1
ESWT treats burn scars by inflammatory mechanisms.

Parameters	Functions	Regulatory factors/mechanisms
Low EFD (0.0024–0.09 mJ/mm^2)	Promotes inflammatory cell recruitment and wound healing	CXCL1、CXCL12 and CXCL13 [23,86]
Moderate EFD (0.11–0.14 mJ/mm^2)	Plays a critical role in macrophage polarization	IL-1、IL-6 and TNF-α [87–89]
Moderate EFD (0.11–0.14 mJ/mm^2)	Regulates immunity and angiogenesis	VEGF [90]
High EFD (0.18–0.30 mJ/mm^2)	Modulates T-cell-related inflammatory responses	IL-2 [17]
0.2 mJ/mm2	Modulates inflammatory responses	Ki67 [91,92]
0.2–0.3 mJ/mm2	Modulates inflammatory responses	p21、p27 [29]
0.30 mJ/mm^2	Regulates inflammatory mediators and cellular activity	[87]
150 pulses	Increased proportion of anti-inflammatory M2 macrophages	TNF、IL-1、PDGF and TGF-β [23]
300 pulses	Increased proportion of anti-inflammatory M2 macrophages	ERK 1/2 pathway [23]

activity of the NF-κB immune signaling pathway, a critical mechanism controlling the expression of inflammatory and pro-fibrotic factors [20,94]. The inhibition of NF-κB not only reduces abnormal ECM accumulation but also mitigates the persistence of inflammation and fibrosis. Additionally, ESWT regulates the expression of ITGα11, disrupting mechanotransduction signaling, which decreases α-SMA expression and fibroblast migration capabilities, thereby influencing the fibrotic process of scars [22].

3.2.3. ESWT suppresses the TGF-β1/Smad pathway to reduce collagen deposition

ESWT plays a critical role in mitigating scar formation by inhibiting the TGF-β1/Smad signaling pathway. TGF-β1 serves as a pivotal regulator in fibrosis, driving fibroblast proliferation, differentiation, and ECM protein synthesis. Its expression is markedly elevated in hypertrophic scars, with prior studies showing that serum TGF-β1 levels in burn patients are approximately twice those of healthy controls. Additionally, overexpression of TGF-β1 and its receptors in fibroblasts further accelerates fibrosis progression [33,99,100]. Through the Smad2/3 signaling pathway, TGF-β1 induces fibroblast-to-myofibroblast differentiation, a key step in fibrotic scar formation [101]. Activation of Smad signaling also promotes abnormal deposition of ECM components such as collagen I and fibronectin, contributing to scar tissue stiffness and fibrosis [102].

ESWT significantly alleviates fibrotic characteristics by interfering with the TGF-β1/Smad signaling pathway. Zhao et al. demonstrated that ESWT downregulates TGF-β1 expression and inhibits Smad2/3 activation, resulting in reduced collagen production in human dermal fibroblasts [102]. This effect is closely linked to the regulation of ID family proteins, including ID-1 and ID-2. Studies indicate that ESWT upregulates ID-1 and ID-2 expression, with ID-1 overexpression shown to inhibit TGF-β1-induced Smad signaling and prevent excessive collagen accumulation [28,103]. Furthermore, ID-2 exhibits broader anti-fibrotic effects. Transgenic mouse models reveal that ID-2 alleviates fibrosis by downregulating Twist-1 expression [24]. During ESWT treatment, Twist-1 expression is significantly suppressed, while the upregulation of ID-1 and ID-2 proteins may induce mesenchymal-to-epithelial transition (MET), reversing fibroblast activation and offering a novel approach to mitigate scar fibrosis [104]. In summary, ESWT suppresses the TGF-β1/Smad signaling pathway and modulates associated protein expression, inhibiting critical steps in immune inflammation and fibrosis. These findings highlight ESWT's potential as a promising treatment for hypertrophic scars.

3.2.4. ESWT activates MMPs to inhibit burn scar fibrosis

ESWT exerts a significant role in ECM degradation and inhibition of scar fibrosis through the activation of MMPs. Abnormal ECM deposition is a core pathological feature of hypertrophic scars (HTS), driven by the excessive proliferation and differentiation of fibroblasts into myofibroblasts. These myofibroblasts, characterized by high α-SMA expression, synthesize excessive ECM components such as collagen and fibronectin, leading to scar stiffness and fibrosis [105]. During wound healing, MMPs and collagenases play critical roles in ECM degradation and remodeling. MMP1 and MMP2, in particular, regulate ECM accumulation and functional balance by breaking down collagen and fibrous proteins [105,106]. However, in fibroblasts, the overproduction of the inflammatory cytokine TGF-β1 suppresses MMP activity, resulting in abnormal ECM deposition and exacerbated fibrosis [107,108]. Studies have shown that ESWT can upregulate MMP1 and MMP2 activity, likely through immune response modulation, thereby promoting ECM degradation and improving the remodeling characteristics of scar tissue [107,109].

In addition to regulating ECM degradation via MMPs, ESWT may closely interact with EMT and MET processes. Research indicates that ESWT reduces the expression and activity of the inflammatory factor TGF-β1, thereby inhibiting EMT-associated cytoskeletal markers such as α-SMA and vimentin, while simultaneously promoting MET [105]. This process reverses fibroblast differentiation into myofibroblasts, mitigating the key drivers of fibrosis. Furthermore, ESWT alters MMP activity levels, enhancing the functional degradation of ECM components and restoring normal tissue structural balance. This degradation process not only reduces excessive ECM accumulation but also releases TGF-β1 from its inactive form trapped within the ECM, further attenuating its fibrotic effects [107]. In summary, ESWT inhibits fibrosis by activating MMPs to reduce ECM accumulation, while simultaneously suppressing TGF-β1 signaling and associated EMT processes. This demonstrates significant therapeutic potential for managing hypertrophic scars, providing an essential foundation for clinical interventions in scar fibrosis.

3.2.5. The fibrosis regulation mechanisms behind ESWT clinical applications

Studies have demonstrated that ESWT exhibits significant regulatory effects on fibrosis-related molecules within various EFD ranges. For instance, EFDs ranging from 0.03 to 0.30 mJ/mm^2 significantly reduced fibronectin mRNA expression after 24 h, while fibronectin protein levels significantly increased after 72 h. This suggests that ESWT may regulate fibronectin at multiple levels, promoting the dynamic balance of fibrosis [29,91]. Additionally, Rinella et al. and Wang et al. used EFDs of 0.32 mJ/mm^2 and 0.11 mJ/mm^2 with 1000 and 500 pulses, respectively, to effectively reduce type I collagen expression and minimize type V collagen accumulation, indicating ESWT's potential to downregulate ECM deposition during fibrosis [21,26,90]. Regarding type III collagen, Wang et al. observed a significant reduction using an EFD of 0.11 mJ/mm^2, further confirming ESWT's specific regulatory effects on different collagen types [110].

Furthermore, Tinazzi et al. discovered that EFDs ranging from 0.20 to 0.25 mJ/mm^2 significantly increased the expression of intracellular adhesion molecule-1 (ICAM-1) and membrane cofactor protein-1 (MCP-1), suggesting that ESWT can modulate the crosstalk between inflammation and fibrosis [111]. ESWT's regulatory role in fibrosis signaling pathways has also been validated through the MAPK and ERK/Akt pathways. For example, Weihs et al. demonstrated that EFDs ranging from 0.030 to 0.19 mJ/mm^2 significantly influenced the ERK pathway, while an EFD of 0.25 mJ/mm^2 with 3000 pulses enhanced the expression of markers associated with cell proliferation and migration, such as PCNA and fibronectin [18,88]. These findings highlight that ESWT, through precise parameter optimization, can upregulate or downregulate the expression of fibrosis-related molecules, ultimately enabling dynamic scar repair (Table 2).

ESWT plays a crucial role in scar repair by modulating fibrosis-related molecules. Its mechanisms include reducing abnormal accumulation of collagen and fibronectin, promoting ECM degradation, and enhancing the regulatory balance of fibroblasts and inflammatory factors. Clinical studies have demonstrated that a six-week treatment protocol with ESWT can dynamically regulate fibrosis-associated signaling pathways, effectively contributing to scar repair [110]. In the future, further optimization of ESWT parameter design, elucidation of its molecular mechanisms in immune-related fibrosis, and integration with other therapeutic approaches will help enhance its precision and efficacy in clinical

Table 2
ESWT treats burn scars by fibrosis modulation mechanisms.

Parameters	Functions	Regulatory factors/mechanisms
0.03–0.30 mJ/mm^2, 24h	Reduced fibronectin expression	Fibronectin mRNA [29]
0.03–0.30 mJ/mm^2, 72h	Increased fibronectin expression	Fibronectin mRNA [26]
0.11 mJ/mm^2,500 pulses	Decreased type III collagen, downregulated ECM deposition	Type III collagen [110]
0.11 mJ/mm^2,500 pulses	Decreased type V collagen, downregulated ECM deposition	Type V collagen [21,26,90]
0.20–0.25 mJ/mm^2	Increased ICAM-1 and MCP-1 expression, regulating the crosstalk between inflammation and fibrosis	ICAM-1、MCP-1 [111]
0.25 mJ/mm^2, 3000 pulses	Enhanced cell proliferation and migration	PCNA, fibronectin [88]
0.030–0.19 mJ/mm^2	Significant impact on the ERK pathway	Akt, P38 [18]
0.32 mJ/mm^2, 1000 pulses	Reduced type I collagen expression	Type I collagen [19,90]

applications, paving the way for new strategies in the treatment of hypertrophic scars.

3.3. ESWT repairs scars by modulating immune- angiogenesis responses

ESWT promotes angiogenesis and regulates immune responses, playing a vital role in alleviating scar formation and enhancing tissue repair. Angiogenesis is a critical step in tissue repair, accelerating the wound healing process by increasing nutrient supply and facilitating cell migration. ESWT significantly upregulates pro-angiogenic factors, including VEGF, its receptor VEGFR, endothelial nitric oxide synthase (eNOS), and hypoxia-inducible factor-1α (HIF-1α), thereby enhancing angiogenic potential [17,41,112]. Additionally, ESWT regulates angiogenic markers such as CD31 and CD105 and differentiation clusters like CD9, CD63, and CD81, further promoting neovascularization [21,56,95]. Studies have shown that ESWT improves tissue remodeling by stimulating fibroblast and endothelial cell proliferation, demonstrating remarkable efficacy, particularly in treating hypertrophic scars and keloids [24,113]. By degrading excessive collagen and modulating pro-inflammatory cytokines, ESWT not only enhances blood supply and perfusion but also alleviates ischemia-related scar complications by improving local microcirculation [114,115]. Moreover, through nitric oxide (NO)-induced regulation of NF-κB activation, ESWT promotes the expression of angiogenic genes and the improvement of the immune microenvironment [116,117]. These mechanisms establish ESWT as an effective intervention for enhancing angiogenesis, regulating immune microenvironments, and repairing scar tissue.

3.3.1. ESWT regulates angiogenesis to promote burn scar repair

ESWT exerts multiple effects on improving the immune microenvironment and promoting scar repair by regulating angiogenesis-related molecules and signaling pathways. Angiogenesis is one of the core mechanisms through which ESWT modulates immunity and tissue regeneration during scar repair. In terms of angiogenesis-related molecules, ESWT significantly upregulates the expression of VEGF, VEGFR, and eNOS, which are critical in the proliferation, migration, and differentiation of endothelial cells [17,41,112]. VEGF, by binding to its receptor VEGFR, activates downstream signaling pathways such as Akt/Erk and p38 MAPK, thereby promoting the formation of new blood vessels [18]. Additionally, the expression of the HIF-1α pathway is notably enhanced by ESWT, which is a vital factor for inducing angiogenesis in hypoxic microenvironments and further strengthens the process by regulating VEGF expression [52,56]. In endothelial cells, ESWT also modulates the expression of molecules such as CD31 and CD105, enhancing functional differentiation of endothelial cells and forming a more stable capillary network [21,56,95].

ESWT improves the local immune status by reducing inflammatory responses during the healing process, thereby regulating the immune microenvironment. Studies have shown that ESWT enhances immune cell recruitment by modulating the expression of ICAM-1 and MCP-1, improving the local inflammatory state [111]. Simultaneously, by stimulating angiogenesis, ESWT increases perfusion and oxygen supply to the local tissue, directly alleviating chronic inflammation caused by ischemia [114,115]. Through the regulation of NF-κB, ESWT significantly reduces the expression of pro-inflammatory factors, such as TNF-α and IL-1β, and further decreases inflammation levels via NO induction [118]. Additionally, ESWT upregulates PCNA and stimulates the formation of new capillaries and myovascular vessels, accelerating tissue repair and improving the immune microenvironment [119].

Research also suggests that ESWT not only promotes localized angiogenesis but also enhances blood flow and microcirculation in distal skin areas, boosting overall repair capacity [115]. In fibrosis-related scar repair, ESWT alleviates excessive ECM deposition and scar tissue hardening by improving angiogenesis and the immune microenvironment. VEGF upregulation not only enhances blood supply but also promotes the restoration of normal tissue structure by improving interactions between fibroblasts and vascular endothelial cells [28]. Moreover, ESWT reduces excessive collagen accumulation and improves the tissue's mechanical properties and repair capacity through the adjustment of the laminin/integrin ratio [95]. In Fioramonti et al.'s study, ESWT was shown to effectively improve scar vascularization and the microenvironment, providing supportive evidence for its clinical application in scar repair [28,86]. In summary, ESWT demonstrates significant potential in promoting scar repair and tissue regeneration through multilayered regulation of angiogenesis and the immune microenvironment.

3.3.2. The angiogenesis regulation mechanisms behind ESWT clinical applications

ESWT demonstrates significant angiogenesis-regulating effects through precise parameter design. Studies indicate that EFD, pulse count, and frequency are key factors influencing its role in promoting angiogenesis. For instance, using an EFD of 0.32 mJ/mm^2 with 1000 pulses significantly upregulates growth factor (GF) expression and exerts positive effects on α-SMA [21]. Tinazzi et al. further confirmed that an EFD of 0.2–0.25 mJ/mm^2 combined with 1000 pulses at 4 Hz significantly increases vascular endothelial growth factor (VEGF) expression, which is crucial for initiating and maintaining angiogenesis [120].

Moreover, varying EFD conditions have differential impacts on angiogenesis. For example, higher EFD levels above 0.2 mJ/mm^2 exhibit stronger effects on regulating burn scar vascularization. However, careful parameter optimization is essential to avoid potential tissue damage [95]. By employing precise parameter design, ESWT achieves both molecular and cellular interventions

in angiogenesis regulation. It not only upregulates angiogenic factor expression but also reduces fibrosis-related abnormal ECM accumulation by improving microcirculation and perfusion (Table 3).

ESWT demonstrates significant clinical potential in promoting scar repair and improving fibrosis by modulating angiogenesis and the immune microenvironment. In terms of angiogenesis, ESWT upregulates key factors such as VEGF, VEGFR, and HIF-1α, activates endothelial cell-associated pathways, and promotes the formation of new capillaries [120]. This not only enhances blood supply to scar tissue but also alleviates chronic inflammation caused by ischemia through improved local perfusion. Clinical studies have shown that ESWT significantly improves hypertrophic scars, keloids, and burn scars by reducing scar thickness, optimizing vascular distribution, and restoring functionality [120]. In the future, optimizing ESWT parameter settings, integrating it with other treatment modalities, and elucidating its molecular mechanisms will further enhance its precision application in scar repair and tissue regeneration, offering novel therapeutic solutions for related conditions.

3.4. ESWT repairs scars by modulating other mechanisms

In addition to modulating inflammation, fibrosis, and angiogenesis, ESWT also enhances scar repair through mechanisms such as promoting apoptosis and activating endogenous stem cells, showcasing its multi-level regulatory potential. These effects not only synergize with immune regulatory mechanisms to optimize inflammatory responses but also interact with angiogenesis and fibrosis modulation processes to accelerate scar tissue remodeling and functional recovery. This multidimensional mechanism provides significant theoretical support and application prospects for the precision treatment of scars.

3.4.1. ESWT repairs scars by modulating apoptosis

ESWT plays a critical role in scar repair by regulating apoptosis. Studies have shown that ESWT exerts a bidirectional modulation on pro-apoptotic factors, such as Bax, and anti-apoptotic factors, such as Bcl-2, depending on EFD settings. At an EFD of 0.2 mJ/mm^2, the activity of pro-apoptotic factors Bax and caspases 3 and 14 was significantly reduced [10,93,121], while at 0.3 mJ/mm^2, their activity was notably elevated, indicating a dose-dependent apoptotic regulation by ESWT [26,92,121] (0–18, 22, 37). Additionally, ESWT at 0.3 mJ/mm^2 dynamically modulated apoptosis-related molecules by activating the ASK1 and Erk/Akt signaling pathways, facilitating the transition of pathological phenotypes toward normal physiological states [18,19]. Within 72 h, the expression levels of Bcl-2 and Bax approached those of normal cells, promoting cellular homeostasis and epidermal repair [10].

Clinically, ESWT has been observed to induce apoptosis in pathological scar cells (HTSKs), thereby improving fibrotic tissues, reducing collagen accumulation, and restoring normal tissue architecture in scarred regions. For instance, Suhr et al. demonstrated that ESWT at 0.3 mJ/mm^2 significantly enhanced caspase pathway activation, promoting apoptosis and improving the appearance and functionality of scars [92]. This mechanism provides a strong theoretical foundation for the use of ESWT in treating hypertrophic and keloid scars. Future efforts to optimize individualized treatment parameters could further enhance its therapeutic efficacy and clinical applicability (Table 3).

3.4.2. ESWT repairs scars by activating stem cells

ESWT may also exert significant therapeutic effects on scars by activating endogenous stem cells. Studies suggest that stem cells in keloids play a critical role in sustaining fibrotic activity and excessive collagen production, both of which are key drivers of pathological scar growth [25,122,123]. By modulating the stem cell microenvironment, ESWT enhances the secretion of anti-inflammatory and reparative factors, targeting the core pathological mechanisms of scar formation. Specifically, the regulation of ITGα11 by ESWT appears to be a key pathway for its effects on stem cells. Overexpression of ITGα11 is typically associated with increased α-SMA expression, cell contraction, and enhanced migratory capacity, which collectively reduce cellular sensitivity to ESWT. However, optimized ESWT parameters, such as appropriate EFD and pulse frequency, have been shown to effectively activate endogenous adipose-derived stem cells (hASCs), increasing the secretion of anti-inflammatory factors (e.g., IL-10) and reparative growth factors (e.g., VEGF). This modulation suppresses excessive fibrosis and promotes tissue regeneration [21]. Additionally, ESWT may restore tissue microenvironment balance by influencing integrin signaling in stem cells, thereby mitigating scar tissue stiffening and abnormal growth. These mechanisms underscore the significant therapeutic potential of ESWT, particularly in inhibiting fibrosis and enhancing tissue repair. This highlights ESWT as a promising strategy for scar treatment and its further optimization could maximize its clinical applications.

Therefore, ESWT demonstrates multifaceted mechanisms in burn scar repair, encompassing immune-inflammatory regulation, fibrosis modulation, and angiogenesis, while also achieving multi-layered effects through promoting apoptosis and activating endogenous stem cells. Among these mechanisms, immune modulation is regarded as a critical component of ESWT's potential, playing a pivotal role throughout processes such as inflammatory response, fibrosis regulation, and angiogenesis. In terms of inflammation regulation, ESWT balances local immune responses by modulating macrophage phenotypes and adjusting the secretion of pro-inflammatory and anti-inflammatory factors. Regarding fibrosis control, ESWT reduces fibroblast activity and excessive ECM deposition by suppressing the TGF-β1/Smad signaling pathway, while simultaneously activating MMPs to promote ECM degradation and remodeling. Additionally, ESWT mitigates fibrosis by modulating EMT and inducing MET, restoring the functionality and elasticity of scar tissue. In angiogenesis, ESWT promotes endothelial cell proliferation and migration by upregulating VEGF, VEGFR, and HIF-1α expression, increasing capillary density and improving blood supply to scar regions. This process not only accelerates tissue repair but also significantly

Table 3
ESWT Treats Burn Scars by angiogenesis regulation and other Mechanisms.

Parameters	Functions	Regulatory factors/mechanisms
0.2–0.25 mJ/mm^2	Initiation and maintenance of angiogenesis	VEGF [120]
>0.2 mJ/mm^2	Improvement of burn scar vascularization	CD105 [95]
0.32 mJ/mm^2,1000 pulses	Improvement of burn scar vascularization	GF、α-SMA [21]
0.2 mJ/mm^2	Reduction of apoptosis	Bax, Caspases [10,93,121]
0.3 mJ/mm^2	Promotion of apoptosis	Bax, Caspases [26,92,121]
0.3 mJ/mm2	Promotion of apoptosis	Ask1/Erk/Akt pathway [18,19]

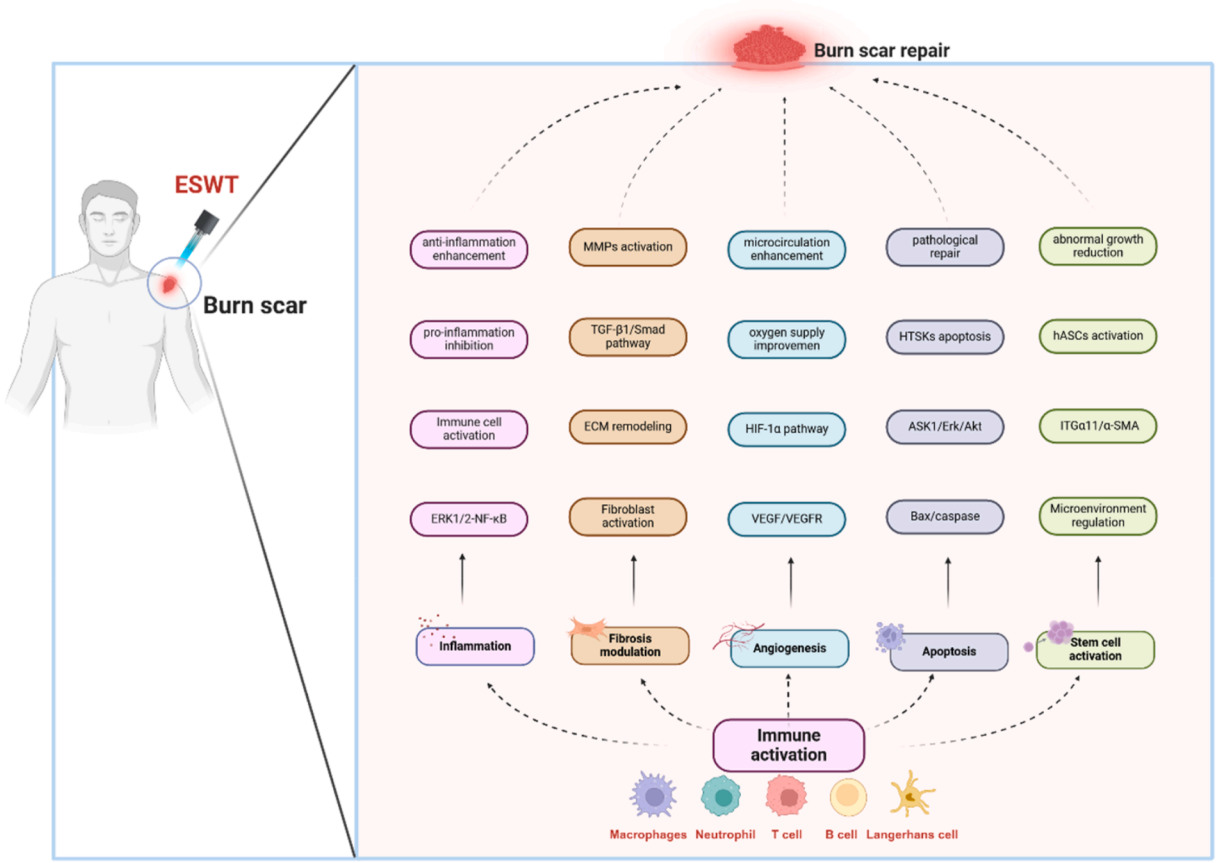

Fig. 3. Overview of immunoactivation-based mechanisms of ESWT in scar repair.

alleviates chronic inflammation caused by local ischemia and nutritional deficiencies. Through these multi-pathway and multi-dimensional synergistic effects, ESWT provides novel mechanistic insights into burn scar treatment and paves the way for the development of precision-based therapeutic strategies (Fig. 3).

4. Clinical application prospects

ESWT demonstrates significant mechanistic advantages and potential clinical value in burn scar repair, leveraging mechanisms such as immune-inflammation regulation, ECM remodeling in fibrosis, angiogenesis, apoptosis, and stem cell activation. At the cellular level, ESWT modulates the proliferation and function of macrophages, fibroblasts, and keratinocytes, thereby promoting early epithelial formation and scar repair during wound healing [29,124]. By suppressing profibrotic factors (e.g., TGF-β1) and fibrosis markers (e.g., α-SMA) while enhancing MMP activity, ESWT reduces abnormal ECM deposition, improves scar elasticity, and restores tissue structure. Furthermore, studies reveal that ESWT can activate endogenous stem cells, enhancing their reparative capacity and accelerating the transition of scar tissue to normal tissue. Among these mechanisms, immune modulation has emerged as a critical research focus. Its core mechanism lies in integrating inflammation regulation with fibrosis and angiogenesis processes, achieving significant improvements in scar repair outcomes. These findings highlight ESWT's potential as a precise and effective therapeutic strategy for treating burn scars, offering a novel direction for both research and clinical application.

Although ESWT has demonstrated significant potential in scar treatment, further research is needed to optimize treatment parameters and explore personalized therapeutic strategies. First, studies should clarify the optimal EFD ranges for different mechanisms and treatment stages. For instance, an EFD as low as 0.0024 mJ/mm^2 can induce cellular and molecular changes during the early inflammatory phase, whereas higher EFDs ranging from 0.11 to 0.30 mJ/mm^2 are more effective in regulating proliferation and apoptosis. Research also indicates that applying ESWT at the highest possible frequency within safe limits offers better outcomes [23]. Future studies should focus on developing standardized treatment protocols tailored to specific scar types to maximize therapeutic efficacy.

Additionally, designing personalized treatment plans based on individual patient characteristics—such as scar thickness, fibrosis severity, and immune status—can further enhance the precision of ESWT. The widespread implementation of randomized controlled trials (RCTs) is also essential. RCTs not only validate the clinical applicability of experimental findings but also address the current lack of human studies [26,125]. Lastly, with advancements in technology, exploring the synergistic effects of ESWT combined with other therapeutic approaches, such as pharmacological interventions or stem cell therapies, holds promise for achieving comprehensive burn scar treatment and advancing precision medicine.

5. Conclusions

In conclusion, ESWT demonstrates multiple mechanisms in burn scar repair, encompassing immune regulation, fibrosis modulation, and angiogenesis, while also exerting multi-layered effects through promoting apoptosis and activating endogenous

stem cells. Among these, immune regulation is considered a key element underlying ESWT's potential mechanisms, spanning the processes of cell proliferation and differentiation, inflammatory response, fibrosis remodeling, and tissue repair. Future studies should further investigate the dynamic roles of immune modulation across different stages of scar repair to provide a scientific basis for optimizing treatment protocols. ESWT sets an exemplary model for precision medicine by leveraging immune regulation, and designing personalized immune-based interventions tailored to individual patient characteristics—such as immune status, scar thickness, and degree of fibrosis—may become a central strategy for future scar therapies.

Consent to participate and publication

All the authors contributed to the writing of the article and thoroughly reviewed the manuscript. They have provided their authorization for its publication.

Authors' contributions

JYX and MZL performed the majority of the literature search and predominantly contributed to the writing of the article. QZY, ZJ, HLL, SWQ, HZH, ZYQ, and GXL assisted with the literature search. All authors read and approved the final manuscript. XB is corresponding author. Yixiang Jin and Zilun Meng contributed equally to this work.

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Declaration of competing interest

The authors declare no conflict of interest.

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