

Review Article

Mesenchymal Stem Cells-Derived Extracellular Vesicles as Nanotherapeutics: An Application for Skin Wound Healing

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The skin covers the entire outer part of the body as the largest organ. Because this organ is directly exposed to microbial, thermal, mechanical, and chemical damage, several factors may injure it, including acute trauma, chronic wounds, or even surgical procedures. Mesenchymal stem cells- (MSCs-) derived extracellular vesicles (EVs) can inhibit the inflammatory response in the early stage of skin wound healing, promote angiogenesis and the proliferation and migration of epithelial cells, and regulate collagen synthesis and inhibit scar proliferation in the later stage. While MSCs-EVs have broad prospects for clinical applications, it will still be a long way to seamless healing. In this brief review, we focus on the role of MSCs-EV in skin wound repair, therapeutic effects, and potential mechanisms of MSCs-EV in reducing scar formation. It is concluded that MSCs-EV can reduce scar formation in skin wound repair by interfering with multiple inflammatory factors, regulating fibroblast proliferation, and expressing type I and type III collagens at different phases.

1. Introduction

The skin, as one of the natural barriers against mechanical forces, infections, and body fluid loss, contributes to maintaining physiological health. After an injury, skin wound healing is initiated rapidly, which may involve multiple healing processes. Of them, scarring, as one of the poor healing outcomes, makes approximately 100 million people experience pain and discomfort yearly [1]. Apart from disfigurement, poor aesthetics, social avoidance, depression, and scarring can result in limited body movement or permanent disability. Therefore, reducing the formation of scars can relieve the patient's physical and psychological pain.

Previous literature reported that MSCs, as a self-renewal and pluripotent differentiated cell type, have therapeutic potential for tissue regeneration and skin wound recovery [2]. However, MSCs, as one of the cell products, have certain

limitations in wound healing therapy due to inducing host immune responses after transplantation. In order to avoid host immune response, MSCs-derived EV has become an alternative treatment for regenerative wound repair. EVs have similar biological functions with their source cells, which accelerate cell self-repair, promote tissue regeneration in damaged areas, restore tissue homeostasis, and eventually accelerate wound recovery [3]. EV encapsulates a variety of bioactive molecules, including mRNA, proteins, non-coding RNAs, and lipids and can deliver these signal molecules into recipient cells as one of the most efficient intercellular communicators [4]. It has been proven to have an obvious curative effect in wound healing treatment. However, it lacks a certain degree of attention to the mechanism of reducing scar formation. This article reviewed recent literature to summarize and discuss the mechanisms of EV regarding reducing scarring in wound repair.

2. Traditional Wound Healing Methods

Conventionally, it is a complex process and involves multiple stages as wound healing is initiated. During the initial stage of wound inflammation, neutrophils secrete reactive oxygen species (ROS) to disinfect the wound. Long-term inflammation caused by dysfunctional T cells and macrophages can contribute to the formation of hypertrophic scars. During the proliferative phase, anti-inflammatory macrophages are predominated and promote fibril production by producing transforming growth factor- β 1 (TGF- β 1). This key collagen stimulator causes collagen fibrils to accumulate at the wound site and causes dermal fibrils to change. During the late remodeling stage, fibroblasts metastasize into myofibroblasts, which can shrink the wound margin, thereby accelerating skin re-epithelialization. However, they can also produce numerous, irregularly arranged collagen bundles, leading to tense, hypercontracted scars.

Among the traditional wound repair methods, current common treatments include skin grafting, skin flap surgery, biological stents, and laser therapy [5]. A series of therapeutic strategies have been taken to accelerate wound healing and improve the aesthetics of scars. Traditional treatments such as corrective surgery, topical corticosteroids, chemotherapeutics, topical applicators, cryotherapy, compression therapy, radiotherapy, topical silicone products, and laser/energy therapy are ineffective or prone to scarring after treatment on wound repair. Until now, there is no systematic description regarding the molecular mechanisms of the formation of scarring. In addition, a lack of clinical evidence to support any treatment can affect the scarring process. Therefore, there has been no consensus on a single optimal treatment regimen.

Although some novel skin substitutes facilitate wound management, the healing effects on many chronic wounds remain unsatisfactory. Artificial skin substitutes are still different from natural skin. In anatomical structure, the absence of a basement membrane may lead to the inability to heal properly. MSCs and MSCs-EVs inhibit excessive collagen production, regulate cellular immunity, and inhibit inflammation in the early stage. Their roles in skin wound repair and further prevention and treatment of scarring are attracting increased attention to investigate their promising clinical potential [6–8].

3. Effects of Mesenchymal Stem Cells on Wound Repair

Skin wound healing remains a severe challenge, causing enormous distress and debilitating effects. Recent improvements in the combination of tissue engineering approaches and cell therapy offer promising therapeutic options for accelerating wound healing of damaged skin in diabetic foot ulcers [9]. Stem cell therapy has been applied to treat various diseases as a new approach, including wound repair and tissue regeneration [10]. Several types of stem cells from diverse origins have been well studied in pre-clinical and clinical settings, such as bone marrow-derived mesenchymal stem cells (BM-MSCs), adipose-derived

mesenchymal stem cells (ADSCs), and circulating angiogenic cells (e.g., endothelial progenitor cells). Adipose tissue is a rich source of ADSCs, verified with improved efficacy in wound healing. During wound healing, this infusion of MSCs contributes to re-epithelialization, immunoregulation, and angiogenesis. In addition, this MSCs-based therapy contributes to attenuating excessive fibrotic remodeling, accelerating the formation of skin appendages, and recruiting endogenous stem cells [11]. As one of the ideal MSCs, ADSCs can be extracted from autologous adipose tissue sufficiently, lessening allograft side effects. After isolation, ADSCs can be cryopreserved for up to six months to guarantee future use [10, 11]. In addition, to collect enough ADSCs for cell-based soft tissue engineering and wound healing, previous literature showed that platelet-rich plasma could be used to promote the proliferation of ADSCs [12]. Stem cells are characterized by self-renewal, proliferation, and differentiation into multiple lineages. Recent methodological advances in extracting and culturing stem cells provide more possibilities to investigate their clinical applications aggressively. These new methods efficiently collect many autologous adult stem cells from patients, which avoids ethical concerns and allogeneic immune barriers. ADSCs have similar surface markers to BM-MSCs, including CD10, CD13, CD29, CD54, CD71, CD106, CD117, and STRO-1. In addition, ADSCs do not express the hematopoietic lineage markers like CD45, CD14, CD16, CD56, CD61, CD62E, CD104, and CD106 and endothelial cell (EC) markers like CD31, CD144, and von Willebrand factor. As stem cells, ADSCs can differentiate into multiple lineages as exposed to appropriate stimuli. Several growth factors can also be secreted, contributing to neo-vascularization. Thus, ASCs can promote the proliferation of human dermal fibroblasts by intercellular communication and activate paracrine secretion during the re-epithelialization stage of wound healing. Thus, MSCs have been recognized with a relatively strong tissue wound repair function and are high-quality cell types in cell-based therapy.

As a highly organized physiological process, skin wound healing aims to restore skin integrity after trauma. This process requires the interaction among multiple cell types, which consists of three overlapping periods, including inflammation, proliferation, and remodeling [13, 14]. Various MSCs are also thought to participate in this process, such as endogenous skin MSCs, which include dermal papilla cells (DPCs) and dermal sheath cells (DSCs), and pericytes and mesenchymal stem cells in adipose tissue [15–20]. However, for most trauma cases, such as deep burns and chronic ulcers, endogenous dermal MSCs are insufficient to complete the whole wound self-repair due to the loss of dermal tissue. Therefore, exogenous MSCs can accelerate wound healing by exerting their physiological therapeutic effects. Despite their identity or origin, MSCs have been reported to have convincing therapeutic effects on wound healing and scarring. MSCs are considered an attractive therapeutic option due to their broad differentiation potential and outstanding paracrine ability. In the past decade, MSCs have rapidly emerged as a cell therapy promoting the healing of skin wounds.

Current evidence to assess the therapeutic effects of MSCs on wound healing is based on BM-MSCs and other sources of MSCs in animal models. Few clinical trials based on autologous BM-MSC transplantation have been published [21–24]. However, as an invasive procedure, bone marrow aspiration is uncomfortable and has a few infections and bleeding complications [25]. Furthermore, bone marrow is a limited resource, and the number of bone marrow cells decreases with age [26]. Therefore, some other MSCs have been reported as alternative options, including ADSCs, dermal-derived MSCs, amniotic fluid-derived MSCs (hAM-dMSCs), and umbilical cord-MSCs (hUC-dMSCs). ADSCs and dermal MSCs are abundant in adipose and skin tissues, extracted by minimally invasive surgery without ethical controversy over their use. All these factors make them suitable substitutes for BMSCs. ADSCs and dermal MSCs have similar biological properties in immunogenicity and differentiation potential [27–32]. Current clinical trials revealed that ADSCs have therapeutic effects on burns and ulcers [33]. Likewise, dermal MSCs also promoted wound healing in clinical trials [34, 35]. Although there are no clinical trials of hAM-dMSCs and hUC-dMSCs in wound healing, all these clinical results demonstrated that MSC-based therapy is safe and effective.

4. Limitations of MSCs in Wound Healing

Despite several advances in MSC-based therapy, many challenges must be overcome before MSCs can be widely used in clinical practice. Deficiencies in the clinical application of MSCs have gradually emerged. Current evidence demonstrates considerable controversy regarding dosing regimens, wound models, and cell populations [36]. Next, no evidence supported that MSCs differentiated into typical resident skin cell phenotypes during skin wound healing [37]. There is evidence that it is the bioactive factors secreted by MSCs that reduce wound inflammation and promote tissue repair [36]. Therefore, the criteria to evaluate the necessity of directly transplanting MSCs onto wounds remain to be determined. Finally, there are no accepted criteria to define the phenotype of MSCs and their functional properties, which is a big challenge. Further clinical trials are needed to investigate the therapeutic effect of MSCs on large patient sizes.

5. Biological Properties of MSCs-EV

Evidence suggests that EVs have specialized functions and play critical roles in coagulation, intercellular signaling, and waste management [38]. To be specific, EV participates in immunoregulation, angiogenesis, cell proliferation, cell differentiation, and cell migration, and in addition, it also attenuates cell apoptosis and maintains a physiological state. Thus, investigating the clinical applications of EV draws our attention [39]. EV is considered an essential carrier of material and information transfer between cells, promotes cell growth, tissue regeneration, and wound repair, and has become a new hot spot in current tissue regeneration and

repair research [40]. Therefore, there are increased clinical studies on EV and its application.

MSC-derived extracellular vesicles (MSC-EVs) have similar biological characteristics to their relevant MSCs, including promoting cell self-repair and tissue regeneration, restoring tissue homeostasis, and accelerating wound repair in the injured area [3]. Recently, some literature reported that MSCs could generate substantial EV. The MSC-EV has been recognized as the main effective paracrine component of MSCs with equivalent biological function to the MSCs [41]. Compared with MSCs, MSCs-EVs have several advantages. MSCs-EVs are always fused directly into recipient cells, presenting a decent biological effect. Next, the inner components of MSCs-EV are protected from degradation with the exosomal membrane. Thus MSCs-EV can reach the target organ and exert its therapeutic effect [42]. MSCs-derived extracellular vesicles can activate a variety of critical signaling cascades related to wound repair [43]. Studies have shown that adipose tissue-derived MSCs-conditioned medium can stimulate skin keratinocyte proliferation and fibroblast migration [44], recruit macrophages and endothelial cells, and promote wound healing [45]. Meanwhile, MSCs-derived extracellular vesicles can affect skin wound healing by reducing scar formation and accumulating myofibroblasts [46].

6. The Role of MSC-EV in Wound Healing and Skin Regeneration

Skin wound healing is a dynamic physiological process and an intrinsic protective mechanism of the skin itself. The classical skin regeneration process can be summarized into three overlapping phases, including the inflammatory phase, proliferative phase (cell proliferation and re-epithelialization), and remodeling phase (Figure 1) [13–15]. The role of MSC-EV in wound healing and skin regeneration mainly focuses on the above three stages. The current study found that EV from MSCs promoted skin wound healing, which is mainly credited with reduced inflammation, re-epithelialization and angiogenesis, proliferation and migration of fibroblasts, and enhanced ECM formation and remodeling [47] (Table 1).

6.1. The Mechanism of Action of MSC-EV in the Inflammatory Phase. As one of the self-defense mechanisms, the inflammatory response is activated as the harmful stimuli are exposed to the organism, and this acute and regulated response promotes wound healing sometimes [62]. Conversely, chronic and dysregulated inflammatory responses always promote fibrosis, the excessive formation of scars, and inhibit re-epithelialization, which eventually impedes wound healing [63]. As one of the critical inflammatory cell types, macrophages have a critical role in skin wound healing. Recent studies demonstrated that macrophages participated in various stages of skin wound healing by converting from pro-inflammatory *M1* phenotype to anti-inflammatory *M2* phenotype. Dysfunctional macrophages may aggravate inflammation or fibrosis of the injured areas

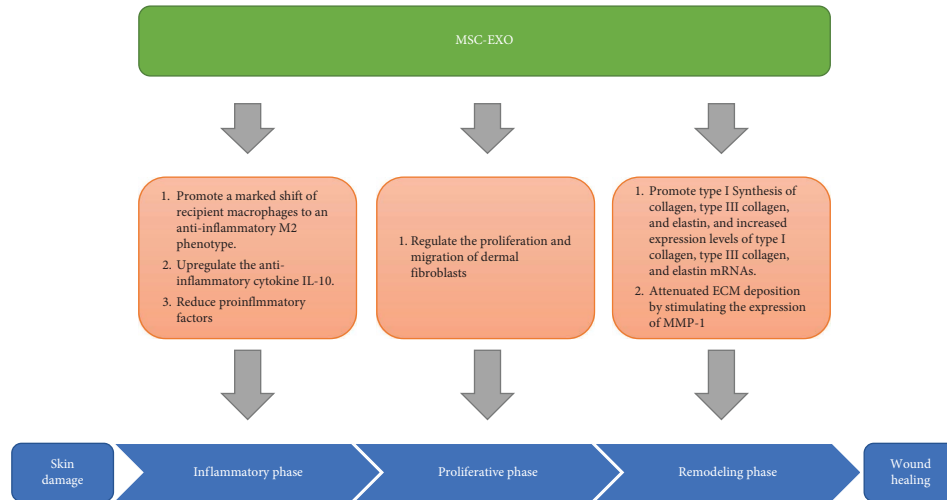


FIGURE 1: Mechanisms of MSC-EV in the treatment of skin lesions.

TABLE 1: Effects of different sources of MSCs-derived exosomes on skin injury repair and its mechanism.

Type	Function and mechanism	References
MSCs-EVs	Promote cell self-repair and tissue regeneration, restore tissue homeostasis, and accelerate wound repair	[3, 39]
	Inhibit the excessive production of collagen, regulate cellular immunity, and inhibit inflammation at an early stage	[6–8]
	Promote cell growth, tissue regeneration, and wound repair and reduce scar formation and accumulation of myofibroblasts	[3, 46]
	Activate a variety of important signaling cascades related to wound repair	[43]
	Promote the transformation of recipient macrophages to the anti-inflammatory M2 phenotype, regulate the activation, differentiation, and proliferation of B lymphocytes, inhibit the proliferation of T lymphocytes, and convert activated T lymphocytes into a T regulatory phenotype	[48–50]
	Induce downregulation of various cytokines, reduce the inflammatory response, and drive upregulation of anti-inflammatory cytokine IL-10	[51–53]
	Activate various signaling pathways in endothelial cells and induce the expression of many trophic factors through inner miRNAs	[54]
	Regulate fibroblast proliferation and migration by regulating the expression of granulation tissue growth factors and its related genes	[55–57]
	Transport its contents into recipient cells to regulate their proliferation and migration	[52, 53, 58]
ADMSCs-EVs	Accelerate wound healing by increasing the production of collagen types I and III at an early stage and inhibiting collagen synthesis in the later stage	[43]
	Stimulate skin keratinocyte proliferation and fibroblast migration	[44]
ASCs-EVs	Promote re-epithelialization and regeneration of skin appendages, increase angiogenesis, inhibit fibrotic remodeling, stimulate endogenous stem cell recruitment, and modulate inflammation	[11]
hUCdMSC-EVs	Promote de novo synthesis of collagen type I and elastin, promote the synthesis of collagen type I, collagen type III, and elastin, and increase the levels of collagen type I, collagen type III, and elastin mRNAs	[56, 59]
	Inhibition of fibroblast-to-myofibroblast differentiation to prevent scarring	[60]
hAEC-EVs	Stimulate the expression of MMP-1 to reduce ECM deposition	[61]

[48]. MSC-derived extracellular vesicles, including EV, promoted a marked shift of recipient macrophages to an anti-inflammatory M2 phenotype [49].

In addition, MSC-EV can modulate the activation, proliferation, and even differentiation of B lymphocytes and inhibit T lymphocytes' proliferation. Previous literature reported that MSC-EV converted activated T lymphocytes

into a T regulatory phenotype with immunosuppressive ability [50, 64]. For the inflammatory factors in skin tissue regeneration, such excessive secretion of cytokines may also further aggravate the skin wound [51]. MSC-EV derived from different MSCs can reduce pro-inflammatory factors, such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and cytokines and chemokines

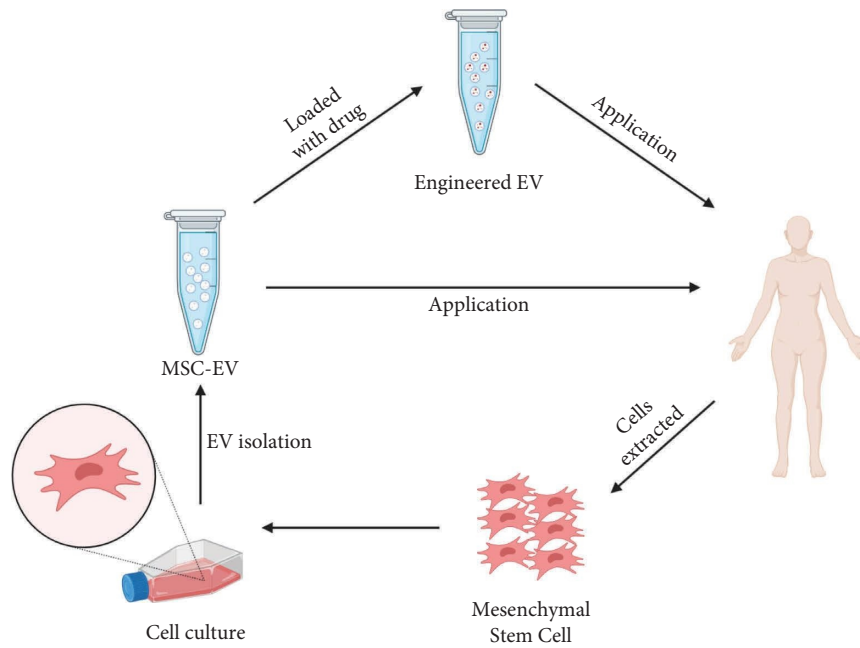


FIGURE 2: Autologous stem cell EV application.

such as tumor necrosis factor- α (TNF- α). Reduced inflammatory responses to multiple stimuli, interleukin 1β , and monocyte chemoattractant protein 1 contribute to skin wound repair. Furthermore, MSCs-EV can upregulate the anti-inflammatory cytokine IL-10 in many injured models, which has been reported to be crucial in controlling skin wound inflammation and scarring [52, 53, 58]. In a recent study, Wang found that MSC-EV significantly inhibited peripheral blood mononuclear cell proliferation and promoted Treg cell transformation and endothelial vascularization [65]. Yu et al.'s study found that EV secreted by human ADMSCs upon H_2O_2 stimulation could enhance flap neovascularization and survival in IR injury in a flap transplantation model rat by reducing inflammatory cell infiltration [66]. It can be observed that the mechanism of MSC-EV for repairing skin damage in the inflammatory phase is complex, including the protection of anti-inflammatory cells and the downregulation of pro-inflammatory factors.

6.2. Behavioral Mechanism of MSC-EV in the Proliferation Phase. During the proliferative phase, we can see neovascularization, collagen deposition, granulation tissue formation, re-epithelialization, and wound shrinkage [54]. Neovascularization is critical in various pathophysiological processes, including skin wound healing and tissue repair [14, 55]. MSC-EV is full of various angiogenesis-related proteins and RNAs, and miRNAs, one of the critical non-coding RNAs, have been identified to activate various signaling pathways in endothelial cells. Additionally, EV can also encapsulate many trophic factors [56].

Cell proliferation and skin re-epithelialization are crucial to skin wound healing. Dermal fibroblasts, participating in wound contraction, extracellular deposition, and tissue

remodeling, are the vital cell types in skin wound healing [57]. After internalized into recipient cells, the exosomal components like proteins and RNAs may regulate the proliferation and migration of dermal fibroblasts through specific signaling pathways and eventually provide structural support for the injured skin [43, 59, 60]. Some investigators attempted to use BMSCs-derived EV to treat fibroblasts from diabetic ulcer wounds. The results showed that EV was dose-dependent on the proliferation and migration of fibroblasts.

6.3. Behavioral Mechanism of MSC-EV during the Remodeling Phase. The extracellular matrix (ECM) comprises four substances: collagen, non-collagen proteins (fibronectin, laminin), elastin, proteoglycans, and aminoglycans. ECM remodeling is closely related to the synthesis and degradation of collagen, which requires a dynamic balance. Any insufficient or excessive ECM formation can lead to non-healing or scarring of wounds. Besides the aforementioned cellular effects, MSC-EV also regulates ECM resynthesis. It has been reported that hUC-dMSCs-derived EV can accelerate *de novo* synthesis of type I collagen and elastin [56]. EV collected during the induction of human-induced pluripotent stem cells (hipsc) to differentiate into dermal MSCs (dMSCs) can promote type I synthesis of collagen, type III collagen [61]. These results demonstrated that MSC-EV could promote the regeneration of ECM and, finally, promote wound repair. By promoting the synthesis of type I and III collagen in the early stage and reducing collagen synthesis later, EV derived from ADSCs could also accelerate skin wound healing [67]. In a mouse skin defect model, hUC-dMSCs-derived EV reduced scar formation by inhibiting the conversion from fibroblasts to myofibroblasts [46]. In a rat model of scarless wound healing, a high concentration of

heme-derived EV attenuated ECM deposition by stimulating the expression of MMP-1 [68]. Furthermore, a study hypothesized that ADSCs-EV restrained type II/I collagen formation by acting directly on fibroblasts [69]. In addition, previous literature observed that EV could be recruited around skin wounds and could exert relevant biological functions to accelerate wound repair. Some histological studies also observed that collagen synthesis was increased in the early stage but was decreased in the later stage when undergoing EV treatment, which leads to inhibition of scar formation [59]. All these results suggest that MSC-EV plays an essential role in ECM remodeling, which may be recognized as a possible mechanism for reducing scarring.

7. Future Directions

In the past decades, the therapeutic effect of MSCs and MSC-EV on wound repair and skin regeneration has been intensively studied. However, due to the limitations of MSCs, more and more scholars have shifted their goals to the study of MSCs-EVs, hoping to further apply them to clinical treatment. At present, autologous stem cell-EV is gradually becoming the mainstream trend of clinical treatment. Engineering autologous stem cell-derived EVs has also led to a broader application of exosomes in clinical therapy (Figure 2). As a promising technique, MSC-EV therapy accelerates wound healing and reduces scarring. Therefore, as cell-free replacement therapy, MSC-EV has the superiority of convenient preparation, storage and transportation, convenient administration, and easy administration when selected with high therapeutic efficacy and no risk of immune rejection and tumorigenesis. Therefore, MSC-EV has significant skin regeneration potential and may have the possibility to replace conventional MSC therapy. The molecular mechanism of MSC-EV promoting skin regeneration will be fully revealed through further research on its specific content and function. Currently, most of the mechanisms described previously mainly remain in the animal testing stage. Thus, more clinical trials are needed to clarify the therapeutic effects of MSC-EVs on patients with skin lesions.

Data Availability

The datasets generated and analyzed during the present study are available from the corresponding authors upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

X-YB and H-HZ conceptualized the review. M-ST performed the literature search and data analysis. Y-RW and T-WC wrote the section of the table. RR was responsible for the figures. Q-FL and X-NY drafted and critically revised the work. All authors contributed to the article and approved the submitted version. X-YB, H-HZ, and M-ST contributed equally to this work.

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