Mesenchymal Stromal Cell Preconditioning:
The Next Step Toward a Customized
Treatment For Severe Burn

Brice Magne, Jean-Jacques Lataillade, and Marina Trouillas

Over the last century, the clinical management of severe skin burns significantly progressed with the development of burn care units, topical antimicrobials, resuscitation methods, early eschar excision surgeries, and skin grafts. Despite these considerable advances, the present treatment of severe burns remains burdensome, and patients are highly susceptible to skin engraftment failure, infections, organ dysfunction, and hypertrophic scarring. Recent researches have focused on mesenchymal stromal cell (MSC) therapy and hold great promises for tissue repair, as reported in several animal studies and clinical cases. In the present review, we will provide an up-to-date outlook of the pathophysiology of severe skin burns, clinical treatment modalities and current limitations. We will then focus on MSCs and their potential in the burn wound healing both in vitro and in vivo studies. A specific attention will be paid to the cell preconditioning approach, as a means of improving the MSC efficacy in the treatment of major skin burns. In particular, we will debate how several preconditioning cues would modulate the MSC properties to better match up with the burn pathophysiology in the course of the cell therapy. Finally, we will discuss the clinical interest and feasibility of a MSC-based therapy in comparison to their paracrine derivatives, including microvesicles and conditioned media for the treatment of major skin burn injuries.

Keywords: major skin burn injuries and pathophysiology, mesenchymal stromal cells, cell preconditioning, clinical use

Thermal burns can lead to the disruption of the cutaneous barrier and leave the body unprotected against the surrounding environment. In 2018, the World Health Organization* recorded 180,000 burn-related deaths per year with a high percentage of cases occurring in low- and middle-income countries [1,2]. Although the incidence, the severity, and the mortality rate following a burn injury have decreased [2], the management of major skin burns still remains challenging in terms of surgery and scar formation [3–5].

This review presents the limits of the classical management of severe skin burns and tackles interesting therapeutic alternatives using cell-based therapies and improved by cell preconditioning strategies.

Severe Thermal Burns

Burn pathophysiology and healing

Burn is a complex trauma whose severity depends on wound size, depth, and location. But other factors can influence the burn severity, including age, burn localization, and other related injuries. Burn is one of the most severe traumas, as it impairs the normal wound healing process and leads to irreversible functional and esthetical damages.

Burn pathophysiology. Depending on its etiology, intensity, and duration, the burn injury can trigger protein denaturation and cell membrane integrity loss at the local level, leading to a so-called coagulative necrosis [6,7]. Clinically, the burn wound can be dissected into three severity areas from the center of the wound to the periphery [8]. The center of the wound is called the coagulation zone, as the tissue is irreversibly lost. Surrounding the coagulation zone, the zone of stasis is poorly perfused and can rapidly turn into necrosis. The most external zone is referred to as the hyperemia zone, where vasodilation is governed by an acute and local inflammatory reaction. To avoid ischemia-driven burn wound progression, wound care management and fluid resuscitation are critical.

Necrotic burn tissues release large amounts of damage associated molecular patterns (DAMPs), including toxic lipid-protein complexes [9], extracellular matrix (ECM) fragments, and cytoplasmic cell content. DAMPs activate

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the inflammasome through the Toll-like receptors (TLRs)/nuclear factor-kappa B (NFκB) pathway and initiate the systemic production of large amounts of inflammatory molecules [10–13]. Along with this systemic inflammatory response, the increased capillary permeability results in edema formation in the interstitial space and hypovolemia. Simultaneously, increased systemic vascular resistance contributes to reduce the cardiac output and leads to a so-called burn shock (Fig. 1). After about 3 days, hypermetabolism becomes established in burn patients, as a normal body response to cope with dehydration and hypovolemia-induced heat loss. Hypermetabolism is driven by catecholamines.

FIG. 1. Pathophysiology of full thickness burn injuries. This schematic summarizes the main biological events following a full-thickness burn injury, according to the Jackson’s pathophysiological model [8]. At local level, in the zone of coagulation necrosis (1), the burn injury causes full destructions of all skin layers. Burn toxins, such as lipid–protein complexes, tissue necrosis, and ischemia, all contribute to trigger an intense and long-lasting inflammatory response that spreads to the surrounding stasis zones. Massive release of inflammatory mediators (2) (such as catecholamines, cytokines, and ROS) causes pain, as well as increased vascular dilation, permeability, and resistance (3). As a short-term result, extravascular fluids accumulate to form interstitial edemas and skin blisters or leak out of the body, contributing to patient’s dehydration, hypothermia, and tissue hypoxia (4). Immune suppression is also thought to develop as a long-term consequence of chronic inflammation, leaving the body defenseless against pathogens and bacteria (5) and causing sepsis. After few days, massive systemic metabolic and inflammatory dysregulations alter the normal wound healing process leading to hypertrophic scars. Altogether, these pathological changes can lead to a lethal multiple organ failure. ROS, reactive oxygen species.
stress hormones, and inflammatory mediators and triggers glycolysis, lipolysis, and proteolysis. After a severe burn trauma, hypermetabolism and hyperinflammation usually persist for years [10], leading to lean body mass breakdown, wound healing impairment, insulin resistance, immune suppression, organ dysfunction, and hypertrophic scarring (Fig. 1).

Burn wound healing. Cutaneous injuries initiate a cascade of events that tightly regulate the wound healing, according to three distinct but overlapping phases known as inflammation, proliferation, and remodeling (Fig. 2) [14,15]. The dysregulation of one of these phases might alter the normal repair process, causing epithelialization delays and pathological scars. Accordingly, several studies from the Eming’s group highlighted the key role of the inflammation phase in wound healing duration and fibrosis emergence [16,17].

Traumatic burn injuries are characterized by an extreme and persistent inflammatory response driven by catecholamines, cortisol, and inflammatory cytokines (Fig. 2) [10]. Although today the factors influencing the burn wound healing have not been clearly identified, the exaggerated inflammatory response is thought to be paramount in burn pathogenesis. Catecholamine driven inflammation is indeed known to slow down the epithelialization process and the granulation tissue formation. In particular, long-lasting activity of beta-adrenergic agonists has been shown to trigger both neutrophil persistence and keratinocyte migration impairment during wound healing [18,19]. Hyperinflammation is also thought to alter the T_{H1}/T_{H2} ratio, thus contributing to both immune suppression and fibrogenic responses in burn patients [20–23]. According to this paradigm, serum expression levels of early interleukin 1β (IL-1β), decorin,
and late transforming growth factor beta 1 (TGF-β1) were shown to predict the appearance of hypertrophic scars in burn patients [24].

In addition to the excessive inflammatory response, many other factors are believed to play a pivotal role in the development of hypertrophic scars, including myofibroblasts [25], mechanical stresses [26], and delayed wound healing [27–29]. However, whether these factors are the origins or the consequences of burn fibrogenesis still remains a matter of debate today.

**Current treatments and limitations**

To return to a normal wound healing process, several treatments are required to treat patients with major burn injuries [30]. They include heavy surgical procedures, intensive cares, wound dressing nursing, adapted nutrition, and sterile confinement (Table 1).

The surgical management of severe burns begins with the removal of necrotic tissues. This step is essential to clean up the wound from toxic cues and bacteria, curb local inflammation, and limit mechanical stresses. This surgery is followed by the covering of the wound bed using different kinds of grafts (ie, skin autografts, allografts, and skin substitutes) applied according to diverse surgical methods [4]. When donor sites are insufficient, alternatives to skin autografts can be used to reform the cutaneous barrier and limit the infectious ingress. In these particular cases, a two-stage procedure is carried out to restore the dermal compartment using collagenous matrices such as Integra™ [31] or cadaveric allografts [32] and the epidermal compartment using cultured epidermal autografts (CEAs) [33,34]. These alternatives provide a permanent covering of the burn wound and improve patient survival rates [35–37]. But the use of CEAs is still limited by a variable epidermal grafting efficiency [35,38–41], as a consequence of the immune and metabolic state of the patient, the immaturity of the newly formed dermal–epidermal junction (DEJ) resulting in skin blistering [42], the poor vascularization of the wound bed, and the high susceptibility to infections [30]. These obstacles therefore result in delayed wound repair and might contribute to the lack of functionality of the repaired tissue [34,43].

Given that infections are responsible in some cases of skin graft failure and sepsis, they have become a major therapeutic target. Several treatments such as topical antimicrobials or systemic antibiotics are highly effective to combat infections. Accordingly, clinicians most often agree to deliver topical antimicrobials until reaching full wound closure [44]. However, systematic practice is under debate, because of the growing bacterial drug resistance and the negative effect of certain drugs on wound closure. A challenging research area therefore seeks to develop novel antibacterial treatments for burn applications [45].

Resuscitation is one of the other major key points in the stabilization of patients with major burns. Large-volume resuscitation fluids contain crystalloids (ie, Ringer lactate) and may have negative effects on the organs and might contribute to the lack of functionality of the repaired tissue [34,43].

**Table 1. Global Burn Treatments and Management**

<table>
<thead>
<tr>
<th>Therapeutic targeting</th>
<th>Strategies</th>
<th>Targeted effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of cutaneous barrier</td>
<td>Wound coverage and grafting</td>
<td>Wound closure with auto or allogeneic skin graft, skin substitutes</td>
</tr>
<tr>
<td>Burn wound conversion</td>
<td>MSC therapy</td>
<td>Wound closure</td>
</tr>
<tr>
<td>Infection</td>
<td>Negative pressure therapy, Bradykinin antagonist</td>
<td>Improving blood flow and tissue survival, Limiting vasodilatation and permeability</td>
</tr>
<tr>
<td>Infection</td>
<td>Escharectomy, Topical antibiotics (silver sulfadiazine), Systemic antibiotics</td>
<td>Restraining bacterial colonization, Protecting the wound from pathogens, Protecting the whole body from pathogens</td>
</tr>
<tr>
<td>Hyperinflammation</td>
<td>Escharectomy, Vitamin supplementation, Fluid resuscitation (crystalloids and colloidos), Nitric oxide inhibitors (methylene blue)</td>
<td>Reducing the release of inflammatory cues, Limiting oxidative stress, Fighting hypovolemia, Reducing vascular permeability</td>
</tr>
<tr>
<td>Hypermetabolism</td>
<td>Thermoregulation, Enteral nutrition, Carbohydrate and fat intake monitoring</td>
<td>Increasing room temperature to 33°C, Preserving intestinal mucosal integrity and decreasing stress hormone release, Limiting hyperglycemia and improving immune function</td>
</tr>
<tr>
<td>Hypertrophic scarring</td>
<td>Protein supplementation, Vitamin supplementation, Hormonal and pharmacological therapy (insulin, oxandrolone, testosterone, ketoconazole, IGF-1, propranolol)</td>
<td>Reducing lean body mass drop, Improving wound healing and immune function, Improving wound healing and limiting insulin resistance</td>
</tr>
<tr>
<td>Hypertrophic scarring</td>
<td>Surgery and grafting, Mechanical treatment (pressure therapy, splinting, physiotherapy), Anti-inflammatory treatment</td>
<td>Diminishing wound contraction, Improving scar appearance, Limiting collagen production</td>
</tr>
</tbody>
</table>

The data shown in the table are extracted and summarized from previous reviews [13,30,46,48,51,126,127].

IGF-1, insulin-like growth factor-1; MSC, mesenchymal stromal cell.
and are sometimes supplemented with colloids (such as plasma or albumin). Although necessary to compensate for hypovolemia and burn shock, the excessive use of resuscitation fluids has been correlated with coagulative, pulmonary, and immunologic side effects [46]. Moreover, resuscitation fluids often induce hypernatremia, a well-known inhibitor of skin graft take [47]. Therefore, there is still a dreadful need for resuscitation fluid volume and composition optimizations.

Hyperinflammation plays a major role in burn pathophysiology. However, it is unclear whether reducing it would slow down the disease progression in humans. To investigate this possibility, several treatment modalities have been designed such as TLR antagonists, oxidative stress inhibitors, or inflammatory cytokine blockers [13,46] and are under current investigation in phase I clinical trials.

Hypermetabolism also is a major component of the burn pathophysiology, as it disturbs the normal wound healing process and hormonal balance [48]. Anabolic agents, such as propranolol, have been evaluated in clinical trials and shown to improve the burn wound healing [49] and reduce hypertrophic scarring [50]. However, their systematic use does not seem appropriate due to unwanted side effects.

To counteract hypertrophic scarring, the main treatments remain surgery and negative pressure therapy [51]. The direct targeting of the fibrogenic TGF-β1 signaling pathway has been early abandoned, as TGF-β1 knocked-out mice are known to develop systemic autoimmune disorders resulting in early death [52]. Other anti-scarring strategies have been investigated, such as reactive oxygen species (ROS) inhibition [53], vascular endothelial growth factor (VEGF) blockade [54], or peroxisome proliferator-activated receptor-γ activation [55,56], but none of them has led to a definitive solution.

Despite the broad range of strategies developed to treat severe burns, there still remain today many hurdles to be addressed, such as the healing time and the scar formation. However, novel cell-based therapies seem to hold great promises for the future of the burn wound management.

**Mesenchymal Stromal Cell-Based Therapy**

Mesenchymal stromal cells (MSCs) are fibroblastic cells that were originally found in the bone marrow [57] and later isolated from many other tissue sources [58] such as the gingiva [59], the adipose tissue [60], or the perinatal tissues [61]. MSCs are defined as plastic adherent cells, expressing specific surface markers (CD73+, CD90+, CD105+, CD34+, CD45−, CD11b−, CD14−, CD19−, CD79α−, HLA-DR−) and able to differentiate into osteocytes, chondrocytes, and adipocytes in vitro [62].

These cells have drawn much attention over the past decades due to their ability for tissue repair and immune tolerance. The use of MSCs in cell therapy was initially based on the hypothesis of their in situ differentiation to regenerate injured tissues. But it gradually became apparent that MSCs hold their therapeutic efficacy from their ability to modulate the surrounding cell responses through paracrine mechanisms [63]. Accordingly, MSCs have been shown to secrete a wide range of bioactive molecules, including cytokines, chemokines, growth factors, and lipid mediators [64]. In recent years, MSC-based therapies have therefore emerged as novel interesting strategies to improve the wound healing of a wide range of cutaneous diseases [65] and, more particularly, skin burn injuries [66].

**MSCs in skin wound healing**

MSCs have been reported to contribute to the wound healing resolution and scar mitigation by impacting on inflammation, bacterial clearance, reepithelialization, vascularization, granulation tissue formation, and ECM remodeling (Fig. 2).

The inflammation phase of wound healing can be regulated by MSCs due to their known immunomodulatory properties. Zhang et al. have indeed demonstrated that MSCs are able to modulate the inflammatory milieu and promote wound repair as a consequence of the polarization of macrophages from a pro-inflammatory to an anti-inflammatory phenotype [67]. Other studies have shown that MSCs can secrete tumor necrosis factor alpha (TNF-α)-stimulated gene/protein 6 (TSG-6), an anti-inflammatory cue known to impede TNF-α-driven inflammation and fibrosis during wound healing [68,69].

Angiogenesis and wound closure can also be controlled by MSCs to avoid chronic wound emergence. Accordingly, several studies have demonstrated that MSCs are able to stimulate acute wound closure [70] and neovascularization [71] through the paracrine release of growth factors in vivo. This paracrine action was shown to enhance keratinocyte and dermal fibroblast migration, as well as endothelial tube formation using MSC-conditioned medium or MSC-derived microvesicles in vitro [70,72–74].

Matrix remodeling and scar mitigation can also be orchestrated by MSCs in the final stages of wound repair. The use of MSCs or their derived microvesicles/exosomes resulted in a significant reduction of α-smooth muscle actin (α-SMA), collagen expression, and a transition to a low TGF-β1/TGF-β3 ratio in acute wound animal models [69,75]. These antifibrotic activities are possibly mediated by TSG-6 [69], mi-RNAs inhibiting TGF-β2/SMAD2 pathway [75], or matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) balance [76,77].

**MSCs in burn wound healing**

**Preclinical studies.** As outlined in Table 2, MSCs have shown their beneficial effect on each stage of the burn wound healing in many animal models of burn [66].

In response to hyperinflammation, MSCs have been shown to secrete modulatory factors that limit immune cell accumulation and inflammatory cytokine production at both local [78,79] and systemic levels [80]. In particular, MSC-derived TSG-6 has been reported to reduce the burn-induced inflammation through P38 and c-Jun N-terminal kinase (JNK) signaling pathways [81]. Likewise, MiR-181c contained in MSC-secreted exosomes appeared to downregulate the TLR4-mediated inflammation in burn rats [82]. In addition to play on inflammatory pathways, MSCs administered at the burn site were shown to guide macrophage polarization toward a M2 reparative phenotype [79,83].

After burn, the proliferation phase of wound healing is significantly slowed down. Interestingly, MSCs [84] or their derived microvesicles [73,85] have been shown to counteract this effect by accelerating wound closure and neovascularization [78,86]. Accordingly, MSC administration resulted in angiopoietin (ANG)-1/2 gene upregulation in several animal models of third degree burn [84,87].

Burn injuries often result in hypertrophic scars, because of a dysregulated matrix remodeling. MSCs were shown to mitigate this burn-induced scarring through the regulation of
### Table 2. Summary of Preclinical Studies Using Mesenchymal Stromal Cell-Based Therapy to Treat Thermal Burn Injuries

<table>
<thead>
<tr>
<th>Species</th>
<th>MSC origin</th>
<th>Number of cells</th>
<th>Methods of MSC application</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>BM-MSC, human, xenogeneic</td>
<td>500,000 cells/cm²</td>
<td>Intradermal injections around the wound and topical applications in Matrigel on the wound directly after the burn</td>
<td>Enhancement of wound closure and angiogenesis</td>
<td>[84]</td>
</tr>
<tr>
<td>Rat</td>
<td>BM-MSC, human, xenogeneic</td>
<td>2,000,000 cells/rat</td>
<td>Injections into the muscle immediately after the burn</td>
<td>Decrease of systemic inflammation</td>
<td>[208]</td>
</tr>
<tr>
<td></td>
<td>BM-MSC, allogeneic</td>
<td>1,000,000 cells per stasis zone (×6)</td>
<td>Subcutaneous injections around the wound, 30 min after burn</td>
<td>Enhancement of tissue viability in the stasis zone and decrease of systemic inflammation</td>
<td>[209]</td>
</tr>
<tr>
<td></td>
<td>UC-MSC, human</td>
<td>5,000,000 cells</td>
<td>Tail vein injections at day 3 after burn</td>
<td>Enhancement of wound closure, angiogenesis and remodeling, and decrease of inflammation</td>
<td>[78]</td>
</tr>
<tr>
<td></td>
<td>BM-MSC, mouse, xenogeneic</td>
<td>5,000,000 cells/rat</td>
<td>Injections into the muscle immediately after the burn</td>
<td>Increase of reepithelialization and angiogenesis and decrease of inflammation</td>
<td>[80]</td>
</tr>
<tr>
<td></td>
<td>UC-MSC, human, xenogeneic</td>
<td>1,130,000 cells/cm²</td>
<td>Subcutaneous injections, 24 h after burn</td>
<td>Enhancement of wound closure and granulation tissue formation and decrease of inflammation</td>
<td>[210]</td>
</tr>
<tr>
<td></td>
<td>UC-MSC, human, xenogeneic</td>
<td>5,000,000 cells/animal</td>
<td>Tail vein injections directly after burn</td>
<td>Decrease of systemic inflammation</td>
<td>[81]</td>
</tr>
<tr>
<td></td>
<td>BM-MSC, allogenic, or autologous</td>
<td>40,000 cells/cm²</td>
<td>Escharectomy 2 days after burn and direct cell application with a pipette onto the wound</td>
<td>Enhancement of wound closure and angiogenesis</td>
<td>[211]</td>
</tr>
<tr>
<td></td>
<td>BM-MSC, allogeneic</td>
<td>20,000 cells/injection</td>
<td>Escharectomy 2 days after burn and direct cell application with a pipette onto the wound</td>
<td>Decrease of inflammation and increase of vessel formation at day 7</td>
<td>[212]</td>
</tr>
<tr>
<td></td>
<td>BM-MSC, allogeneic</td>
<td>30,000,000 cells/cm²</td>
<td>Escharectomy 4 days after burn and cell application in fibrin gel onto the wound</td>
<td>Enhancement of wound closure and absence of wound contractures, formation of hair follicle-like structures, and sebaceous glands</td>
<td>[88]</td>
</tr>
<tr>
<td>ASC, allogeneic</td>
<td></td>
<td>200,000 cells/mL of fibrin</td>
<td>Escharectomy 1 day after burn and cell application in fibrin gel onto the wound</td>
<td>Enhancement of angiogenesis and inflammation modulation toward a M2 phenotype</td>
<td>[83]</td>
</tr>
<tr>
<td>BM-MSC, allogeneic</td>
<td></td>
<td>500,000 cells/cm²</td>
<td>Escharectomy 3 days after burn and cell seeding onto a Small intestinal submucosa covering the wound</td>
<td>Enhancement of wound closure and angiogenesis</td>
<td>[213]</td>
</tr>
<tr>
<td>Pig</td>
<td>BM-MSC, autologous</td>
<td>100,000 cells/cm²</td>
<td>Application of cells in a collagen matrix onto the burn eschar</td>
<td>Enhancement of wound closure and angiogenesis</td>
<td>[214]</td>
</tr>
<tr>
<td></td>
<td>BM-MSC, rabbit, xenogeneic</td>
<td>2,000,000 cells/cm²</td>
<td>Escharectomy directly after burn and grafting of acellular dermal matrices. On days 7 and 14 after burn, cell spraying in fibrin gel</td>
<td>Enhancement of vascularization and hair follicle development</td>
<td>[92]</td>
</tr>
<tr>
<td></td>
<td>BM-MSC, allogeneic</td>
<td>1,000,000 cells/cm²</td>
<td>Escharectomy and cell application in fibrin gel onto the wound</td>
<td>Enhancement of wound closure</td>
<td>[215]</td>
</tr>
<tr>
<td>ADRC, autologous</td>
<td></td>
<td>250,000 cells/cm²</td>
<td>Escharectomy 2 days after burn and cell spraying in fibrin gel or dermal injection</td>
<td>Enhancement of wound closure and angiogenesis, reduction of inflammatory cell infiltration</td>
<td>[86]</td>
</tr>
<tr>
<td>ASC, allogeneic</td>
<td></td>
<td>15,000–150,000/cm²</td>
<td>Escharectomy 4 days after burn and cell application in functionalized hydrogels</td>
<td>Enhancement of angiogenesis</td>
<td>[94]</td>
</tr>
</tbody>
</table>

Highlighted in **bold** and *italic*: methods with an easiest translation to clinic.

ADRC, adipose derived regenerative cells; ASC, adipose stromal cells; BM-MSC, bone marrow mesenchymal stromal cell; UC-MSC, umbilical cord mesenchymal stromal cell.
excessive collagen deposition and fibrotic growth factor expression (ie, TGF-β1) [78,79]. In addition to their regulatory effect on matrix deposition, some investigators have even claimed that MSCs could have a favorable impact on adnexal tissue repair, especially on hair follicles and sebaceous glands [88,89].

Regarding infection and sepsis, MSCs can exert a bactericidal activity through direct and indirect mechanisms. They can secrete antimicrobial peptides and proteins such as LL-37 [90] or stimulate macrophage phagocytosis through phosphoinositide 3-kinase activation and prostaglandin E2 (PGE2) production [91].

**Limitations of the current preclinical models.** Despite major beneficial outcomes, MSC treatment strategies used in preclinical burn models remain difficult to apply in clinical practice. As reported in Table 2, the burn eschar is rarely removed in preclinical studies, while it is the standard practice in the clinics. Likewise, skin grafts remain poorly used in research studies, while they are essential for patients. Recently, a few studies have although come closer to the clinical practice, using both MSCs and dermal grafts to treat burns [92]. This combination was shown to reduce fibrosis and improve skin engraftment and angiogenesis in early time post-treatment [93,94]. Another concern is the time at which MSCs are administered. Research studies often use them immediately after burn induction, while this scenario appears clinically barely possible, especially in case of autologous treatments. Early treatment could yet be of real interest to limit burn-induced inflammation and necrosis spreading. However, this option implies that autologous MSCs or MSC-derived products are already banked and readily available. To reach this goal, time, dose, and mode of MSC administration will still have to be optimized to significantly improve the clinical treatment of burns [95].

**Clinical case reports**

Current clinical case studies. In 2005, Rasulov et al. were the first to report the successful use of MSCs and skin grafts to treat a 45-year-old woman suffering from a 30% total body surface area (TBSA) full-thickness burn [96]. Since then, only a few other similar cases have been reported in the literature (Table 3). MSC therapy was generally used in combination with a surgical treatment allowing the removal of the eschar and the application of an autograft. In these clinical studies, the MSC therapy was strikingly shown to attenuate pain [96] and scarring [97,98] and promote skin engraftment [96,99] through granulation tissue formation.

<table>
<thead>
<tr>
<th>%TBSA</th>
<th>Number of patients, gender, age</th>
<th>MSC therapy</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1, Female, 45 years old</td>
<td>BM-MSC, allogeneic</td>
<td>Topical application of cells after escharectomy and 4 days later application of autografts combined with cells (on autograft and donor site)</td>
<td>Rapid formation of granulation tissue, neangiogenesis, and better graft take</td>
</tr>
<tr>
<td>30</td>
<td>1, Male, 26 years old</td>
<td>BM-MSC, allogeneic</td>
<td>Cell spraying in fibrin matrix after escharectomy, 35 days later application of an expanded autologous skin graft with cells</td>
<td>Better granulation, tissue formation, reepithelialization from the wound margins, and angiogenesis</td>
</tr>
<tr>
<td>60 and 40</td>
<td>2, Female, 22 years old, male, 41 years old</td>
<td>BM-MSC, autologous</td>
<td>Not mentioned</td>
<td>Covering of the wound with a cell loaded collagen sponge</td>
</tr>
<tr>
<td>From 10 to 25</td>
<td>60, Female and male, from 15 to 30 years old</td>
<td>BM-MSC, autologous and UC-MSC allogeneic</td>
<td>Topical or subcutaneous injections of cells at day 2 and 10 after escharectomy</td>
<td>Better wound healing, hospitalization time shortage</td>
</tr>
<tr>
<td>80</td>
<td>1, Male, 19 years old</td>
<td>BM-MSC, autologous</td>
<td>Subcutaneous cell injections after scar excision and autologous skin grafting</td>
<td>Less skin graft contraction, less scar complications</td>
</tr>
</tbody>
</table>

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$a\%TBSA$ only refers to the extent of the third-degree burns and might not encompass the entire burn surface area of the patient. TBSA, total body surface area.
Although several clinical studies have reported no adverse effects in the use of autologous and allogeneic MSC (Table 3), it is still hard to conclude on the best donor source option, due to the very few number of patients involved in these trials. Autologous cells are advantageous in terms of immune tolerance. However, as they come from a pathological environment they may hold a disadvantage of using these secretory products is to avoid the use of cells that may induce a risk of tumorigenesis, immunogenicity, embolus formation, and pathogen transmission. Moreover, these products might be easier to bring to the market, as they can be framed under the current pharmaceutical regulations. However, secretory product standardization might be difficult to set in place, due to the variability observed among various cell sources and donors. Accordingly, MSC-derived secretomes originating from unrelated tissue sources were recently shown to contain different profiles of neurotrophic and neurogenic factors. In other studies, MSC secretory products originating from different donors were reported to bear disparate immunomodulatory effects. At last, cell-derived MSC products are known to be less efficient than MSCs themselves, especially in inflammatory disease models.

**Cell preconditioning.** Cell-based and cell-derived product therapies both face critical issues that limit their wide clinical use. While cell-based therapies have to cope with interdonor variability and cell exhaustion, cell-derived products lack effectiveness. Preconditioning, also known as priming or licensing, is a strategy used to improve the response of a tissue or cell population to a particular environment. This approach was first reported in the literature in 1986 by Reimer et al. who successfully improved the myocardium resilience to ischemia by exposing it to repeated short cycles of hypoxia.

In the context of cell therapy, the preconditioning approach can help prepare MSCs to a pathological environment by stimulating protective and survival pathways. Preconditioning can also help design customized cell therapies through the promotion of specific signaling pathways, targeting tissue homeostasis dysfunction or disease. In fact, a recent report showed that the reduced immunomodulatory functions of MSCs induced by a long-term exposure to palmitate, a known factor found in type 2 diabetes environment, could be rescued by a short preconditioning of these cells. Our laboratory has thus showed that the immune suppression property of MSC-derived products is strongly improved using priming method. Interestingly, other investigators have also shown that the preconditioning approach could also serve to minimize interdonor variability.
MSC Preconditioning Approach in Severe Burn Cell Therapy

As described by Caplan and Correa in 2011, wound healing is a biological process in which the preconditioning paradigm is at stake. Upon injury, resident and recruited cells get primed by mechanical and biological stressors that initiate the wound repair process [123]. Similarly, the burn wound gives rise to different priming stressors at early, middle, and late stages, altering cell behaviors at both local and systemic levels. Therefore, the treatment of burns must be adapted to the stage of the disease to reach high efficacy. In this section, we will review the preconditioning modalities that may potentiate the MSC therapy at each stage of the burn trauma. Hence, we will sequentially dissect the burn pathophysiology and give an overview of the priming modalities susceptible to improve MSC therapeutic efficacy (summary in Fig. 3 and Table 4).

MSC preconditioning strategy to tackle early-stage burn responses

Early pathophysiological responses to major burns are characterized by infections, hyperinflammatory responses, and hypermetabolism. These features prevent the burn wound from healing spontaneously and appear to be governed by an accumulation of ROS/reactive nitrogen species (RNS) [124,125], stress hormones, including catecholamines [126–128], and free fatty acids (FFAs) [48]. In this section, we will emphasize the potential of mild inflammatory primings to augment MSC therapeutic effects during early burns.

**Fighting wound infections.** To prevent postburn infections, mild inflammatory primings are interesting strategies, as they promote direct and indirect MSC antimicrobial activities. To our current knowledge, MSCs are able to synthesize four different antimicrobial peptides, including LL-37, beta-defensin 2, hepcidin, and lipocalin-2 [90]. In an ex vivo model of lung injury, lipopolysaccharide (LPS) was reported to promote the MSC-derived synthesis of LL-37 [129]. Recent observations in our laboratory also showed that low-dose IL-1β primed MSCs could secrete high levels of fibroblast growth factor (FGF)-7 (unpublished data), a factor known to promote peripheral blood mononuclear cell (PBMC) survival and phagocytic activity [130].

**Mitigating the hyperinflammatory response.** After traumatic burn injuries, DAMP, pathogen-associated molecular pattern (PAMP), and stress hormones activate the JNK signaling pathway through G-protein coupled receptors and initiate an inflammatory cascade [127]. To attenuate this pathological process, inflammation-related cues have been the most commonly used priming agents [131–134]. Mild inflammatory licensings are indeed known to make MSCs secrete a...
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<sup>a</sup>In vivo studies.

AA, arachidonic acid; ANG, angiopoietin; α-SMA, α-smooth muscle actin; COL, collagen; C3a, complement component 3a; CO, carbon monoxide; COX-2, cyclooxygenase 2; DSS, dextran sulfate sodium; ECM, extracellular matrix; FGF-2, fibroblast growth factor; GM-CSF, granulocyte macrophage-colony stimulating factor; HIF-1α, hypoxia-inducible factor 1-alpha; IFIT1, interferon induced protein with tetrapartically repeats 1; IFN-γ, interferon-γ; IL, interleukin; HGF, hepatocyte growth factor; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; MT3-MMP, membrane-type 3 matrix metalloproteinase; MX1, interferon-induced GTP-binding protein; NK, natural killer; PBMC, peripheral blood mononuclear cell; PMA, phorbol myristate acetate; PMN, polymorphonuclear neutrophils; SOD2, superoxide dismutase 2; STC-1, stanniocalcin; TGF-β1, transforming growth factor beta 1; TNF-α, tumor necrosis factor alpha; TSG-6, TNF-stimulated gene/protein 6.
wide range of anti-inflammatory molecules such as TGF-β1, IDO (indoleamine 2,3-dioxygenase), TSG-6, hepatocyte growth factor (HGF), galectins, and semaphorins [131,135–138]. Recently, a study showed that TNF-α and LPS primedMSCs could alleviate the inflammatory reaction in a scald burn rat model, as highlighted by reduced systemic levels of TNF-α, IL-1β, and IL-6 [81]. In another study, the neurogenic and pro-inflammatory Substance P, known to be released in high amounts after burn [139], was shown to induce the secretion of TGF-β1 from primedMSCs and improve the ability of these cells to suppress CD4+ T cell activities [140]. Inflammatory primings can also have an indirect impact on immune cell functions. Accordingly, inflammation-licensed MSCs are able to synthesize high levels of PGE2 and Lipoxin A4, two lipid inducers of efferocytosis and phagocytosis [117,141]. In another study, Song et al. successfully polarized macrophages toward a M2-like phenotype using IL-1β stimulatedMSCs and observed a diminution of TNF-α synthesis and an increase in IL-10 release in response to LPS [142].

Apart from inflammatory cytokines, stress hormones can also promote antioxidative and anti-inflammatory secretions in MSCs. In a recent study, epinephrine was shown to activate MSC immunomodulation when cocultured with LPS-treated macrophages by regulating key inflammatory cytokines, including TNF-α, IL-1β, IL-1RA, and IL-10 [143]. This effect was confirmed in a rat model of lung injury, where primedMSCs reduced inflammation, edema formation, and hemorrhage. Exendin-4, a glucagon-like peptide-1 homolog, was shown to trigger the synthesis and the activity of antioxidative enzymes such as glutathione, glutathione peroxidase, and superoxide dismutase in hydrogen peroxide-intoxicatedMSC [144]. In the same study, Exendin-4 stimulation reduced the production of malondialdehyde, a lipid peroxidation end product found in burns.

Other studies have also reported a better ability ofMSCs to mitigate inflammatory processes after a hypoxic or ROS preconditioning. Accordingly, mild hypoxia [145] and hydrogen peroxide [68] licensedMSCs were able to suppress the proliferation of activated PBMCs, in a TSG-6 dependent mechanism [68]. In accordance with these in vitro observations, the use of a conditioned medium from hypoxicMSCs was reported to reduce the amount of inflammatory and oxidative stress mediators, including IL-17, interferon-γ (IFN-γ), inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2), and JNK in an experimental autoimmune encephalomyelitis mouse model [146].

Suppressing hypermetabolism. To cope with hypothermia, a catabolic switch is often observed in burn patients, which in turn stimulates the process of thermogenesis. This metabolic change leads to excessive glycolysis, proteolysis, and lipolysis and contributes to lean body mass breakdown [128]. As a consequence, elevated plasma levels of triglycerides and FFAs are found in both animals and humans with major burns [48,127,147]. Saturated and mono-unsaturated FFAs are known to support TLR4 inflammation [148], contribute to insulin resistance [48] and, therefore, impair the normal wound healing process. Inflammation-licensed MSCs have been shown to bridle metabolic dysregulations. In particular, TNF-α and LPS preconditionedMSCs were able to minimize the body temperature drop early after injury in a scald burn rat model [81]. MSCs were also shown to contribute to insulin sensitization through the blockade of the NLRP3 (NOD-like receptor protein 3) and the IRS-1 (insulin receptor substrate 1) [149] by secreting STC-1 (stanniocalcin-1) [150], an antioxidative and anti-inflammatory protein, known to be upregulated after a 3D-spheroid culture [151] or an apoptotic signal [152] preconditioning ofMSCs.

**MSC preconditioning strategy to combat middle-stage burn responses**

As discussed earlier in this review, the treatment of deep and extensive burns requires a surgical act that includes burn eschar excision to impede necrosis progression and skin grafting to recreate a functional barrier. However, due to the dysregulated metabolic and inflammatory state of burn patients, skin donor sites and burn wounds struggle to heal rapidly. As a result, comorbidities and pathological scars develop due to delayed reepithelialization [153]. Herein, we will provide an overview of the licensing modalities that could drive MSCs toward pro-healing and reparative activities to improve the middle-stage burn wound healing. In particular, we will emphasize the contribution of both the hypoxic and inflammatory primings in MSC-mediated wound closure, angiogenesis, and tissue protection.

**Fighting tissue viability loss, ischemic injury, and necrosis.** Retardation in burn eschar removal is known to promote the extension of the coagulation necrosis to the surrounding stasis zone [154]. This pathological progression therefore results in greater tissue viability loss, ischemic injuries, and necrosis. Hypoxia is an interesting priming to combat these tissue alterations as it stimulates the MSC synthesis of pro-survival factors such as VEGF, insulin-like growth factor-1 (IGF-1), FGF-2, and HGF [70,155]. Several animal models of reperfusion injury or wound healing have underlined the benefit of hypoxia-preconditionedMSCs in terms of tissue survival and neovascularization using direct administration of cells [156], conditioned media [70], or microvesicles [157]. From a mechanistic point of view, hypoxia would activate prosurvival and pro-angiogenic pathways inMSCs, including Akt and e-Met [156].

As for hypoxia, inflammatory licensings can also activate pro-survival and trophic factors inMSCs. Under low stimulation levels of IL-1β and TNF-α stimulation, for example, MSCs can release high levels of VEGF and HGF and activate the pro-survival extracellular signal-regulated kinase (ERK)1/2 signaling pathway in airway epithelial cells [158]. PrimingMSC with IL-1β, TNF-α, and NO could also enhance secretion of pro-angiogenic mediators and promote tissue survival in model of radiation-induced intestinal injury [159].

**Improving donor site healing.** Slow- or nonhealing skin donor sites are major curbs in the management of severe burns, as they lead to increased occurrence of infections and prolonged hospitalization times. In an attempt to improve the repair of these donor sites, the MSC preconditioning strategy can serve to trigger the secretion ofMSC-derived trophic factors accelerating local wound closure.

Inflammatory-primedMSCs are known to accelerate cutaneous wound closure. In a recent study, Broekman et al. successfully improved the proliferation and migration of epithelial cells through an epidermal growth factor receptor (EGFR) dependent mechanism using IL-1β and TNF-α
licensed MSCs [158]. Licensing MSCs with S100A8/A9, a calcium-binding DAMP protein known to activate the TLR4 signaling, were also shown to accelerate wound closure in a full-thickness skin excisional murine model through IL-32, MMP-27, and complement component 3a (C3a) upregulation [160]. In other studies, hypoxia caused MSCs to release pro-migratory factors stimulating the migration of epithelial cells in vitro [70,156] and accelerating the closure of excisional wounds in vivo [145]. Lipid mediators such as all-trans retinoic acid [161] and arachidonic acid (AA) [162] have also been reported to promote MSC-driven tissue repair and acceleration of wound closure in excisional skin wound mouse models. In particular, the AA priming of MSCs was shown to regulate fibronectin degradation and wound closure through the activation of the mTORC2 (mechanistic target of rapamycin complex 2) pathway and the expression of MT3 (membrane-type-3)-MMP [162].

**Promoting skin engraftment.** Although many studies have reported the beneficial effect of primed MSCs on wound closure, very little is known about their ability to help skin graft take in large tissue defects. Based on clinical observations, both functional blood supply and mature DEJ would be needed to prevent skin graft viability loss and blistering. Therefore, MSC licensings are expected to target pro-angiogenic and DEJ remodeling responses to positively impact on skin graft take.

Hypoxia-preconditioned MSCs were shown to secrete high protein levels of VEGF and ANG-1 and induced better endothelial tube formation in vitro [163,164]. Once injected with endothelial cells, hypoxic MSCs were reported to promote graft viability and vascularization and to reduce contraction in a model of full-thickness skin excision [93]. In a very different setting, exosomes from hypoxic MSCs were shown to promote fat graft survival through enhanced angiogenesis and reduced inflammation [165].

Inflammation-related primings may also influence MSC-mediated DEJ remodeling. Both TGF-β1 and TNF-α licensed MSCs improved type-VII collagen deposition and mitigated skin blistering in a model of regressive epidermolysis bullosa [166]. Other studies reported that IFN-γ [131] and IL-1β [138] preconditioned MSCs secrete high levels of TGF-β1, a growth factor known to play pivotal roles in DEJ formation [167–170].

**MSC preconditioning strategy to bypass late-stage burn responses**

After the hyperinflammatory reaction, the pathophysiology of severe burns evolves toward immune suppression and hypertrophic scarring [154,171]. As previously mentioned in this review, this pathological switch partly ensues from a systemic dysregulated expression of the TLR downstream mediators [13], which include IL-10, IL-4, IL-13, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1β, IL-2, and IFN-γ [10,172]. The expression levels of several growth factors, such as TGF-β1 and VEGF, are also increased in the late stages of the burn trauma, leading to hypertrophic scars [173,174]. In this complex pathological system, the use of licensed MSCs is expected to reverse the immune suppression and mitigate the scarring response. Herein, a specific attention will be drawn to hypoxic and strong inflammatory MSC preconditionings.

**Reactivating the immune system.** Myeloid-derived suppressor cells (MDSCs) are a heterogeneous cell population initially discovered in tumors and later described in burns [175]. These cells play significant roles in acquired immune system suppression and angiogenesis promotion [176,177]. The mobilization of MDSC is driven by VEGF and GM-CSF and leads to the release of Arginase, RNS, and ROS, all of which are implicated in inflammatory processes, bacterial clearance activity, and immune dysfunction [177]. Cancer research studies have shown that immune system reactivation could be accomplished by suppressing MDSC activities either through induced differentiation into mature myeloid cells or mobilization and expansion arrest [177]. Although the role of MDSC on postburn immune suppression has not been studied in depth like in cancer, one might assume that inhibiting these cells in a late burn context could improve immune reactivity. To our knowledge, the impact of the MSC preconditioning on MDSCs has scarcely been studied. What we know at best is that tumor-educated MSCs can promote MDSC growth and activity [178]. But an emerging body of evidences is now suggesting that under specific priming conditions MSCs could repress MDSC activities and reactivates the immune system.

TLR agonists are known to regulate MSC immunomodulatory activities. They can thus trigger antagonistic inflammatory responses in MSCs, depending on the priming dose or on the presence of other priming agents. Lately, our team showed that MSCs can rescue LPS-intoxicated T cell survival, after a priming with both LPS and pamidronate, but not with LPS alone [179]. High-dose LPS and IFN-γ preconditioned MSCs were recently shown to prevent LPS-activated B cells from secreting IL-10, a well-known repressor of T<sub>H</sub>1 cell subset activation [180]. The LPS priming also triggered MSC derived synthesis of IL-8 and macrophage migration inhibitory factor, two promoting factors of polymorphonuclear neutrophil survival, migration, and function [181].

In addition to their direct contribution to MSC-driven immune stimulation, TLR agonists are likely to influence interactions between MSCs and MDSC. Accordingly, the preconditioning of MSCs with CpG oligodeoxynucleotide [182] or poly(I:C) [183] was shown to induce the production of IL-12, a putative MDSC differentiation inducer, along with vitamin A metabolites and vitamin D3 [184]. TLR agonists therefore constitute privileged priming cues to direct MSC immunomodulatory functions. However, because their mechanisms of action still remain poorly understood, conflicting data have emerged in the literature [185,186], highlighting the complexity of these priming cues and the need for further investigations especially regarding the dose. Analogously to TLR agonists, ROS primings can modify MSC immunomodulatory properties depending on the other priming cues expressed in the local milieu. Recently, Tsou et al. showed that carbon monoxide (CO) and AA primed MSC release high levels of pro-inflammatory prostaglandins, while CO and DHA (docosahexaenoic acid) primed MSC synthesize anti-inflammatory resolvins [187]. As a consequence of lipid catabolism and thermogenesis, circulating saturated FAs, such as AA, are found in excess in the early stage of the burn pathophysiology and persist over time [147]. CO-primed MSC might therefore be noxious if used at the onset of the burn pathology, as they could sustain
or worsen the hyperinflammatory response. If used later, however, they might help reactivate the immune system. These interesting data therefore demonstrate the importance of carefully choosing a preconditioning that is adapted to the stage of disease pathophysiology.

Aside from TLR agonists and ROS, other factors have been reported to modulate the effect of MSC on the immune system. For example, Zhou et al. highlighted the significance of the MSC-to-T cell ratio as it can trigger both stimulation and inhibition of T cell expansion in vitro. Accordingly, MSCs can stimulate the proliferation of activated CD4 and CD8 T cell subsets at low MSC-to-T cell ratios, while they are inhibitory at higher ratios [188].

Harnessing the development of hypertrophic scars. While hypertrophic scars are common postburn sequelae, their pathogenesis remains largely unknown. Clinical and experimental observations have led to the hypothesis that hypertrophic scars would stem from aberrant outgrowth and survival of myofibroblasts, imbalanced ECM deposition [189–191], and overactivated TGF-β signaling [191]. MDSCs have also been designated as putative targets in scarring processes. In addition to secrete pro-fibrotic ROS and TGF-β1, these cells are known to suppress the immune system activity through MyD88 [192], a regulator protein found in excess in hypertrophic scars [13]. Given the actual need for an antiscarring treatment and the scarcity of candidates for it, the MSC therapy has surfaced as a possible solution. Here again, the success of such a therapy must be considered within the scope of the licensing approach, since MSCs can both be pro- and antifibrotic, depending on their microenvironment [193].

Hypoxia is known to trigger antifibrotic mechanisms in MSCs, involving both leptins [194] and HIF-1α (hypoxia-inducible factor 1-alpha) [195], through collagen and Z-SMA downregulation. In particular, hypoxic MSCs were shown to decrease the expression level of connective tissue growth factor, a downstream mediator of fibrosis, and increase the expression of HGF, a well-known TGF-β1 signaling inhibitor [196, 197].

Recently, a study highlighted the central role of the tumor-suppressive gene p53 in the antiscarring effect of MSC [198]. In particular, p53-silenced MSCs were shown to promote fibroblast proliferation through iNOS production and myofibroblast conversion. The tumor-suppressive gene p53 is known to be involved in growth arrest, apoptosis, and antiangiogenesis, as it triggers the synthesis of key molecules such as insulin-like growth factor-binding protein 3 (IGFBP-3) and 14-3-3σ [199]. To improve MSC antiscarring effects, the activation of the tumor-suppressive gene p53 could therefore be an interesting option. This activation can be achieved through the use of stress signal primings, including radiation, hypoxia, or deoxyribonucleic acid damage [199].

Excessive vascularization is known to contribute to scar formation [173]. Promoting MSC antiangiogenic responses using well-defined licensing cues could therefore be a way to mitigate the emergence of hypertrophic scars after burns. As previously mentioned, the priming effect of inflammatory signals on MSCs can have an impact on angiogenesis but it appears to be highly dose dependent. As a result, the inflammatory priming of MSCs has both been shown to support the release of pro-angiogenic mediators at low doses [159] and suppress the endothelial cell migration, tubule formation, and in vivo vasculoprotection at higher doses [200–202]. These conflicting data can be explained by the release of TIMP-1, a well-known angiogenesis antagonist, differentially expressed under inflammatory licensing conditions. TIMP-1 is indeed overexpressed in MSCs primed with elevated doses of pro-inflammatory mediators [200], while it remains at a baseline expression level in low dose priming conditions [137].

Interestingly, TGF-β1-primed MSCs have been also recently shown to release high protein levels of IGFBP-3 [203], a growth factor known to block VEGF and MMP-9 pathways in vitro and in vivo models of angiogenesis and vessel sprouting [204, 205]. Therefore, the TGF-β1 licensing of MSCs could be used to block MDSC activity, as it relies on JAK2 (Janus kinase 2)/STAT3 (signal transducer and activator of transcription 3) and VEGF signaling [184].

Toward the Clinical Use of MSC Preconditionings for Burn Treatment

Presently, there are only five reported clinical cases where MSC-based therapies were used to treat major burns (Table 3). In the majority of them, MSCs were applied during the middle stage of the burn disease progression, when reepithelialization, tissue survival, and skin graft take needed to be promoted. As reported in this review, hypoxic and mild inflammatory preconditionings are therefore appealing candidates to improve the MSC therapy at this specific pathological stage. However, these priming modalities might also be of interest to treat early burn stages to help mitigate hypermetabolism, hyperinflammation, and wound infections.

Although preconditioning approaches open up new therapeutic avenues in the field of cell therapy, a particular attention has to be drawn on preconditioning development and pathological context of use. In this review, we indeed reported that distinct priming doses and environments could promote antagonistic therapeutic outcomes. In that way, we specifically highlighted inflammatory and hypoxic/ROS preconditionings, but this might apply for many other licensing modalities. Therefore, there still is a need for thorough and comprehensive studies ensuring the benefit of a specific priming protocol for a chosen disease or pathological event.

As reported in this review, a standardized priming dose and priming duration need to be found for the clinical translation of the preconditioning approach. At the cell therapy level, other questions will also have to be answered such as the dose and the administration route of primed MSC or primed MSC-derived products. Preclinical studies will therefore be required to explore the best therapeutic options. Although many questions remain to be answered, the clinical preconditioning approach can be attainable. Indeed, in terms of safety, Guess et al. reported no sign of toxicity, tumorigenesis, or biodistribution of IFN-γ-primed MSC [206]. Few clinical studies have already been performed to evaluate the safety and efficacy of primed MSC. Hypoxic allogeneic MSCs were, for example, shown to improve nonischemic cardiomyopathy, as highlighted by a strengthening of the left ventricular ejection fraction in patients [207].

Conclusion and Perspectives

Because of a complex pathophysiology, the treatment of deep and extensive burns remains a challenge today.
However, the MSC therapy holds great promises in terms of safety, adaptability, and feasibility. Depending on the pathological target and the stage of the disease progression, the MSC potency can further be improved using well-characterized preconditioning protocols. Now that preclinical studies have demonstrated the real interest of this approach to improve the burn wound healing, the proof of safety and efficacy remains to be done in major burn patients.

Author Disclosure Statement

No competing financial interests exist.

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