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Application of nanomedicine and mesenchymal stem cells in burn injuries for the elderly patients

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ABSTRACT

Burns not only damage the skin barrier, but also cause a series of inflammatory reactions and oxidative stress states. Among them, elderly patients are prone to suffer severe burns due to degenerative changes of their skin caused by aging factors, such as atrophy and thinning, etc. After burns, the body will continuously release inflammatory factors, resulting in systemic inflammatory response syndrome (SIRS) and oxidative stress, which are related to the poor treatment effect and the poor prognosis of elderly burn patients. It seems to be difficult for conventional treatments to control the disease development of elderly burn patients effectively. Considering the rapidly increasing elderly population, it is priority to understand the pathological process and the mechanisms to formulate more appropriate treatment strategies for elderly burn patients. In recent years, owing to considerable advances in nanotechnology, a variety of nanomaterials have been developed for wound healing and inflammation regulation. Its good biocompatibility, cell proliferation stimulation and antibacterial properties make the clinical treatment strategy more optimized. Concurrently, mesenchymal stem cells (MSCs) have also been used in the burns field and have been proven effective in not only controlling the level of inflammation and regulating the systemic immune balance, but also promoting wound healing and vascularization. Here, this review covers burns classification, the pathological process of elderly burn patients, and the research progress of nanotechnology and MSCs in burns. Eventually, we summarize the advantages and challenges of emerging strategies such as nanotechnology and MSCs in the treatment of elderly burn patients, expecting to promote the clinical transformation.

1. Introduction

In modern burns medicine, advanced age is still a well-established risk factor contributing to the high mortality of burns patients. Although significant progress has been made in burns treatment and specialist care in recent years, elderly burn patients are still a vulnerable and challenging group in burns discipline [1]. In recent decades, although advancements in treatment of elderly burn patients [2], several studies emphasize that the prognosis and mortality of elderly patients are still much worse than younger burns patients [3].

Aging is a common risk factor for many diseases and trauma [4]. According to the prediction of the World Health Organization, the number of people aged 60 years will rise from 900 million to 2 billion between 2015 and 2050 and the aging rate of the population is increasing more rapidly than ever [5]. Countries around the world are about to face major challenges brought about by aging population. As the global are gradually entering an aging society, the proportion of elderly burn patients in specialist care is expected to increase accordingly [6]. Moreover, with the development of economy, the multiplication of population and the advocacy of national policies, the elderly population living alone in

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the community has grown relatively fast in recent years. These elderly people are particularly vulnerable to burns due to their impaired vision, impaired judgment and coordination, lower mobility, and slower response to danger [1,7].

Burns are a common traumatic injury in our daily life, which may lead to severe disability or even death. The cause of burns may be friction, cold, heat, radiation, chemical or electricity, but most burns are mainly caused by thermal injuries, including fire, hot objects, or scalds [8]. Although all burns involve tissue destruction caused by energy transfer, different causes can lead to different disease outcomes, which may be associated to different pathophysiological responses [9]. Just as elderly burn patients have a higher shock rate and mortality due to the physiological characteristics of the heart, lung, kidney degeneration and the concomitant primary diseases of cardiovascular diseases. Another reason why elderly burn patients have a poorer prognosis and a higher mortality compared to younger patients is the increased incidence in elderly individuals of an "inflammatory aging" phenomenon, which is a continuous low-grade inflammation state [10], leading to excessive inflammation in elderly burn patients for a long period. Besides, advanced age accentuates the depressed immune response after burns, delayed initial inflammatory response, abnormal regulation of immune cells such as monocytes, and delayed wound healing [11–13]. Indeed, elderly burn patients are more prone to complications, such as multiple organ dysfunction syndrome (MODS), inhalation injury, wound infection, and acute respiratory distress syndrome (ARDS) [14,15] and these are closely correlated to the high mortality rate of elderly burn patients [16]. At the same time, the decrease in collagen and elastin content, hyaluronic acid and vascularization reduction in the aged skin compared with young people are also responsible for the poor prognosis of elderly burn patients. Therefore, a better understanding of the pathological state of the elderly with burns is helpful to improve the treatment strategies and the prognosis of patients.

The causes of burns and age factors determine the treatment of burns, which is usually individualized. Skin grafting of the burn wound is one of the most important measures to reduce the mortality of ordinary burns patients suffering severe burns [17,18]. However, for elderly patients, adverse systemic responses and postoperative complications always lead to a poor prognosis, so surgical treatment should be cautious [16]. It is necessary to adopt new intervention measures to alleviate the excessive inflammation state and adverse responses caused by surgery in elderly burn patients. For the past few years, the cutting-edge nanotechnology presents an unprecedented opportunity for current burns treatment strategies. It is impressive that numerous nano-drug delivery systems (nano-DDSs) have been created and pressed into fields related to burns infections and skin repair. Data from several studies have also demonstrated that nano-DDS have the following advantages: (1) nano-DDS have good compatibility with burned skin and can also provide a beneficial damp environment; (2) nano-DDS can anchor drug targets to applied areas and improve drug retention; (3) They can also maintain the drug release and prolong the drug concentration action time [19,20]. Furthermore, some other innovative therapeutic modalities such as MSCs have flourished in the field of burn wound healing and regenerative medicine [21,22]. Except for differentiating into new tissues [23,24], MSCs could adjust the immune response after injury by increasing the release rate of anti-inflammatory factors and reducing the release rate of pro-inflammatory cytokines [25], especially under systemic inflammation such as blood and spleen [26]. Consequently, MSCs therapy have become a new treatment strategy for patients with severe burns and elderly burn patients with many complications due to their unique anti-inflammatory and wound healing potential. It is worth mentioning that compared with embryonic stem cells, some MSCs such as dental pulp stem cells (DPSCs) are easier to clinically transform due to the advantages of easy availability, non-invasive collection, non-ethics, and abundant donors for clinical applications.

Herein, we first present the classification of burns, the pathological process and possible muscle atrophy later of elderly burn patients. We then discuss the research progress of nanotechnology and mesenchymal stem cells to better match the pathophysiology of elderly burns and provide an up-to-date outlook for the current limitations.

2. Burns classification

An understanding of normal skin structure and pathological mechanisms of the skin after burn is crucial for the application of nanotechnology and MSCs in burn wounds. In general, the skin is divided from top to bottom into epidermis, dermis, and hypodermis (Fig. 1). Thus, classification of the severity of burn injuries is usually evaluated based on the depth and percentage of total body surface area (TBSA) of the damage wound. Burns that affect the outermost layer of the skin—epidermis is classed as first-degree burns (superficial burns); the epidermis becomes red, and the pain experienced is of limited duration. Second degree burns are divided into superficial second-degree and deep second-degree burns. Superficial second-degree burns are defined by the injury extending the entire epidermis and part of the nipple layer; the skin becomes red, swollen, painful, and blistered, requiring wound care rather than surgery and it generally heals faster than deep second degree. Deep second-degree burns are deep and below the papillary dermis, but there are still parts of the dermis and cutaneous appendages; the skin becomes red and white, edema is obvious, pain is dull, and small embolized vascular network is visible. The degree burns need require surgery and will scar. Third degree burns are also called full-thickness burns. The skin epidermis and dermis are completely destroyed, including the subcutaneous tissues, and even muscles and bones. A layer of necrotic tissue covers the wound surface, which is burnt black, and the pain disappears. Third degree burns require surgery and will leave large scar tissue (Fig. 2). Importantly, according to the size of the wound, burns can be classified as minor and major burns. The minor burns are mainly superficial burns, usually defined as the burns size is less than 10% TBSA. For the classification of major burns, there is currently no clear definition in the medical community. Some guidelines are used to indicate major burns: more than 30% TBSA in children, more than 20% TBSA in adults and more than 10% TBSA in elderly patients [9,27]. Obviously, due to a failing immune system, age-related skin changes, and several medical comorbidities, the guidelines for diagnosis and treatment of burns are significantly stricter on the definition of major burns in the elderly than in adults and children. This assessment criterion is critical for elderly burns because when physical partial burns exceed this point, the loss of fluid in the damaged microvasculature can lead to hypovolemic shock, which is a fatal blow to elderly burn patients.

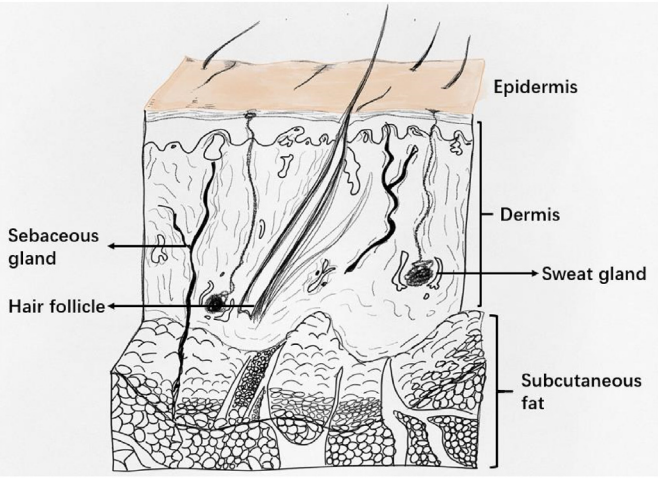

Fig. 1. Schematic illustration of the normal skin structure.

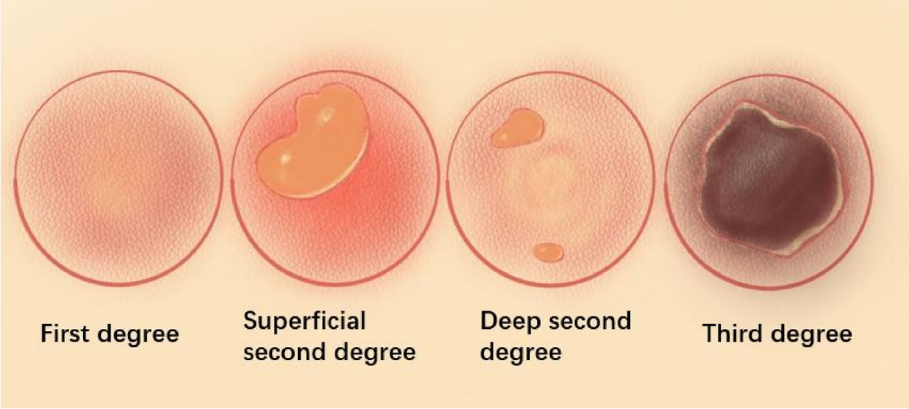

Fig. 2. Brief schematic illustration of first to third degree burns.

3. The pathological of elderly burns

Understanding the pathological process of the elderly burns is not only the basis for the treatment of burns, but also the basis for the prevention, alleviation, and treatment of the corresponding disease states of the elderly burn patients. The initial response of burns is the rapid appearance of inflammation and hypermetabolism and the subsequent consequence is chronic dysfunction of the immune system [27], which is extremely unfavorable for elderly burn patients, especially those with underlying diseases. During the aging process, several physiological changes occur in different organ systems, including reduced functional reserve capacity and immunosenescence, which lead to a diminished ability to adapt to the aggravating environment after burn [16,28]. Therefore, some studies have shown that when studying the pathophysiology of burn wounds, burn wounds can be regarded as a special "organ". Clinical studies have also demonstrated that the elderly develop hypovolemic and hypermetabolic responses within a few hours of burns, as well as severe immune dysregulation and infection, which are responsible for the intricate cellular mechanisms of burn [9].

3.1. Local responses and infection of burn wound

The pathophysiological changes of both burns and scalds are caused by thermal diffusion. A sudden increase in the temperature of the skin surface will cause the blood vessels in this area to respond quickly, releasing heat by vasodilatation. The rapid transfer of heat leads to the loss of skin barrier function, denaturation of proteins and finally loss of cell plasma membrane integrity [29]. The inherent factors such as atrophic skin thinning, and reduced microcirculation make the elderly more vulnerable to more severe and deeper burn. From the perspective of the injury skin structure, the burn wound is mainly divided into three zones. The zone of coagulation at the central portion of the burn wound is generally considered to consist of devitalized tissue. The zone of coagulation is surrounded by the zone of stasis, which is characterized by poor blood perfusion, mixing of living/dead cells and exuberant inflammation. The zone of stasis frequently progresses and gradually becomes necrotic within the first 48 h after the burn [30]. On the outermost region of the burn wound is a hyperemic zone of inflammatory vasodilatation. As a result, the initial burn wound will be expanded in area and depth, which will easily aggravate the inflammatory and immunosuppressed state of the elderly patients. Notably, the apoptosis of vascular endothelial cells caused by severe burns destroys the already poor in microcirculatory system in the elderly patients that predisposes the elderly to multiple organ failure [31]. Furthermore, in the presence of underlying lesions, immunosenescence also induces an increase in systemic proinflammatory cytokine levels in the elderly individuals in combination with post-burn inflammatory states and oxidative stress, ultimately leading to an increased risk of age-related complications and death [28]. But if the primary disease and burn wound infection are improved, these pathological changes can be reversed [9].

In exploring the pathophysiology of burns in the elderly, one must attempt to understand the mechanisms behind the resulting associated responses. The main mechanism involved in the pathogenesis of burn wounds is an inflammatory reaction that causes microvascular damage, thus promoting the progression of damage to tissue already destroyed by heat [32]. The central element is that various pathways are triggered to release inflammatory mediators and produce large quantities of reactive oxygen species (ROS). After severe burn injure, the immune system is immediately activated to recognize endogenous factors such as damage-associated molecular patterns (DAMPs) and their exogenous counterparts, pathogen-associated molecular pattern molecules (PAMPs) via pattern recognition receptors Toll-like receptors (TLRs) and NOD-like receptors (NLRs) [9]. The ligation of TLRs and NLRs by the specific ligands triggers the excessive secretion of cytokines and inflammatory mediators, leading to activation of nuclear factor κB (NF-κB), a transcription activator factor involved in the modulation of inflammation and immunity. NF-κB is thought to modulate the induction of multiple inflammatory mediators, including tumor necrosis factor (TNF-α), IL-1, IL-6, and IL-8 [33]. The release of these inflammatory mediators further exacerbates the hyper-inflammatory state in the elderly leading to the development of a compromised adaptive immune response, resulting in increased susceptibility to infection. Indeed, elderly burn patients with uncontrolled release of inflammatory mediators have a significantly increased risk of SIRS and MODS, which is one of the reasons for their higher mortality [13]. In addition, the marked apoptosis of organ cells frequently triggered by burns may also be related to increased expression of proapoptotic factors in response to inflammation, including Bax and caspase-3 [32].

3.2. Inflammatory cytokines and oxidative stress

In the early stage of burns in elderly patients, systemic hypovolemia is often the most fatal, but after a series of clinical treatments such as volume expansion, most patients can pass the burns shock period smoothly. However, subsequent infection control and hyperinflammatory has become decisive factors in the prognosis of elderly burn patients. Tissue damage and protein denaturation caused by burns also results in profound hypermetabolism that involves increased production of proinflammatory cytokines and formation of ROS, such as IL-6, TNF-α, catecholamines, glucocorticoids, glucagon and dopamine [32,34]. These regulatory substances then enter the blood circulation, causing systemic inflammation and acute hypermetabolic response [35]. It is thought that the severity of the hypermetabolic response following burns increases with age [16]. Some studies have also shown that elevated levels of these cytokines in burns patients are associated with higher mortality, increased incidence of MODS and sepsis [36]. These complications are

the result of immune dysregulation caused by the combination of burns and age.

The research teams of Boyd and Singh et al. found the aged have higher levels of inflammatory cytokines such as TNF-α and IL-6, which also lead to weakened immune response, making elderly burn patients more susceptible to pneumonia, delayed wound healing, and dysregulated inflammation [37,38]. TNF-α is generally considered to have the effect of amplifying inflammatory mediator responses and inducing apoptosis of damaged cells. However, this cytokine is also believed to increase the formation of ROS and accelerate lipid metabolism, thereby increasing the catabolism of burns patients and forming an acute hypermetabolic state [39,40]. Idrovo et al. demonstrated in a mouse model of elderly burns that aged animals are prone to increased liver damage after skin burns due to dysregulation of lipid metabolism and impaired antioxidant response [41]. At the same time, the adverse effects of TNFα in the minor burns have also been confirmed in mouse models of mild burns [42]. IL-6 plays multiple roles in the immune regulation and inflammatory process of the body. It is a pro-inflammatory and anti-inflammatory cytokine with hormone-like characteristics. Therefore, it is difficult to determine the specific role of IL-6 after burns. Wolsk et al. injected recombinant human IL-6 into healthy volunteers to mimic the hyper-catabolism state of burns, indicating that IL-6 can increase energy expenditure and fat metabolism in burns patients [43]. Interestingly, the elderly burn patients do take longer to restitute after loss of body mass. Jeschke et al. also found that 17 inflammatory mediators, such as IL-6, IL-8, IL-10, G-CSF and MCP-1, were significantly increased in burns patients by comparing with the serum cytokines of burned and normal people, and burn patients showed obvious SIRS long after the burns [44]. These inflammatory cytokines continued to rise for several days in the mouse burns model, and similar phenomena were also observed in severely burned pediatric patients [45]. Two prospective studies on IL-10 also found that the increase in IL-10 concentration is related to the increased mortality of patients with sepsis and the high incidence of SIRS [46,47]. Gauglitz and Hur et al. proposed the use of IL-6, IL-10 and MCP-1 as a prognostic predictor of burns by observing the changes of cytokines in surviving and dead burns patients [48,49]. The regulation of inflammatory cytokines in burns patients is extremely complicated. Understanding the role of each factor will help to better understand the pathophysiological progress of elderly burn patients, so as to develop better strategies for individualized care.

In addition to inflammation and hypermetabolic responses, oxidative stress is also one of the higher risks factors leading to high mortality in elderly burn patients. OFRs (oxygen free radicals) are molecules that can exist independently and have unpaired electrons, so that they can highly react with other molecules [50]. OFRs and their derivatives H_2O_2, lipid peroxides (LPO) and singlet oxygen ($1O_2$) are collectively referred to as reactive oxygen species (ROS), which can produce oxygen toxicity, and are closely related to many pathological processes, such as cardiovascular disease, ischemia reperfusion injury, etc. [51]. In fact, there is a delicate balance between OFRs and antioxidants and cell-repair enzymes in the normal physiologic condition, which protect cells from the harmful effects of free radicals [28]. In the early stage of elderly burns treatment, active fluid resuscitation will cause oxygen to quickly enter the ischemic tissue to produce hydrogen peroxide and superoxide, which are clearly identified as deleterious. Secondly, apart from xanthine oxidase, the main sources of OFRs in burn wounds also include complement activation and adherent-activated neutrophils, which are recognized by DAMPs and PAMPs, leading to excessive leukocyte recruitment, fever, and tachypnoea [33,50,52]. OFRs are also clearly interlinked to aging, and there are more OFRs in the elderly burn patients. Excessive production of OFRs can cause lipid peroxidation, DNA, and protein denaturation, making damaged cells suffer a second blow, which may accelerate the aging and death of patients [53,54]. Several studies demonstrated that lipid peroxidation is believed to be closely associated with the degree of burn complications in the elderly and is an important cause of cell death after oxidative damage to cellular membranes [55]. Under the compound action of these harmful factors, the process of burn wound healing in the inflammatory phase stagnates, thus incurring serious damage to the overall physical function of elderly burn patients.

Furthermore, the cardiovascular dysfunction in elderly burn patients can further exacerbate the vascular permeability that promotes continuous outflow of intravascular fluid and plasma proteins, which can be attributed to direct thermal trauma and increased levels of oxidative stress and inflammatory mediators [33]. Thermal trauma has a direct effect on mast cells (MCs), which are thought to mediate vasoactivity, resulting in the secretion of histamine [56]. This secretion leads to a further increase in xanthine oxidase activity and the production of ROS after burns through different mechanisms. Therefore, the application of antioxidants is necessary for burns patients, especially elderly burn patients. This has been proven in animal experiments and some clinical trials, where high doses of antioxidants ascorbic acid (Vitamin C) can significantly reduce the fluid requirements of rats after burns and these antioxidants have been routinely used in the treatment of burns patients in many burns' centers [57,58].

Undoubtedly, due to aging-related factors and extremely complicated burns pathophysiological process, it is very challenging to control wound infection and oxidative stress in elderly burn patients. A deeper exploration and understanding of the pathological mechanism of burns is essential for the individualized treatment of elderly burn patients.

3.3. Muscle atrophy in elderly burn patients

Two of the most puzzling factors affecting wound healing in elderly burn patients are inflammation and muscle atrophy. Most burns patients who receive the best of treatment are expected to heal, but for elderly burn patients, muscle atrophy seems to be an inevitable problem. Muscle atrophy refers to the decrease in the cross-sectional area of muscle fibers, the number of myonuclear, and the protein content, leading to the loss of muscle mass and strength in the body [59]. As a highly controlled and complex phenomenon, it is also associated with an increased risk of mortality in patients [60]. Muscle atrophy occurs in many diseases, including burns and trauma, sepsis, diabetes and cancer-associated cachexia [61].

Most elderly people have the problem of sarcopenic obesity, due to the changes of various components in the body related to the senescence [62]. Sarcopenic obesity is a physiological phenomenon that muscle mass decreases and Visceral fat increases with age [63]. Therefore, for elderly burn patients, deep second-degree burns and full-thickness burns are more likely to occur due to the loss of cutaneous moisture and collagen and the reduction of subcutaneous fat. As such, the elderly burn patients are more prone to muscle atrophy and rarely form hypertrophic and keloid scars. At the same time, the wounds healing of elderly burn patients are usually affected by various inflammatory factors and high metabolism, which aggravate the occurrence of such complications [64]. Furthermore, there is a significant link between the degree of damage and high metabolism and muscle catabolism [65].

The mechanism of muscle atrophy after burns is undoubtedly extremely complex, but some recent insights have shown that growth factors such as insulin-like growth factor-I (IGF-I) and pro-inflammatory cytokines such as IL-1 and TNF-α are involved in the occurrence of muscle atrophy after burns [66]. In the case of most muscles with high metabolic decomposition, the concentration of IGF-I will be significantly reduced, which can be changed by systemic infusions to alleviate muscle decomposition after burns [67]. Hart et al. also showed that there is a significant correlation between the hypermetabolic state of severely burns patients and the degree of protein loss in the legs [68]. Studies in animal muscle atrophy models showed that ubiquitin-proteasome is also the main pathway associated to the acceleration of proteolysis caused by burns and excessive glucocorticoids. In the process of muscle atrophy after burns, ubiquitin binds to proteins through a series of different enzymes and targeted destruction, leading to increased muscle proteolysis [69,70].

High metabolic state leads to increased levels of various hormones in the body, serious protein loss and increased muscle catabolism. Although anabolic agents such as propranolol has been shown effective to improve wound healing and lessen scar formation in clinical trials, they are not suitable for precision medicine due to additional side effects [71]. Similarly, the synthesis of muscle protein is affected by the level of oxidative stress and inflammation [72,73]. Studies have shown that ROS have a significant role in muscle homeostasis and are involved in muscle atrophy associated with decreased neuromuscular activity levels [73]. These factors can lead to increased proteolysis, decreased protein synthesis and muscle atrophy [72], which is extremely unfavorable for the prognosis of elderly burn patients who are in a state of inflammation for a long time. Therefore, improving the hypermetabolic state of elderly burn patients as soon as possible, regulating the level of inflammation and increasing the level of nutrition have become important measures to prevent muscle atrophy.

4. Nanotechnology-based application for burn wound healing

Wound healing after burns is a complex and orderly biological process [74], including four overlapping phases: hemostasis, inflammation, tissue proliferation and remodeling [75]. In the process of wound healing, a large number of epithelial cells, endothelial cells, fibroblasts and other cells are required to participate in the inflammatory repair, proliferation and migration, as well as the signal transmission of various cytokines and growth factors [76]. Under the combined action of these factors, the wound of burns can complete the repair and reconstruction of the defect tissue structure. In this complex process, the treatment and prevention of infection is particularly important. Medicine is a major beneficiary of the advances in nanotechnology. Studies have testified that the revolution of nanotechnology has enabled some nano compounds and nanoparticles to provide an unprecedented opportunity in improving treatment efficacy, preventing side effects, and overcoming antibiotic resistance [77,78]. In the era of translational medicine, many nanomaterials have been used in burn wound treatment and drug delivery by virtue of their immense ability to maintain drug release, prevent drug degradation, neutralize excess ROS, and mitigate inflammation (Fig. 3).

4.1. Inorganic nanoparticles

Naturally at the forefront are inorganic nanoparticles, including the metallic nanoparticles and carbon-based nanoparticles etc. [78]. Of those, the most prominent nano-inorganic product in burn and wound

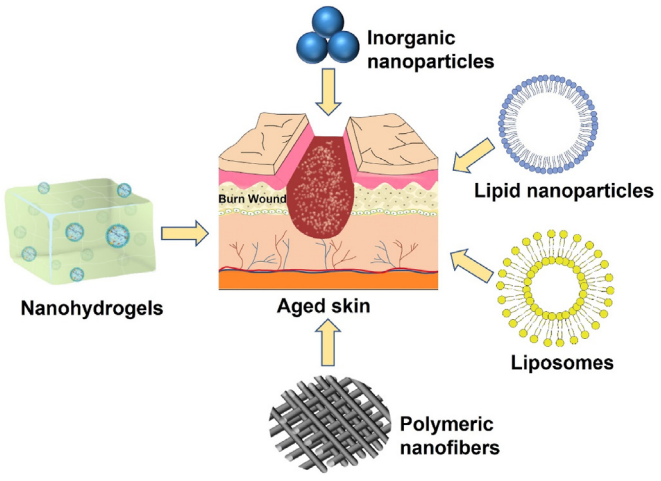

Fig. 3. Nanomaterials in burn wound treatment and aged skin regeneration. Collagen and elastin in the aged skin has a reduced quality and vascularization is decreased.

treatment is nanosilver [79]. Attribute to its strong antimicrobial activity, pure silver nanoparticles fabricated on the nanoscale induce an elevation in TGF-β, VEGF to decrease in the inflammatory response and increase rate of wound healing [80]. Another study also showed that silver nanoparticles and hydrogels containing silver nanoparticles not only can be used to heal burn wound infections without cytotoxicity, but also show excellent wound dressing capacity [78]. In addition, down-regulation of metalloproteinases is also one of the mechanisms of action of silver nanoparticles-based dressings to promote wound healing. The characteristics of gold nanoparticles are similar to those of silver nanoparticles. Lee et al. found that phytochemical-decorated Au nanoparticles (Phyto-AuNPs) may have antioxidant effects and help accelerate and activate biomolecules (VEGF and Ang-2) in the healing mechanism of burned rat skin [81]. In another study, Fan et al. developed a nano-TiO2/collagen-chitosan porous scaffold as a tissue engineering scaffold for wound repairing [82]. The addition of nano-TiO2 not only elevates the stability, antibacterial properties and but also enhance the tensile strength of the composite, while the interaction with the collagen or chitosan provides a moist environment for cell growth and migration in the wound surface, which provides favorable conditions for wound healing. Thus, the release of metal ions from the nanoparticles with a wide range of antimicrobial activity and the ability of the nanoparticles themselves to cross the cell membrane make the metallic nanoparticles play an important role in the prevention of infection. Although the metallic nanoparticles are beneficial for both wound inflammation control and wound healing applications, some new safety assessments and biological-grade production processes are also needed because metal ions can adversely affect human health and the environment. What's more, the expensive cost of these metallic nanoparticles would limit their widespread use. This highlights the numerous challenges from drug development to clinical use.

Carbon-based nanoparticles include well-known graphene-based nanomaterials, carbon quantum dots and carbon nanotubes. The various physicochemical properties of carbon-based nanomaterials permit a favorable tissue microenvironment and drug delivery capacity to promote cell growth, thus contributing to wound repair. Graphene-based nanomaterials have been widely used in the manufacture of cellular scaffolds, agent carriers and biosensors due to their outstanding large specific surface area, excellent mechanical strength, and surpassing biocompatibility [83]. The antibacterial activity of graphene sheet strongly depends on the accessible area and the collision between its sharp edges and bacteria, also known as the nano-knives mechanism [84]. However, early graphene materials showed obvious cytotoxicity, mainly including induction of apoptosis and reduction of cell adhesion. With the advancement of nanotechnology and the emergence of multiple functionalization methods, new graphene materials exhibit reduced cytotoxicity and higher cell viability [85]. For example, a novel wound dressing based on Ag/graphene polymer hydrogel, reported by fan et al., showed a higher wound healing rate in a short period of time when curing full-thickness skin wound [86]. Moreover, the mechanical properties of the hydrogel combined with graphene are better, and the suitable moisture environment around the wound can still be maintained under high stresses, which is beneficial for wound healing. Hussein et al. applied ultrasonicated graphene oxide (UGO) to wound healing in a rat skin defect model, and the results showed that the average rate of wound healing with 1% UGO was not significantly different from that of bFGF group (Fig. 4A) [87]. It has been reported that the reduced graphene oxide (rGO)/Ag nanocomposites scaffold incorporated the natural anti-inflammatory, antioxidant compound curcumin can enhance skin wetness, promote cellular attachment, and have the best effect on wound healing (Fig. 4B–D) [88]. Furthermore, the super conductivity and biocompatibility of graphene have also been introduced into tissue engineering as an alternative tool for application. As a biomimetic conductive niche, flexible and conductive graphene sheets can simulate the micro-environment of native heart to further promote the maturation of hiPSC-derived cardiomyocytes (hiPSC-CMs) [89]. These results

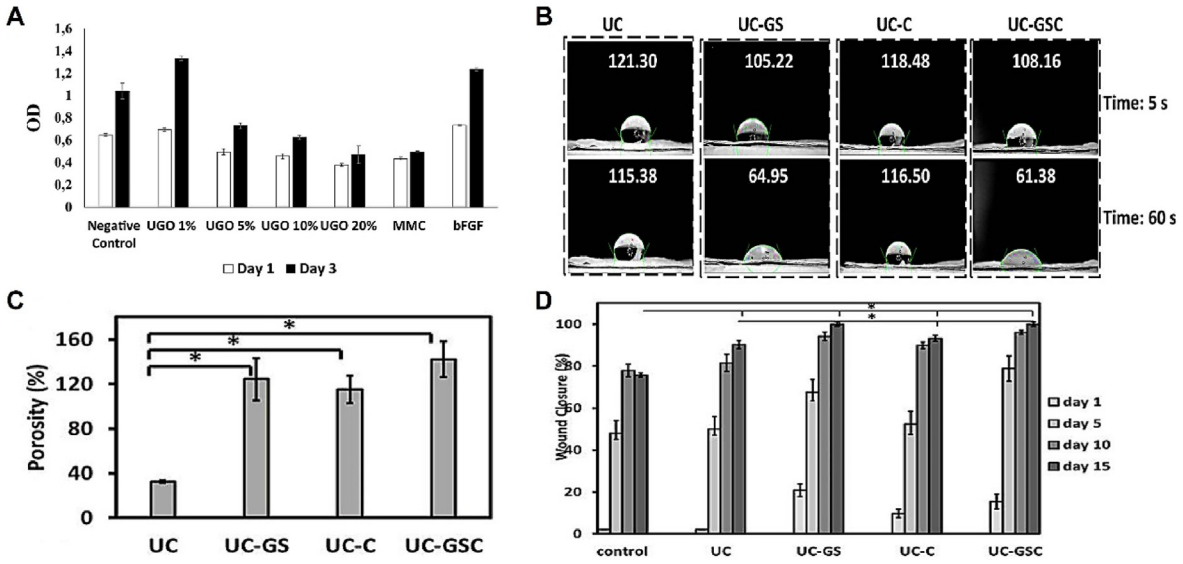

Fig. 4. Schematic representations of the results. (A) Cell proliferation of epithelial wound repair using optical density (OD) measurements. The results showed that 1% UGO was similar to bFGF in increasing fibroblast growth. (B) Contact angle measurements of the scaffolds after 5 s and 60 s contact to water droplet. Here, the incorporation of nanocomposites increases the hydrophilicity and wettability of the scaffold surface. (C) Higher porosities and a higher number of available spaces among nanofibers with the incorporation of curcumin or rGO/Ag nanocomposites compared to the bare scaffold, UC. (D) Under the same conditions, UC-GS and UC-GSC nanocomposites showed a faster wound healing rate. UC, polymer of polyurethane/cellulose; UC-GS, UC contained rGO/Ag nanocomposites; UC-C, UC contained curcumin; UC-GCS, UC contained rGO/Ag nanocomposites and curcumin.
Notes: (A) Reprinted from Hussein, K.H, Abdelhamid H.N, Zou X.D et al. Ultrasonicated graphene oxide enhances bone and skin wound regeneration. Mater Sci Eng C Mater Biol Appl, 2019; 94:484–492. Copyright 2019, with permission from ELSEVIER. (B-D) Esmaeili E, Eslami-Arshaghi T, Hosseinzadeh S et al. The biomedical potential of cellulose acetate/polyurethane nanofibrous mats containing reduced graphene oxide/silver nanocomposites and curcumin: antimicrobial performance and cutaneous wound healing. Int J Biol Macromol. 2020; 152:418–427. Copyright 2020, with permission from ELSEVIER.

suggest that improved graphene is a promising material for skin tissue regeneration and an application material that affects gene expression of locally resident cells. And owing to the large specific surface area, Carbon nanotubes are also used in wound healing by carrying more drugs in the tube or bonded on the surface. It is worth mentioning that carbon quantum dots, as the latest material in carbon-based nanomaterials, are considered to have antibacterial and antibiofilm efficacy [90]. Interestingly, single quantum dots can be tuned to glow in any color and are widely used as tracers or dyes in biomedicine [91].

4.2. Liposomes and lipid nanoparticles

Liposomes are bilayer vesicles with amphipathic nature, which are beneficial to improve the stability and prolong release time of drugs, and are considered as promising drug delivery systems [92]. Furthermore, this hydrophilic property enables liposomes to carry hydrophilic drugs such as growth factors and form a local humid environment after delivery to the wound, which is extremely conducive to burn wound healing [93]. Based on common liposomes, Xu et al. developed a novel liposome with hydrogel core of silk fibroin for the treatment of deep second-degree scalded mice [94]. Their conclusions demonstrated that liposome with hydrogel core of silk fibroin can effectively encapsulate basic fibroblast growth factor (bFGF) and maintain its stability. The liposomes with silk fibroin hydrogel core carrying bFGF (SF-bFGF-LIP) can efficiently elevated wound contraction in deep second-degree scalded mice through inducing endogenous VEGF expression, granulation tissue formation and re-epithelization. Nevertheless, the low stability of liposomes is one of its common demerits in clinical applications. Therefore, lipid nanoparticles introduced to overcome the limitations of common liposomes have become an effective strategy. For example, propylene glycol nanoliposomes containing curcumin have also been shown to be more effective in the treatment of animals subjected to second degree burns than alone [95]. The experimental results found out that the newly prepared nanoliposomes have high encapsulation efficiency and sustained release behavior, and the antibacterial effect of the low dose of formulation was found to be like the silver sulfadiazine (SSD) medical cream 1%, which can effectively improve the infection and injury of burn wounds. In another related study, Ternullo et al. also confirmed the aforementioned view [96]. They designed the curcumin-in-deformable liposomes-in-chitosan-hydrogel as an advanced wound dressing, enabled the prolonged retention time of curcumin and the sustained skin penetration of curcumin, allowing it to significantly improve chronic wounds therapy. The combination with the hydrogel prevents the liposomes from being rapidly removed locally in the skin, and lipid nanoparticles can carry lipophilic drugs that cannot be incorporated into the hydrogel. As reported by Gao et al., hydrogels containing nanoparticle-stabilized liposomes can achieve effective antimicrobial delivery during topically applied onto mouse skin [97]. This suggests that the combination of nanoparticle-stabilized liposome technology and hydrogel technology provides a unique and powerful skin dressing for targeted burn wound infection and wound healing.

4.3. Nanohydrogels

Nanohydrogels are considered as one of the ideal dressings for wound treatment: three-dimensional (3D) water-swollen polymeric networks endows it the ability to absorb excess exudates produced by the wound; high biocompatibility and biodegradability; its non-adhesive property allows oxygen to permeate the wound [98]. Compared with conventional hydrogels, hydrogels incorporated with these nanofillers have the unique properties of both hydrogels and nanoparticles, mainly involving intramolecular crosslinking, and have stronger mechanical properties. Nanohydrogels can better retain the load of drugs and have more choice of delivery routes due to its small size and longer half-life [99]. Such a small size of nanohydrogel is easy to precisely control and cell targeting. As designed by Gao et al., combining degradable polyacrylamide-based nanoparticles with hydrogels can avoid uptake by macrophages and deliver agents to target cells with precision [99]. Bacterial

nanocellulose/acrylic hydrogels (BNC/AA) fabricated by Xi Loh et al. using electron beam irradiation showed a rapid cell attachment with human dermal fibroblasts (HDFs) and the limitation of cell migration [100]. At the molecular level of wound healing, the nanohydrogel significantly affected nine wound-healing-related genes (IL-6, IL-10, MMP-2, CTSK, FGF7, GM-CSF, TGF-β, COX2, and F3), which all involved in multiple interrelated roles, such as neovascularization and re-epithelialization. The results indicate that the nanohydrogel is a friendly wound dressing material that accelerates wound healing.

Additionally, some protein nanohydrogels that are more sensitive to external stimuli, with stronger modifying functional groups and specific recognition capabilities have also been developed [101]. The extremely small size of protein nanohydrogels allows them to combine hydrophobic as well as hydrophilic drugs to easily cross the blood-brain barrier. Of particular focus is an injectable multifunctional nanocomposite hydrogel. Shear-thinning nanocomposites hydrogels made from κCA and nanosilicates have higher physiological stability and blood clotting effect by physically reinforcing the hydrogel network structure (Fig. 5A–C) [102]. Among them, nanosilicates allows sustained drug release during wound treatment and enhanced platelet adhesion. Therefore, the nanocomposite hydrogel could be used as an injectable therapeutic agent and drug carrier to promote wound healing and tissue regeneration.

4.4. Polymer nanofibers

Nanofibers are mainly prepared from natural or synthetic polymers, aiming to mimic collagen fibrils in the extracellular matrix (ECM) and provide favorable conditions for cell attachment and drug carriage in burn wounds [103]. Among the various processes for manufacturing nanofibers, electrospinning is the most commonly used method for generating nanofibers, with relatively low cost and easy mass production [104]. Electrospun polymer nanofibers are a promising candidate for therapeutic drug-controlled delivery platforms due to its high area to volume ratio, high porosity, and adjustable morphology [105]. Through electrospinning technology, both small molecule drugs and active factors can be separately or simultaneously incorporated into the porous structure or on the surface of nanofibers for optimal treatment strategies. The mechanical properties and degradability of electrospun nanofibers allow them to be tuned for specific uses, for instance, the electrospun nanofiber-assembled aerogels have extraordinary flexibility and elasticity [106]. This porous nano-aerogel promotes wound hemostasis by reducing clotting time during contact with blood [98], while also having the potential to promote scar-free wound closure [107]. Shan et al. prepared a silk fibroin/gelatin electrospun nanofibrous dressing functionalized with astragaloside IV by electrospinning nanotechnology to explore its therapeutic effect on deep partial thickness burn wounds [108]. In contrast to the control group, the prepared functionalized nanofibrous dressing showed excellent biocompatibility in vitro and significantly improved cell attachment and proliferation on the dressing, and the cells gradually confluent into typical keratinocyte morphology. Further in vivo studies also showed that the composite flexible nanofibrous dressing accelerated the skin wound healing and inhibited scarring in burn rats by promoting the production and organized and regular arrangement of type I collagen.

Besides, the simultaneously combination of nanofibers and other nanomaterials can achieve better synergistic effects on wound repair and skin regeneration. According to report of Kheradvar et al., vitamin E-loaded starch nanoparticle incorporated in silk fibroin-Poly(vinyl alcohol)-Aloe vera nanofiber can increase the proliferation of fibroblasts and accelerates the formation of collagen in skin wound in vivo [109]. And this nanocomposite can also protect cells from toxic oxidation products by enhancing antioxidant activity and is a promising wound dressing. In another plan, researchers used electrospinning technology to incorporate magnetic nanoparticles into electrospun nanofiber

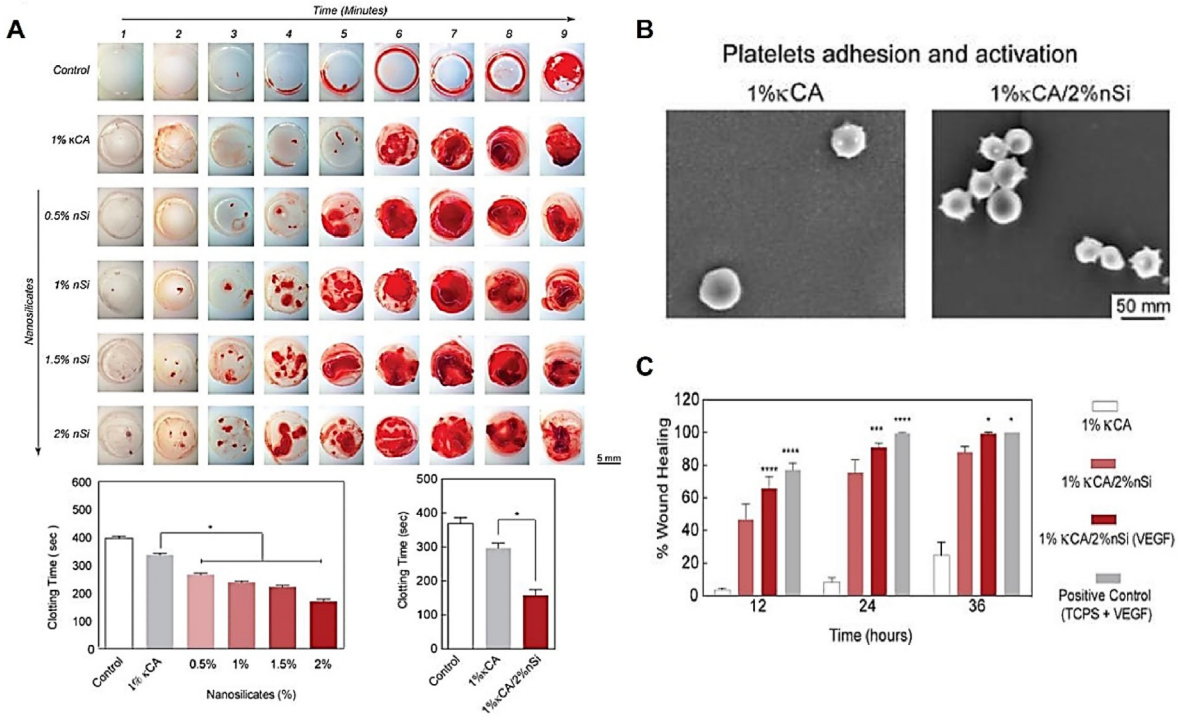

Fig. 5. Nanoengineered injectable hydrogels including nanosilicates and κCA for wound healing application. (A) The images showed different concentrations of nanosilicate and κCA in relation to whole blood coagulation kinetics with clotting time and activated clotting time. The addition of κCA and κCA/Si nanocomposite significantly decrease clotting time and accelerate blood clotting. (B) The SEM images of hydrogel surface showed that κCA-nanosilicate hydrogels have enhanced adhesion of platelets in comparison to κCA. And the nanoengineered injectable hydrogels also activated platelets. (C) The quantitative result for wound healing showed that κCA-nanosilicates enhanced VEGF release and promoted almost complete wound closure after 36 h.

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three-dimensional scaffolds for functional and application exploration [110]. Data indicated that the nanofibrous scaffolds with magnetic nanoparticles enabled NIH 3T3 cells to exhibit high cell viability while maintaining the magnetic properties, making the composite material possible to have outstanding advantages in specific magnetic field therapy.

In conclusion, with the innovation of nanotechnology, the application of various combinations of different types of nanomaterials to burn wound treatment is still the future of this field.

5. MSCs in burn wound healing

Just like the emerging therapies brought about by nanotechnology, MSCs therapy is also playing an increasingly important role in the treatment of complicated burn wounds. With the rapid development of stem cell research in recent years, many studies have shown that MSCs can effectively intervene in multiple processes of wound repair and accelerate wound healing [22,111,112].

MSCs are a kind of pluripotent adult stem cells which originate from mesoderm with the ability of self-renewal and multidirectional differentiation. MSCs are derived from a wide range of tissues, including bone marrow, fat, dental pulp, etc. and they can differentiate into osteoblasts, chondroblasts, adipocytes and other cells under specific induction conditions [113,114]. In 2006, Mansilla et al. showed that there are cells with the same phenotype as bone marrow mesenchymal stem cells (BM-MSCs) in serum after large skin burns [115]. Interestingly, MSCS have been shown to secrete exosomes that are enriched in the extracellular environment. Studies have proven that MSC-exosomes can play a pivotal role in different stages of inflammatory response by transporting different bioactive factors [116]. Therefore, stem cells and their products may produce active effects in burn wound healing.

5.1. Immunomodulatory properties of MSCs in burns

Inflammation is a self-defense mechanism in response to harmful stimulus [117], however, chronic inflammation may delay wound healing and promote the formation of fibrosis and excessive scar [118]. Most of MSCs have immunomodulatory properties and can regulate the inflammatory phase of burn wound healing. Studies have shown that MSCs can inhibit T cell proliferation and regulate immune response via transforming growth factor-β(TGF-β) and hepatocyte growth factor (HGF). Similarly, the release of large amounts of pro-inflammatory substances P after burns also induces MSCs to secrete TGF- β1 and increases its ability to inhibit CD4+T cells activity [119]. Furthermore, MSC also showed a polarization effect on inducing macrophages toward anti-inflammatory M2 phenotype [120]. In 2020, Albashari et al. showed that heparin (HeP) hydrogels containing basic fibroblast growth factor (bFGF) and DPSCs could reduce the release of pro-inflammatory factors by inhibiting the activation of microglia/macrophages, acting together to reduce tissue inflammation after spinal cord injury [121]. The latest research results show that hMSCs can release a key bioactive factor, IGF-1, which can significantly reduce vascular endothelial cell apoptosis induced by burns through PI3K/Akt/Foxo3a signal pathway, protecting the endothelial barrier and preventing MODS [31]. Animal model studies have shown that adipose-derived mesenchymal stem cells (ADSCs) can also secrete immunosuppressive factors which can reduce the serum levels of TNF-α and IL-4 during the acute inflammatory phase, thereby reducing the inflammatory response [122,123]. BM-MSCs have also been shown to attenuate the release of pro-inflammatory cytokines such as TNF-α and nitric oxide by up regulating anti-inflammatory cytokines TGF-β and IL-10 [124]. Of those, IL-10 has been proved to be related to the control of cutaneous wound inflammation in several disease models [125,126]. In 2016, Liu et al. found that human umbilical cord-MSCs could attenuate excessive inflammation in the acute phase of severely burn in rats through the anti-inflammatory pathway of secreting tumor necrosis factor (TNF)-a–stimulated gene/protein 6 (TSG-6) (Fig. 6A–D) [127]. Interestingly, TSG-6 secreted by hMSCs have also been demonstrated to prevent the formation of hypertrophic scars during the cutaneous wound-healing process [128]. In addition, MSCs could produce anti-inflammatory effects by activating multiple signaling cascades, inhibiting apoptosis, and promoting cell proliferation. BM-MSCs can restore the normal parameters of various organs in LPS-induced rat sepsis model by reducing the expression of the NF-kB and activating STAT3 and MAPK signaling pathways [129] Another study has also shown that high levels of inflammation induced by burns can be alleviated by hUC-MSCs-exosomes loading miRNA181c through inhibiting Toll-like receptor 4 (TLR4) signaling pathways [126]. In a rat model of deep second degree burns, Zhang et al. asserted that hUC-MSCs-Ex could accelerate wound closure by overexpressing Wnt4 and activating Wnt/β-catenin in skin cells, and then activating AKT pathway to inhibit skin cell apoptosis induced by acute burns [130]. These signal cascades are considered to be important regulators of inflammatory response. Because of these biological characteristics, such as coordinating the activity of inflammatory cells and inhibiting the harmful effects of inflammatory cytokines, MSCs have incomparable potential compared with other common treatment methods in the treatment of severe and elderly burn patients in a stage of hyperinflammatory.

5.2. The function of MSCs during proliferation and wound remodeling

It is universally acknowledged that an appropriate level of inflammation can reduce pathogens and repair damage by recruiting immune cells, which has a positive effect on wound healing. However, for elderly burn patients who are in the hyperinflammatory stage for a long time, it will postpone cutaneous healing. In the process of wound healing, MSCs not only inhibit the inflammatory response through a variety of ways, but also promote the cells proliferation, collagen production and angiogenesis, promoting wound closure and avoid its chronicity [21]. In general, TGF-β1 secreted by MSCs can regulate inflammatory processes, improve the rate of burn wound healing and enhance vascular formation and collagen production through a variety of receptors and intracellular signaling mechanisms [131]. In addition, the mechanism of wound re-epithelialization induced by MSCs may be due to its paracrine effects of growth factors and cytokines (e.g., TGF-β, FGF and EGF), which can induce the proliferation, differentiation and migration of progenitor cells in healthy peripheral skin [132]. In 2006, Rasulov et al. claimed in the study of rats that the application of MSCs in burns reduced the infiltration of inflammatory cells, promoted the generation of new cells and reduced the formation of granulation tissue [133]. In a similar study, Ha et al. used MSCs transfected with hepatocyte growth factor (HGF) to treat burned rats. The results suggested that the wound healing of the experimental group was significantly faster, the thickness of the epidermis became thicker, and the content of collagen I was lower than the control group [134]. When Xue et al. locally injected human MSCs into mouse model of burn wounds, they found that after stem cells injection, the number of neoangiogenesis increased significantly and the wounds healed significantly accelerated [135]. They also showed burned mouse injected with stem cells are more effective in restoring activity and weight. Furthermore, Singer et al. also confirmed that MSCs can increase the level of neovascularization and VEGF in burn wounds [136]. They showed that stem cells can not only speed up the healing of burn wounds, but also prevent burns from getting worse. In the animal model of third-degree burn, it was also confirmed that MSCs can up-regulate the angiopoietin (ANG)-1/2 gene, thus promoting vascularization [137]. This is a good signal for the clinical application of MSCs to elderly burn patients, because elderly burn patients often have high inflammation due to their insufficient self-recovery ability, which leads to wound deterioration. Therefore, effective vascularization and augmented collagen production is essential for cutaneous wound healing to achieve its biological function and it is also one of the key factors for the application of stem cell tissue engineering.

Concerning the effect of collagen, Liu et al. applied the collagen

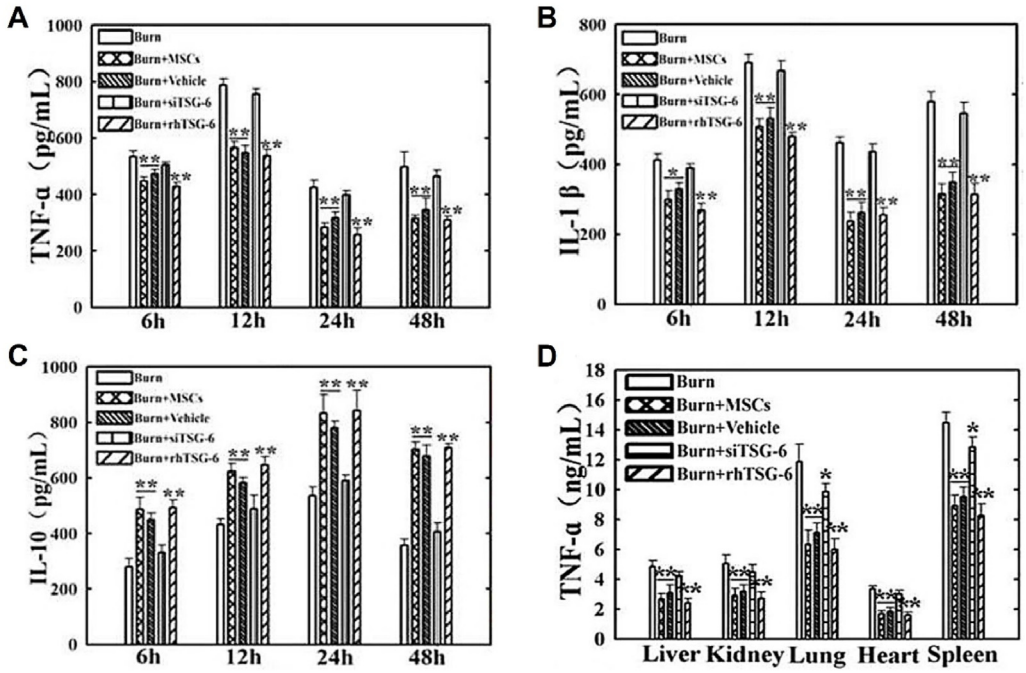

Fig. 6. The Effects of MSC and TSG-6 on the systemic inflammatory response induced by severe burn and the expression of the inflammatory cytokines in vital organs at 24 h after severe burn. (A–C) Human umbilical cord-MSCs treatment significantly increased anti-inflammatory cytokine of IL-10 expression and decreased pro-inflammatory cytokines of TNF-α and IL-1β expression post severe burn. But administrations of hUC-MSCs with TSG-6 siRNA knockdown significantly reduced the therapeutic effect of hUC-MSCs. And hUC-MSCs with rhTSG-6 administration greatly improved the levels of the pro-inflammatory and anti-inflammatory cytokines. (D) At 24 h after severe burn, administration hUC-MSC and hUC-MSC with rhTSG-6 still had good anti-inflammatory effects for these inflammatory cytokines such as TNF-α in vital organs. A sterisk (*) and double asterisk (**) stand for $p < 0.05$ and $p < 0.01$ compared with burn group, respectively.
Notes: Reprinted from Liu L, Song H, Duan H et al. TSG-6 secreted by human umbilical cord-MSCs attenuates severe burn-induced excessive inflammation via inhibiting activations of P38 and JNK signaling. Sci Rep. 2016; 6:30121. Copyright 2016, with permission from Springer Nature.

scaffold combining with MSCs to the burns surface of pigs and found that it can induce better wound healing, better vascularization, less skin keratinization and less muscle atrophy [138]. Similarly, mansilla et al. used the combination of acellular dermal matrix containing anti-CD44 antibody and MSCs to treat burn wounds in pigs. The research results showed that the combined application of MSCs and dermal matrix can not only promote healing of burn wounds, but also stimulate the formation of hair follicles and the regeneration of muscles and ribs [139]. In the mouse burns model, Lough et al. isolated LGR6+ epithelial stem cells from the mouse cutaneous appendages for the treatment of burn wounds. The results showed that compared with the control group, the wounds injected with LGR6+ epithelial stem cells healed better with the increased levels of intravascular growth factor, platelet derived growth factor (PDGF) and EGF. In addition, the neoangiogenesis and new hair follicles in the wounds of mice were improved [140]. In another experiment, researchers combined fibrin glue and MSCs to treat the back of burn wounds in rats. The experimental results showed that the healing speed of the fibrin-binding stem cell treatment group is significantly faster than that of the fibrin glue group and the stem cell group. At the same time, the sebaceous glands proliferation are obvious and the hair follicle-like structures are appearing [141]. Obviously, the multidirectional differentiation ability of MSCs play an indispensable role in burn wound healing, as well as collagen. Moreover, MSCs have also been shown to play a possible role in the prevention of muscle atrophy progression after burns. In a study by Xu et al., they used MSCs derived from autologous bone marrow to treat burn wounds and found that the contraction after the wound healing was significantly decreased [142]. Briefly, the clinical application of MSC is wide, and many clinical trials have been carried out.

Furthermore, MSC therapy alone may has certain limitations, so it could be enhanced with different nanotechnology-based platforms. In one study Burmeister et al. reported the use of a combination of adipose-derived stem cells (ASCs) and PEG-fibrin hydrogels in a porcine model of debrided burn wounds [143]. The results of in vivo observations depicted that the number of blood vessels at the wound increases in a therapeutic dose-dependent manner when PEG-fibrin hydrogels are used as the delivery vehicles for ASC. Specifically, the scaffolding provided by PEG-fibrin hydrogels would make wound contraction more significant, while the incorporation of ASC also accelerated wound healing. In another related study, on-site delivery of mouse bone marrow stem cells based on a porous polyethyleneglycol–polyurethane (PEG–PU) scaffold were explored as an effective tool for wound tissue repair [144]. The studies suggest that the presence of porous polymer networks protected BMSCs from oxidative stress and inflammation, enhanced stem cell engraftment, and accelerated neovascularization and wound tissue closure process. Therefore, according to different burn wound conditions, the combination of nanotechnology and MSCs is more conducive to wound treatment and prognosis.

Although numerous studies on the treatment of burn wounds with MSCs have shown their positive effects in the treatment process, there are still some different views. The results of Lorder et al. revealed that compared with burns mice treated with saline injections, the experimental group mice with MSCs injections showed no significant differences in blood-brain barrier proliferation and vascularization [145]. Thus, exploring the role and clinical application of MSCs in burn wound healing requires continuous in-depth and practice.

6. The application advantages of nanomedicine and MSCs in the treatment of elderly burns

Based on the previously description, the application advantages of nanotechnology and MSCs in the elderly burn wound healing have so far focused on prevention of infection, faster wound healing capabilities, and prevention of muscle atrophy. In general, the elderly has higher baseline levels of pro-inflammatory cytokines, so that the second stage of burn treatment in the elderly is predominantly to control the infection and

systemic inflammatory response [3]. In fact, burn wound infection is a surgical emergency that requires surgical excision and antibiotic treatment [146]. Emergency surgery is usually necessary in young patients, but there is still some disagreement regarding surgery for burn wounds in the elderly patients with multiple comorbidities or generalized frailty. In recent years, compared with the increased surgical risk in the elderly population, the combined application of advanced nanoplatforms and MSCs is emerging as a new approach to inhibit burn infection in the elderly. For example, the application of gold nanoparticles in burn wounds is also considered to have excellent antibacterial and antioxidant properties, thereby promoting the healing process. For elderly burn patients with high oxidative stress level, local treatment with gold nanoparticles could provide favorable conditions for burn wound healing by reducing oxidative stress, which has been confirmed in rat models [147]. Moreover, randomized clinical trials (RCTs) have revealed that chitosan-nanocrystalline silver dressings have superior wound healing properties, which can significantly shorten wound healing time through improving the bacterial clearance rate of infected wounds and accelerating re-epithelization [148]. This is clearly beneficial to ameliorate the delayed wound healing process in the elderly associated with an altered inflammatory response [149]. The anti-inflammatory activity of nano-silver material might be achieved by reducing the release of inflammatory factors and neutrophil infiltration and inducing apoptosis in inflammatory cells [148,150]. Therefore, nanomaterials may become a new paradigm to replace antibiotics in the treatment of burn infections in the elderly.

MSCs are more pleiotropic in the treatment of elderly burns. The unique immunomodulatory effects of MSCS allow them to decrease the circulating cytokines and numerous inflammatory products produced by burns in the elderly [28]. In the inflammatory phase of burn wound healing in the elderly, MSCs can inhibit the proliferation of T cells and TNF-α, regulate the secretion of cytokines, attenuate oxidative stress, and inflammatory response, and thus improve the overall microenvironment of the wound [2]. During the proliferative phase, MSCs could also accelerate wound healing in the elderly by promoting epidermal or dermal regeneration, by augmenting cell proliferation and migration, and enhancing collagen production in the remodeling phase of wound healing [151]. It is worth mentioning that MSC also plays an important role in skin grafting of wounds in the elderly. It is well known that burn wound excision and skin grafting are conventional therapeutic strategies for treating burn wounds. This can be challenging for the elderly, which can be attributed to their thinner dermis, high susceptibility to infection and longer wound healing time [16]. At present, various skin substitutes including porcine substitutes have been explored as alternative strategies to avoid complications caused by autologous skin grafts in the elderly [152]. MSCs-based skin substitutes may also play a role as an alternative to skin grafts in the future. Subcutaneous transplantation of amniotic membrane combined with ASCs in burned rats reduces the infiltration of inflammatory cells in the dermis and significantly accelerates wound healing [153]. In a clinical treatment, significant skin regeneration and epithelization with the milder degree of scarring were confirmed following BMMSCs/artificial dermis composite graft treatment of severely burned patients [154]. In conclusion, these results show the potential role of MSCs in the elderly burn wounds to modulate inflammation, improve skin regeneration, and limit the degree of scarring and muscle contracture.

7. Discussion

Burn care and wound healing pose a very complex problem in the field of medicine. In the past few decades, the treatment and care of burns in children and adults have been significantly improved; however, the treatment and care of burns in the elderly has not been paid much attention [155]. Given as many countries as possible and regions around the world gradually enter an aging society, it is extremely important to concern about the recovery of elderly burn patients. Under the combined influence of aging and their own diseases, elderly burn patients are vulnerable to deeper burns, inadequate immunologic response, and poor wound healing, resulting in poor mortality and prognosis. Not only elderly burn patients, but also elderly patients with other diseases and traumas require longer hospitalization than younger patients [156]. Hence, it is very necessary to study the pathological process of elderly burn patients.

The pathophysiological process of the elderly burns is similar to that of normal adult burns, but the elderly are in a low-grade inflammatory state for a long time so that the inflammation state of the elderly after burns is more difficult to control [10]. When the physiological barrier-skin is burned, the body will release numerous inflammatory factors, OFRs, etc., making the body in a pathological state such as high inflammation and oxidative stress. These pathological reactions will further aggravate the development of elderly burn patients [9]. At the same time, aging will also bring an increase in OFRs, which is also a fatal blow to the elderly who are in the state of high metabolism after burns. Moreover, most elderly people have the loss of skin moisture and collagen and the decrease of subcutaneous fat, so the elderly are more likely to suffer from severe burns. These factors have posed great challenges to the treatment of elderly burn patients and their muscle atrophy and will change the burn treatment strategies in the near future.

Though the application of nanomaterials and MSCs have made various advances in the field of regenerative medicine, there is still a great explore space for the treatment of chronic and senile burns. The ability of nanomaterials in local bacterial control and anti-oxidation and their personalized design for different wound conditions make their wide application in the field of geriatric burns have great potential. And MSCs also have significant abilities in anti-inflammatory modulation, immune regulation, angiogenesis promotion, wound healing, and prevention of muscle atrophy, so they play an important role in all the stages of wounds repair [21,75]. Especially for elderly burn patients with postoperative complications such as uncontrollable wound inflammation and slow wound healing, the tissue engineering treatment strategy based on the combination of nanotechnology and MSCs is undoubtedly a suitable solution. For instance, the application of MSCs combined with various hydrogels in burn wounds has achieved remarkable results in recent years [21]. Interestingly, MSCs derived from different tissues do not have the same differentiation potential, but they exhibit a high degree of similarity in general physical properties and most biological effects [157]. Therefore, it may not be considered as a barrier that which source of MSCs should be chosen. However, transplantation of different stages and delivery modes of MSCs into wound could lead to different biological effects, which are closely related to the paracrine effect of MSCs and the cellular microenvironment. Once MSCs are removed from the microenvironment, their response to environmental cues and paracrine effects can be altered. As our appreciation of the nanoscale world improves, different platforms such as delivery systems or 3D scaffolds based on nanomaterials may be able to effectively overcome these problems.

Hence, while MSCs have been proven to be an advanced tool for regenerative medicine, there are still many unsolved problems regarding the clinical application of MSCs. It is well known that early treatment is crucial to limit the spread of inflammation and necrosis caused by burns. MSCs usually take effect immediately after burns implantation. However, the clinical MSCs-based therapy is hardly used in the inflammatory reaction phase of burns. On the contrary, most clinical case reports showed that MSCs was mostly used in the proliferative stage of burn wound healing, rather than the remodeling phase [142]. Meanwhile it is almost impossible for autologous stem cells to be used in this situation. For this, it is imperative to develop and produce standardized MSCs for clinical application. Secondly, a clinically standardized treatment plan including the dosage of cell preparations, the route and mode of administration, and the duration of action also need to be evaluated and determined by professionals. Additionally, the exact mechanism of MSCs in many aspects of burns has not been well elucidated. These factors have restricted the wide application of MSCs in clinical practice. With the continuous

in-depth study of the biological characteristics of MSCs by scientific researchers and the advancement of nanomaterials, both therapeutic strategies will provide more benefits to elderly burn patients.

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CRediT author contribution statement

Wei Xiong: Writing–Original Draft, Investigation, Term. **Rui Zhang, Heng Zhou:** Writing – review & editing, Resources. **Ye Liu, Ming Liang, Keshen Li:** Visualization. **Xingxiang Duan, David P. Chen, Yu Luo:** Investigation, Term. **Jia Xu, Yilong Ai:** Conceptualization, Writing–review&editing. **Yan He, Qingsong Ye:** Conceptualization, Writing–review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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