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Burn injury: Challenges and advances in burn wound healing, infection, pain and scarring

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ABSTRACT

Severe burn injuries are the most traumatic and physically debilitating injuries affecting nearly every organ system and leading to significant morbidity and mortality. Early burn wound excision and skin grafting are common clinical practices that have significantly improved the outcomes for severe burn injured patients by reducing mortality rate and days of hospital stay. However, slow wound healing, infection, pain, and hypertrophic scarring continue to remain a major challenge in burn research and management. In the present article, we review and discuss issues in the current treatment of burn injuries; the advances and novel strategies developed in the past decade that have improved burn management; and also, pioneer ideas and studies in burn research which aims to enhance burn wound care with a focus on burn wound infection, pain management, treatments for scarring and skin tissue engineering.
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1. Introduction

Severe burn injuries are the most traumatic and physically debilitating injuries affecting nearly every organ system and leading to significant morbidity and mortality. In Australia, over 10,000 people are hospitalised each year because of severe burn or scald injuries. According to the World Health Organisation (WHO), 180,000 deaths annually are related to burn injury and in 2004, nearly 11 million people worldwide were severely burned and required medical treatment [1]. Both small burn and large severe burn injuries initiate the wound healing process which consists of several highly integrated and overlapping phases: inflammation, cell recruitment, matrix deposition, epithelialization and tissue remodelling. In additional to local wound repair, severe large burns also stimulate a persistent pathophysiological stress response and a systemic hypermetabolic-catabolic condition. These pathophysiological changes have great effects on the pharmacokinetics and pharmacodynamics of drug use in the treatment of severe burn injuries. Early burn wound excision and skin grafting are common clinical practices that have significantly improved the outcomes for severe burn patients by reducing mortality rate and days of hospital stay [2]. However, slow wound healing, infection, pain, and hypertrophic scarring continue to remain as major challenges in burn management and research. In the present article, we discuss the challenges, advances and novel strategies in burn management and research with a focus on burn wound infection, pain management, treatments of scarring and skin tissue engineering.

Abbreviations: WHO, World Health Organisation; TBSA, Total body surface area; NIKS, Near-diploid Immortalised Keratinocyte S; NPWT, Negative pressure wound therapy; NPWTi, Negative pressure wound therapy instillation; NPWTci, Negative pressure wound therapy continuous instillation; MDR, Multi-drug resistant; MRSA, Methacillin resistant staphylococcus aureus; VRE, Vancomycin resistant enterococci; ESBL, Extended-spectrum beta-lactamases; VISA, Vancomycin intermediate susceptible staphylococcus aureus; EPE, Enhanced permeability and retention effect; PK, Pharmacokinetics; PD, Pharmacodynamics; IV, Intravenous; IV-PCA, Intravenous patient-controlled analgesia; TRP, Transient receptor potential; TRPV1, Transient receptor potential vanilloid-1; KO, knockout; Na_v, Voltage gated sodium channels; MSCs, Mesenchymal stem cells; ADSCs, Adipose derived stem cells; TLRs, Toll-like receptors; TGFβ1, Transforming growth factor-beta1; MMPs, Matrix metalloproteinases; VEGF, Vascular endothelial growth factor; IL-6, Interleukin-6; ECM, Extracellular matrix; PDL, Pulsed dye lasers; Nd:YAG, Neodymium-doped yttrium-aluminium-garnet; NAFL, Non-ablative fractional lasers; AFL, Ablative fractional lasers; PCL, Poly (ε-caprolactone); PU, Polyurethane; PGA, Poly (glycolic acid); PLLA, Poly (L-lactide); 3D, 3-Dimensional; CAD, Computer-aided design; PLA, Poly (lactic acid); PLGA, Poly (lactide-*co*-glycolide).

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2. Clinical practice in the treatment of burn injury

2.1. Skin grafting

When burns or scald injuries are deep partial-thickness in the dermis or completely destroy all skin layers, wounds cannot be closed by

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the primary healing process or by suturing [3], rather additional surgical procedures are required. The gold-standard treatment for partial- and full-thickness burn injuries is early excision of necrotic tissue followed by autologous skin grafting (Fig. 1). Skin grafting involves the transplantation of healthy skin from an undamaged donor site of the patient to the wound site. Autologous skin grafts can be full thickness, consisting of epidermis and dermis, or split-thickness, consisting of the epidermis and upper part of the dermis. Unfortunately, in practice, donor skin is extremely limited for patients with severe burn injury >50% total body surface area (TBSA) [4,5]. This problem can be overcome by repeated harvesting of the donor sites over a period of time. However, healing of donor sites can be slow with additional scarring and possible pigmentation disorder [6,7]. While autografts can be meshed to increase the available surface area of the graft up to four times, the meshing process compromises the quality of the original graft and the recipient area heals with an irregular meshed pattern [8] and can result in severe scarring [9].

2.2. Skin substitutes

Skin substitutes could protect large burn wounds when donor skin is limited, to enhance wound healing, increase the dermal component of healed wound, reduce inflammatory responses and subsequent scarring [10–13]. Since 2000, over 30 new skin substitutes have been tested or used in the treatment of burn injuries (Table 1). Skin substitutes can be categorized into biological substitutes, synthetic substitutes or a combination of both. Biological substitutes can be further categorized into 1) natural scaffolds such as Alloderm, an intact, de-cellurised and dermal human matrix, 2) constructed scaffolds such as Integra, composed of lyophilized collagen, supplemented and cross-linked, or 3) cultured scaffolds, such as cultured epithelial graft, autologous cultured fibroblasts and keratinocytes. Biological skin substitutes have components that resemble natural skin, yet these skin substitutes are relatively simple compared to the complexities of human skin. The majority of skin substitutes available for clinical practice contain allogenic biological products, and the risk of disease transmission poses as a limitation particularly for natural biological skin substitutes. Despite extensive and strict sterilization procedures, current methods are insufficient to certify biological skin substitutes to be free of any unknown diseases or prion diseases from animal material, such as Creutzefled-Jakob disease [14]. Furthermore, there is evidence to suggest that allogeneic skin is highly immunogenic and that cellular remnants in the extracellular matrices (ECM) may be responsible for reduced skin graft take or even rejection [9]. Human derived allogenic skin is further limited by its supply. Autologous biomaterials have the advantage of culturing cells for a large surface area from a small skin biopsy, however culturing cells is time consuming and may comprise wound healing [15,16].

In contrast to biological substitutes, synthetic substitutes are free from any risk of disease transmission. However, only a few synthetic skin substitutes are on the market today. Although synthetic materials have greater structural integrity compared to natural products, its poor bioactivity remains a major concern [17]. In addition, poor host response may lead to negative effects on scar quality. Despite limitations in materials and cost, the development of bio-engineered skin is increasing due to innovative possibilities with new techniques and biomaterials, providing a glimpse into a promising future. These steps have promoted a shift in focus from traditional surgical interventions to skin tissue-engineered regeneration.

2.3. Wound dressings

Wound dressings are developed for wound coverage to aid re-epithelialization, prevent wound infection, skin desiccation, and further skin damage. Wound dressings can be categorized into four groups: biological dressings; conventional dressings; biosynthetic dressings and antimicrobial dressings. Biological dressings include cadaver allograft skin (transplantation between individuals of the same species), xenograft (transplantation between individuals of different species) and human amnion, which have been adopted to temporarily cover wounds for reepithelization. Although biological dressings are effective in terms of improving the quality of wounds for further skin grafting, they cannot be used as a permanent skin replacement due to immunological disparities [8]. Furthermore, many issues are associated with biological dressings, such as inconsistent quality, limited supply, and the risk of pathogen transfer [44]. Conventional dressings which do not contain antibiotics or medications, e.g. Vaseline gauze or silicone sheets are also widely used to temporarily cover wounds during reepithelialisation. However, these dressing tend to adhere to the

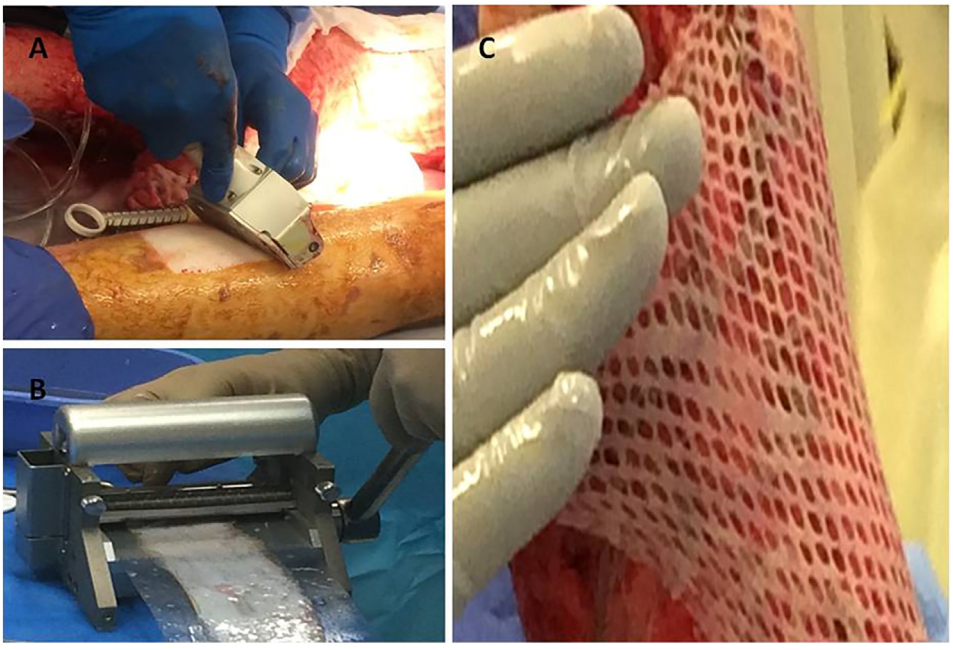

Fig. 1. Autologous skin grafting: (A) partial-thickness skin graft taken from the healthy donor site. (B) Skin graft is meshed to increase the surface area (C) Application of skin graft on the wound bed.

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Table 1
Skin substitutes used in burn care.

Skin substitute	Composition	Cells incorporated
KaroSkin [18]	Human cadaver skin with dermal and epidermal cells	
GraftJacket® [18,19]	Human acellular pre-meshed dermis	
StrataGraft™ [20]	Human dermal fibroblasts and stratified epidermis derived from Near-diploid Immortalised Keratinocyte S (NIKS)	
GlyaDerm® [21,22]	Glycerol preserved acellular dermal collagen-elastin matrix	
OASIS® Wound Matrix [23]	Porcine acellular lyophilized small intestinal collagen matrix	
XenoDerm [24,25]	Lyophilised acellular porcine dermis	
Permacol™ [26]	Porcine acellular diisocyanite cross-linked dermis	
PermaDerm™ [27,28]	Autologous keratinocytes and fibroblasts cultured with bovine collagen	
OrCel® [29]	Bilayered type I collagen matrix	Allogenic neonatal foreskin keratinocytes and fibroblasts
RenoSkin® [30]	Bilayer dermal matrix – silicone film and porous crosslinked bovine collagen	
TransCyte® [31,32]	Porcine collagen-coated nylon mesh	Allogenic neonatal human foreskin fibroblasts
Integra® [33–35]	Cross-linked bovine tendon collagen and glycosaminoglycan, and polysiloxane (silicone)	
Pelnac® [36,37]	Porcine tendon derived atelocolla gen type I, sponge layer with silicone film	
Hyalograft 3D [23]	Hyaluronic acid membrane	Autologous fibroblasts
Dermagraft® [38]	Bioabsorbable polygalactin mesh matrix	Human neonatal fibroblasts
TissueTech Autograft System [18]	Microperforated hyaluronic acid membrane	Autologous keratinocytes and fibroblasts
Suprathel® [39–42]	Synthetic copolymer – dl-lactide (>70%), trimethylenecarbonate and ε-caprolactone	
Laserskin® [43]	Hyaluronic acid membrane	Autologous keratinocytes and fibroblasts
MySkin™ [18,28]	Silicone support with a specially formulated surface coating	Autologous keratinocytes

wound surface and their need for frequent changes traumatizes the newly epithelialized surface and delays healing [45,46]. Biosynthetic dressings are designed to use materials that mimic the function of skin by replacing the epidermis or dermis, or both. Examples include Biobrane® and TransCyte®. Antimicrobial dressings are widely used in burn management to prevent wound infection, by minimising bacterial colonisation. A number of antimicrobial dressings have been introduced to burn care. These products can contain either silver (e.g. Aquacel AG), nano-crystalline silver (e.g. ACTICOAT), cadexomer iodine (e.g. Iodosrob), or honey as antimicrobials. Application of silver compounds on burn wounds was a major milestone in topical burn therapy, which remarkably reduced the incidence of burn wound induced sepsis and death.

2.4. Negative pressure wound therapy (NPWT)

Negative pressure wound therapy (NPWT; also known as vacuum assisted closure, topical negative pressure therapy or microdeformational wound therapy) is currently utilised in wound care for both large and small burns. It was first demonstrated to be effective at halting partial thickness wound progression compared to most other pharmacological means available [47,48]. NPWT was further utilised as part of temporary abdominal closure in acute burn patients or in a high risk burns patient who underwent pre-operative optimisation prior to skin grafting [49,50]. Considering burn injury as the most traumatic and composite wounds, the use of NPWT has been acknowledged to be helpful by allowing surgical teams to effectively manage acute burns, as well as their chronic sequelae. Numerous case reports have been published supporting the ability of NPWT to improve both split thickness or full thickness skin graft take, allowing early mobilisation of patients [51–55]. Additionally, this effect has been demonstrated both in the acute setting and when excising burn scar contractures [54,56–58].

The use of NPWT with skin substitutes or templates, such as Integra® has been utilised in clinical practice to improve poor skin graft take and infection [59,60], as NPWT has been hypothesized to prevent shear. Additionally, the optimised NPWT environment is thought to contribute to accelerated wound healing [61–63]. More studies have also shown that NPWT can also be effective to promote wound healing using Matriderm® or Pelnac® skin substitute with split skin graft [64,65]. The positive outcomes of NPWT associated with improved graft and dermal substitute take in burn injury has been attributed to reduced wound infection [54,66–68]. A case control study demonstrated a significantly reduced number of infections in the NPWT treatment compared to normal therapy [68]. Additionally, a study using a porcine burn model with locally applied *Pseudomonas aeruginosa* infection [69] found that NPWT effectively reduced bacterial proliferation and alleviated sepsis progression compared to usual wound treatment. Cytokine analysis and histopathological examinations confirmed that NPWT reduces wound inflammation and infection.

Recent evolutions in NPWT involve combining use with instillation or continuous irrigation. NPWT instillation (NPWTi) is a cyclical process whereby a solution of choice is instilled into a wound covered by NPWT dressings. Comparatively, NPWT continuous irrigation (NPWTci) is non-cyclical. This method involves the continuous irrigation of solution into the foam and wound bed, while the suction action of NPWT is continuously applied at the same time. Although, there are no clinical case reports on NPWTi and NPWTci systems in burn injury, these advanced systems could play a beneficial role in future burn wound management

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via reducing number of treatment days, accelerated clearance of infection and wound closure [70]. A study assessing NPWTi suggested that NPWTi may promote wound granulation rates compared to normal NPWT [71]. When antimicrobial solutions were used in conjunction with NPWTi, a lower bioburden load was found when compared to standard dressings soaked with the same antimicrobial solution. This finding suggests that NPWTi has the potential to increase the efficacy of the antimicrobial solutions in burn care.

3. Burn wound infection: challenges and innovations

Wound infection is a major challenge in burn care and is the most common cause of mortality after burn injury [72–74]. Pathogens have evolved overtime in line with innovations and antibiotic use [75]. Currently, multi-drug resistant (MDR) organisms and fungi present a major challenge [76]. With limited new antibiotics [77] innovations enhancing the effectiveness of currently available topical and systemic antimicrobials is paramount to improve morbidity and mortality in burn patients.

Bacterial organisms causing burn wound infection can be classified into two groups, gram negative and gram positive (Table 2). Gram negative bacteria cause most burn wound infections, with similar incidence, prevalence and pathogens regardless of geography or institution [78,79]. Burn wound infection by *Pseudomonas aeruginosa*, *Klebsiella pneumonia* and *Escherchia coli* and the gram positive organism *Staphylococcus aureus* are independent predictors of mortality [72]. *Staphylococcus aureus* is the major cause of gram-positive burn wound infections globally [74] and a common cause of septicaemia [76,80]. Methacillin resistant *Staphylococcus aureus* (MRSA) is now the major pathogen in some burn centres [74] and vancomycin resistant enterococci (VRE) although not as common, appears to be highly virulent [74].

3.1. Topical antimicrobial agents

Topical application of antimicrobial agents began with the application of sulfathiazole dressing to burns in 1940's [81]. With the discovery of the antibacterial properties of silver [82], silver sulfadiazine dressings have been the standard of care since 1968 [83]. Recent systematic reviews and meta-analysis report silver sulfadiazine to have poorer healing outcomes and little evidence of effectiveness in preventing wound infection than alternate dressings [84,85]. Mechanisms believed to be responsible for these outcomes are the requirement for regular wound dressing changes, poor eschar penetration and cytotoxicity of silver to keratinocytes and fibroblasts delaying wound healing [85–87]. A further issue is the recent report of resistance to silver in clinical isolates [88].

Table 2
Common pathogens causing burn wound infection.

Group	Species	Antibiotic treatment
Gram negative	*Psuedomonas aeruginosa*	Pipercillin-tazobactam
	Actinetobacter baumanni	Carbapenems
	Enterobacteriaceae	Cephalosporins
Gram positive	*Staphylococcus aureus*	Penicillins
	Streptococcus	Penicillins
	Enterococcus	Penicillins
Fungi	*Candida* spp.	Amphotericin B, Micafungin
	Non-albicans *Candida*	Amphotericin B
	Aspergillus	Caspofungin
	Blastomycosis	Fluconazole
Viruses	Herpes simplex	Acyclovir
	Varicella-zoster	Acyclovir
Drug resistant strains	MRSA	Vancomycin
	VRE	Linezolid
	(Extended-spectrum beta-lactamases) ESBL	Carnbapenems
	MDR *P. aeruginosa*	Colistin

Numerous innovative approaches have then been investigated in the past decade to achieve alternate topical antimicrobial treatment for burn wounds which do not compromised wound healing, require less dressing changes and induce minimal antibiotic resistance (Table 3). Innovations generally involve new methods of delivering well-established antibiotics, alternative antimicrobials such as curcumin [89,90] or synthetic antimicrobial agents such as LLKKK18 [91], an antimicrobial peptide. Clinical trials comparing novel dressings containing LLKKK18 to the silver dressings in human burn cohorts will likely challenge conventional practice in the near future. Further investigation of the effectiveness of novel dressings against MDR bacteria is also required.

3.2. Systemic antibiotics

Overtime treatment with various systemic antibiotics have propagated the evolution of micro-organisms causing morbidity and mortality in burns [76]. Currently, drug resistant organisms pose a difficult challenge. MRSA is the most common resistant organism encountered in burns and is normally treated with an ancient antibiotic, vancomycin [76,92]. Despite various measures to control and treat MRSA, the organism has continued to evolve with vancomycin-intermediate susceptible *Staphylococcus aureus* (VISA), a developing strain. New antimicrobials including oxazolidiones, streptogramins, tigecycline, daptomycin, dalbavancin [74,76] remain an important addition to the antibiotic armamentarium to combat such infections [93].

In many burn centers, the predominant organisms are the gram negative pathogens *Pseudomonas aeruginosa* and *Acinetobacter baumanni* [76,78,79]. Resistance of these organisms to antibiotics, including reserve antibiotics such as the carbopenams [76], has seen increasing reliance on the use of old antibiotics [74]. Colistin, a polymyxin antibiotic, was once abandoned due to extensive side effects (neurotoxicity and nephrotoxicity) but has recently been reinvigorated to combat MDR gram-negative organisms [94]. This new reliance on colistin has triggered various efforts to redevelop and re-engineer the antibiotic [94]. One such effort is the utilisation of nano-antibiotic polymer therapeutics in which colistin is conjugated to dextrin. The dextrin-colistin conjugate exploits the enhanced permeability and retention effect (EPE) [95] enabling the molecule to be delivered preferentially to burn wounds and in a greater concentration for a prolonged duration with less systemic side effects. Pre-clinical studies establishing antimicrobial spectrum, pharmacodynamics and pharmacokinetic properties in an animal model have shown a reduced toxicity profile with favourable pharmacological properties [96,97].

Efforts to improve drug delivery of current antibiotics also offers promise. Critically illness patients post severe burn injuries have substantially altered physiology, which may profoundly lower antibiotic tissue concentrations culminating in therapeutic failure and the emergence of resistance. Physiological changes include altered fluid balance, a hyperdynamic circulation, renal and hepatic dysfunction and organ support [98]. Methods to improve drug delivery involve regular monitoring of antibiotic concentrations and the delivery of antibiotics via continuous infusion rather than bolus regimes [99]. For example a recent study demonstrated improved outcomes when *P. aeruginosa* infection was treated via extended infusions of pipercillin-tazobactem [100].

3.3. Anti-fungal infection

The incidence of fungal infections is increasing [101–103] with candida species being the most common [104]. In the USA, fungi are responsible for approximately two thirds of invasive burn wound infections [75] and is the fourth most common organism isolated in blood cultures [104]. Fungal infections, particularly non-candida infections such as *Aspergillus* spp. and moulds are associated with high mortality due to sepsis with multi-organ failure [76]. Clinically, fungal infection has an added comorbid effect equivalent to an additional burn involving 33% of the total body surface [105]. The most effective

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Table 3
A summary of studies in topical antimicrobials.

Studies	Antimicrobial	Delivery system	Organisms tested	Year
1	Ciprofloxacin	Keratin hydrogel	*S. aureus*, *Psuedomonas*	2016
2	Gentamicin	Soy protein films	*Psuedomonas*	2015
3	Curcumin	Gel-core hyaluosomes	Nil	2015
4	Curcumin	Nanoparticle incapsulation	MRSA, *Psuedomonas*	2015
5	LLKKK18	Carbopol® hydrogel	Nil	2015
6	Gentamicin	Hybrid bi-layer wound dressing	*Psuedomonas*	2015
7	Nitric oxide	Polymeric film	*Acinetobacter baumanii*	2014
8	Mupirocin	Liposomes in hydrogel	*S. aureus*	2013
9	Gentamicin	Polyglyconate mesh and PDLGA matrix	*Psuedomonas*	2011
10	Lysostaphin	Chitosan-collagen hydrogel	MRSA	2011
11	Fucoidan-chitosan	Hydrogel	Nil	2008
12	Minocyclin	Chitosan film and tegaderm	Nil	2007
13	Chlorhexidine	Bilayered hydrogel and chitosan foam	*S. aureus*, *Psuedomonas*	2000
14	Amphotericin B	Nanoparticle hydrogel	*Candida* spp.	2014
15	Boron/pluronic copolymers	Carbopol-based hydrogel	Bacteria, yeast, fungi	2015

treatment for fungal infection is prevention via removal of burned tissue and closure of wounds [74]. Positive fungal wound cultures and fungaemia particularly if *Aspergillus* spp. or other moulds are cultured, are generally indications for systemic therapy although specific indications for treatment remain unclear [103]. Currently three classes of systemic antifungal drugs are available for treating fungal burn wound infection, including polyenes, azoles and echinocandins [104].

Polyenes such as amphotericin B are first line agents for the treatment of Candida, but its use is often limited by significant nephrotoxicity [74,76,104]. Lipid soluble formulations of amphotericin B although causing less side effects, are substantially expensive [104]. Of the azoles, fluconazole is the empiric choice for invasive candidiasis, although developing resistance is an issue [104]. Echinocandins the newest antifungal agent introduced in 2001, are effective with a unique mechanism of action inhibiting the synthesis of β-1,3-D-glucan polymers and has a more favourable toxicity profile and pharmacokinetics [76,104,106]. As with antibiotics, future research addressing the impact of burn injury induced physiological alterations on the pharmacokinetic profile of systemic antifungal therapies has yet to be elucidated.

Pathogens causing morbidity and mortality in burn wounds continue to evolve in response to dynamic pressure from antibiotic use. Future clinical application of novel antimicrobial wound dressings in place of the established silver dressings is promising. Systemically, challenges include enhancing the effect of current antibiotics through the pursuit of individualized dosing regimens which adjust for in altered physiology after burn wound, and the utilisation of the EPE to enhance systemic delivery are encouraging innovations. Fungal pathogens are emerging as more common and troublesome infections, continued development and enhanced understanding of the clinical use of antifungal drugs will benefit burns patients.

4. Burn pain management: challenges and innovations

Control of burn pain is central to the recovery and reintegration of burn injury patients. Poor control of pain can hamper the healing process due to fear and anxiety induced elevation of stress hormones (such as glucocorticoids). This can lead to long lasting physical and psychological burdens and hospital stay. Three mechanisms are counted to burn pain– nociceptive, neuropathic and inflammatory. Intravenous morphine forms the basis of pain management through early stage post-burn injury, while shorter half-life opioids and nerve blockers are alternative options. During the wound healing process, surgical wound debridement, physiotherapy and dressing changes increase pain levels substantially. Nociceptive pain levels decline as scars mature and physical therapy continues. Additionally, neuropathic type pain may increase at this stage along with pregabalin, gabapentin used for treatment of painful neuropathy.

4.1. Issues of pain management

Post severe burn injury at 48 h, a hypermetabolic response begins which is known to effect on drug clearance rates, pharmacokinetics (PK) and pharmacodynamics (PD). However, lack of literature has been reported on the effect of burn-induced hypermetabolism on drug PK and PD [107,108]. As a result, appropriate dosing for a majority of drugs used in burn pain remains an area requiring further investigation.

Opioid reliance continues to define burn pain care [109]. The side effects of opioid use include: nausea, vomiting, constipation, gastrointestinal dysmotility, dependence and tolerance. Severity of burn pain and duration of treatment also predisposes to tolerance, escalation of doses and high risk of addiction. Moreover, opioid can induce hyperalgesia, an additional overarching state of enhanced pain sensitivity along with increasing doses of opioid [110]. Issues of opioid induced hyperalgesia presents a clinical challenge in the burn injury population [110]. In consideration of these effects, further investigation of opioid treatment options, alternatives, and adjuncts is paramount for burn patient care.

4.2. Treatments for burn pain

4.2.1. Ketamine

Ketamine forms a part of burn pain management for a number of decades, playing a major role in burns procedures since the 1960's due to potent analgesic, sedative and amnesic properties [111–113]. Recent literature exhibited the capability of ketamine to reduce primary and secondary hyperalgesia; while also increasing thermal injury induced mechanical pain thresholds [114,115]. Delivery of ketamine in burns patients can be conducted by intravenous (IV) infusion, intravenous patient-controlled analgesia (IV-PCA), intramuscular, oral and intranasal administration [116–120]. Studies examining the combination of ketamine with other classes of burn-pain pharmacology have been prominent, particularly in an effort to reduce sympathomimetic, sedative and psychomimetic side effects. Ketamine was first combined with benzodiazepines in attempt to reduce these adverse effects [121]. A study reported the positive effects of this combination in burns patients, indicating that ketamine in combination with midazolam successfully reduces the side effects of ketamine [120]. Further study provided evidence that combination of ketamine with propofol can be used to attenuate ketamine's unexpected effects [122]. The range of pharmaceutics utilised in burn pain management provides opportunity to further

investigate ketamine synergism, particularly in the areas of background and breakthrough pain which have not be studied in previous research.

4.2.2. Sedatives and anxiolytics

Benzodiazepines have no analgesic properties but are extensively utilised in burns patients as adjuncts for pain management. It has been shown in recent burns pain studies that anxiety decreases pain tolerance and increases use of pain medications [123,124]. Recent studies exploring benzodiazepines in burns patients have largely centered on combination with other sedatives (such as ketamine and dexamethasone). α2-agonists, similar to benzodiazepines, are used as sedatives and anxiolytics in burns. A clinical trial study of α2-agonists indicated the potential for an additional role in pain reduction. However, this must be in consideration of α2-agonist side effects; reduced sympathetic outflow and hypotension, which have complicated several burn studies to date [125,126].

4.2.3. Neuropathic drugs and pruritus

Pregabalin and gabapentin are anticonvulsants used in the treatment of neuropathic pain of burn injury patients. A case series in 2010 established the efficacy of pregabalin in reducing post-burn neuropathic pain scores of outpatients [127]. Subsequent randomised controlled trial demonstrated the role of pregabalin in both the acute and healing phases of burn injury [128,129], demonstrating reductions of neuropathic pain during the first four weeks of treatment, while additionally reducing pain levels during procedural pain events. Another study found that pregablin had positive effects in reducing post-burn pruritus, suggesting that pregabalin can be used in any patient with moderate to severe pruritus [128]. Secondary to this, recommendation was made to utilise pregabalin in mild itch to achieve the benefit of rapid and complete response.

Gabapentin has also received attention from burn pain investigators. Regarding to the acute setting, conflicting evidence has arisen on the efficacy of gabapentin in reducing acute burn pain and opioid consumption. Studies have shown positive results with gabapentin via reduction of mechanical allodynia in experimental partial thickness wounds [130,131]. However, a randomised controlled trial study demonstrated that burn patients receiving gabapentin on day 1 of injury did not display any significant effects on either opioid consumption or acute burn pain [132]. This work is supported by a double-blinded, placebo-controlled, crossover study, showing no anti-hyperalgesic or opioid enhancing effects when gabapentin was used in an experimental superficial burn model [133]. Similar to pregabalin, gabapentin shows favourable results in the management of post-burn pruritus. Successful use of gabapentin in paediatric burns patients was reported as an alternative to antihistamines [134]. Subsequent studies further established gabapentin as a more effective alternative to antihistamine as monotherapy. Additionally, gabapentin was demonstrated as a first line therapy that leads to greater efficacy at each step up in therapy as part of a burns pruritus protocol. Other notable pharmacological forms of antipruritic therapy include naltrexone, ondansetron and botulinum toxin [135–138]. However, these are lacking substantial evidence and require further investigation in burns populations.

4.3. Future pain targets and considerations

Advances in pain and thermal sensation is essential to the development of future burn pain pharmacology. Identification of polymodal transient receptor potential (TRP) channels has been known to be the most important finding in pain research in the last few decades [139,140]. As part of this family, TRP vanilloid-1 (TRPV1) is a key channel activated by heat, acidosis, chemical mediators and molecules such as capsaicin [141–145]. TRPV2 and TRP melastatin-3 have also been demonstrated to play a role in thermal nociceptive sensation [146,147].

Research using TRPV1 knockout (KO) mice showed that TRPV1 is a principle receptor responsible for thermal hyperalgesia during the acute phase post burn injury (up to 24 h); while a recent study suggests a role for TRPV1 in thermally induced chronic pain [144,148–151]. TRPV1 channels were also found to be involved in thermally induced cell death [152], suggesting TRPV1 to be the target for both agonist and antagonist pain control in burn injury. However, systemic delivery may not be feasible as it has emerged that TRPV1 are implicit in homeostatic roles [153,154]. Overcoming the barriers of systemic TRPV1 modulation remains unclear in burn pain management, therefore, development and local application of TRPV1 modulators is expected to avoid undesirable systemic and central effects.

Voltage gated sodium channels (Na_v) have also garnered attention as pharmacological targets for pain control. While a number of channels have been identified in the literature, the three channel types which show most promise in burn injury are $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$. Both human studies and animal experiments have demonstrated the potential of $Na_v1.7$ in burn patients demonstrating either complete absence of pain response or conversely pathological states of pain [155–158]. Animal models demonstrated the potential utility of $Na_v1.7$ to diminish thermal and mechano-sensation in $Na_v1.7$ knockout mice – particularly, in states of inflammation induced nociception [159,160]. A recent study further confirmed that tetrodotoxin, a $Na_v1.7$ blocker, significantly reduced thermal hyperalgesia and mechanical allodynia in a thermal injury model [161].

Innovation in pain management continues to improve acute and long term outcomes for patients experiencing the trauma of burn injury. However, research surrounding burn pain analgesia can often suffer from a lack of specificity. Future work to improve the current state of management must not fall victim to a one-size-fits-all approach. The patient and burn characteristics, phase of injury, and category of burn pain must all be considered to adequately address the needs of burn teams in their clinical efforts. In consideration of this framework, the continued development and understanding of mechanisms which contribute to burn pain is an essential component for the development and improvement of novel therapies.

5. Scarring and management

With reduced mortality rates associated with severe burn injuries, the aim of burn wound care is shifting towards the management of burn scars [162]. Hypertrophic and keloid scarring in burn patients causes significant morbidity often with poor functional and cosmetic outcomes (Fig. 2). Burn scars can lead to causes many debilitating factors including pain, pruritus, dyspigmentation, heat intolerance, and limited range of motion due to scar contraction. The challenge in the treatment of post burn injury scarring lays on finding new therapeutic targets by an enhanced understanding of scar formation.

Fig. 2. 16-year-old patient with keloid scarring 6 months following a 25% TBSA flame burn injury. The wounds on his left upper arm and left chest were excised and grafted.

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5.1. Stem cells

Stem cell based wound healing therapies represents as a new promising modality for the treatment of fibrosis, scarring and treatment for wound contraction. Post injury, stem cells are heavily involved in all overlapped phases of wound healing [163–165]. Endogenous stem cells migrate to the site of injury during the initial inflammatory phase, where they elicit immunomodulation effects, followed by accelerated wound closure, angiogenesis and re-epithelialization [166]. Mesenchymal stem cells (MSCs) and adipose derived stem cells (ADSCs) have been widely investigated in scar treatment, wound contraction and in the pathophysiology of scar formation [167]. MSCs are defined as self-renewing multipotent stem cells that can be differentiated into various lineages of mesenchymal origin [163]. A number of studies have shown the positive effects of bone marrow-derived MSCs in reducing hypertrophic scarring [168–170] via reduced expression of myofibroblast marker and the down-regulation of collagen I synthesis. Recent studies have further characterized two distinct phenotypes of MSCs involved in the wound healing process: the pro-inflammatory M1 and the anti-inflammatory M2 [166]. This polarization is mediated by different toll-like receptors (TLRs), which respond to various substances in the extracellular milieu and promote MSC phenotype switching accordingly to the current needs of the organism. Specifically, stimulation of TLR3 and TLR4 switches the cell between an anti-inflammatory and pro-inflammatory phenotype, respectively, resulting in control of cell migration, cytokine secretion and ECM deposition. This research leads to a new direction on the precise role of MSCs on wound healing and scar formation.

ADSCs have received considerable attention in skin regeneration as it has potential to regenerate hypodermis, dermis and epidermis [171]. An abundance of studies have supported the efficacy of fat grafting in both aesthetic and reconstructive cases [172–174], which has led to research into the utility of ADSCs in wound healing, regeneration of soft tissue, and reducing scarring [170,174,175] by its remodelling capacity provided by the unique cytokine and growth factor profiles. ADSCs treatment can diminish established hypertrophic scars and keloids by the inhibition of transforming growth factor-beta 1 (TGF-β1) mediated fibroblast differentiation into myofibroblasts [164], and reducing collagen deposition by up-regulating matrix metalloproteinases (MMPS), which are capable of remodeling collagen in the wound site. In a recent study, burn wound exudate was shown to significantly increase ADSC secretion of vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6), a pro-inflammatory cytokine [176]. ADSCs have also been found to promote vascularization and wound healing through VEGF secretion and a decrease in TGF-β1 secretion in a mouse model [168]. In line with these conflicting results, there is evidence that ADSC stimulated cytokines promote granulation and angiogenesis in the wound bed, which has been linked to the production of hypertrophic scars in deep burns. However, few latest conflicting findings demonstrated in addition to increased inflammatory responses, ADSC stimulated cytokines promote granulation and angiogenesis in the wound bed, which linked to the production of hypertrophic scars in deeper burns [177–179]. Therefore, more research into the potential role of ADSCs in burn scar treatment is required.

Innovations for the utility of stem cells in treating scars involve surgical fat grafting with stem cells or introducing novel delivery methods of stem cells into the wound site. A systematic review article showed that fat grafting together with ADSCs enhanced wound angiogenesis, decreased inflammation, improved burn scar size and quality in both murine models and human studies [172]. Sundew-inspired adhesive hydrogels combined with ADSCs was recently reported as an innovative method to deliver ADSCs and was found to promote a “suturing” effect to accelerate wound closure, although the effects on long term tissue remodeling or scar formation is not clear yet [180]. The effective delivery of adipose-derived stromal cells using ECM patch also holds promises to reduce scarring. Stem cell delivery along with an ECM patch can improve cell survival and proliferation, and significantly reduce fibrosis [175]. Whether stem-cell-based therapies can be translated in clinical practice is still in debate. Furthermore, practical barriers associated with stem-cell-based therapies might restrict their utility in scarless wound healing post burn injury [181]. To address this limitation, conditioned media from umbilical cord-MSC cultures may be used to treat wounds. Dermal fibroblasts were found to exhibit characteristics comparable to fetal fibroblasts, showing low capacity to form myofibroblasts [182]. Wounds treated with such umbilical cord-MSC-conditioned media healed faster with decreased collagen accumulation. Additionally, human amniotic-fluid-derived MSC-conditioned media also have the potential to inhibit the pro-fibrotic actions of TGF-β1 and even reverse the myofibroblasts phenotype to a fibroblast-like state in vitro. Taken together, innovations in stem cell studies provide more therapeutic options for treating burn scars.

5.2. Pharmacological approaches

5.2.1. Silicone

Silicone has been one of the gold standard for non-invasive burn scar management of hypertrophic scars for years [183–185]. A recent randomized clinical trial showed that the use of silicone caused a significant reduction in pain and pruritus at 6 months post-burn injury. The use of pressure garments to reduce scar thickness, with silicone provided the most optimal results [186]. Silicone gel sheets, however, are difficult to use in anatomical areas subject to a high range of motion such as joints and can be undesired in exposed areas such as the face. To overcome these challenges, fluid silicone gel has been developed to allow for a thin layer of silicone gel to dry into a transparent silicone sheet [183–185]. Silicone is also being used to develop new devices such as the Embrace, a dynamic stress shielding device showing good results, however, evidence is still limited [187].

5.2.2. Corticosteroids

Injection of corticosteroids into hypertrophic scars has been considered a first-line of treatment for small hypertrophic scars scarring since 1960s. Corticosteroids are reported to reduce the height and volume of scars, decrease pain and pruritus and make scars more pliable [185,188]. Triamcinolone acetonide, a long acting corticosteroid, is commonly used to treat post burn scarring. It is thought that corticosteroids decrease collagen synthesis, attenuate cell proliferation of fibroblasts and keratinocytes, and accelerate collagen degradation by activating collagenase and suppressing TGFβ [189–191]. However, the optimal dose of corticosteroids for treatment have yet to be determined [185,188], and the side effects of its use including hypopigmentation and subcutaneous atrophy [192] only represent a few limitations. A new approach combining corticosteroids (Triamcinolone) and 5-fluorouracil (a pyrimidine analog antimetabolite chemotherapy agent) was shown to reduce pain and have less side effects compared to the use of Triamcinolone alone [193,194]. Furthermore, this combination in use with a pulsed-dye laser has the potential to decrease scar volume and improve softening of hypertrophic scars and keloids [195].

5.2.3. Transforming growth factor-β modulators

TGF-β is a cytokine implicated in the pathogenesis of keloids and hypertrophic scarring. It is produced and released by platelets, fibroblasts, endothelial, epithelial and inflammatory cells and acts as a potent inducer of myofibroblasts differentiation [196]. Previous studies have confirmed that TGF-β1 and TGF-β2 promotes collagen synthesis and scar formation with significantly increased mRNA expression in keloids. In contrast, TGF-β3 is involved in scar prevention. Numerous research and multiple therapies targeting the TGF-β pathway have been proposed as advanced treatments for scars, aiming to reduce TGF-β activities, increase TGF-β3 expression, and utilize TGF-β inhibitors such as decorin [197], proteolytic inhibitors such as mannose-6-phosphate [198] and neutralized antibodies [199]. A recent study used antisense oligonucleotides to block the effect of TGF-β1 over wound healing and

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tissue remodeling [196], and showed significantly reduced expression of TGF-β1 and β2 with upregulation of TGF-β3 [200]. However, to date, only the injection of TGF-β3 into surgical wounds have been used to modulate the TGF-β pathway, demonstrating significant improvements in scar appearance in a randomized, controlled clinical trial [201].

5.2.4. Botulinum toxin A

Botulinum toxin A is a neurotoxin produced by bacteria that inhibits acetylcholine release from a neuron, and suppresses muscle contraction for approximate 2–6 months. Botulinum toxin has shown great potential as an additional tool to improve scar formation. Gassner and colleagues first reported that injection of botulinum toxin into the underlying musculature of wound sites significantly enhanced wound healing and minimized scar formation [202]. When botulinum toxin A is injected into a wound, it causes flaccid paralysis of the surrounding muscle, decreasing mechanical forces and thereby reducing wound tension [196,203]. Increased wound tension has been theorized to stimulate fibroblasts to differentiate into myofibroblasts and increase alpha-smooth muscle actin production, causing the wound to contract. Thereafter, many studies were conducted by intralesional injection of botulinum toxin A to treat keloids or mature scar [204]. Clinical studies followed up to 1 year showed that all patients that received botulinum toxin A had excellent scar regression and flattening of the lesions. Although the underlying mechanisms are still under investigation, researchers suggest that botulinum toxin suppresses fibroblast proliferation and differentiation by inhibiting the expression of TGF-β1 [205]. In a recent study, reduction of the tensile force by botulinum toxin A injection into the musculature adjacent to the wounds may represent a comprehensive mechanism of action for aesthetic improvement of post-surgical scar [206]. All reported studies of botulinum toxin A have focused on the improvement of scars however, whether botulinum toxin A can prevent scar formation has yet to be established, and more extensive research is required.

5.3. Surgical approaches

5.3.1. Fat grafting

Fat grafting as a surgical approach in treatment of burns has several documented benefits and is a rapidly evolving field for scar modulation [207–209]. Functional and aesthetic improvements were shown in split-scar patients with reduced scar thickness and significantly better results in pain, colour, thickness, pliability/movement and shape/relief after 3 months [208]. A study on adherent burn scars showed a significant improvement in elasticity and maximal extension, and of the patient observer scales score at the 3-month follow up [210]. In addition, colour difference remained unaffected [210]. Fat grafting was also reported to enhance wound closure and improve neuropathic pain [211–215], and is further supported by a study that evaluated the effects of fat-grafting on burn-induced neuropathic pain in rat-models [216,217]. Moreover, several case series have demonstrated great improvements in subjective patient ratings of burn scars, with improvements in texture, softness, thickness, colour, and wound healing which were also correlated histological findings [208,218–221]. ADSCs are believed to play a key role in fat grafting as they reduced collagen deposition and promoted vascularization and wound healing.

5.3.2. Laser therapy for scar modulation

Keloid and hypertrophic scarring occurs by the loss of control mechanisms involved in biosynthesis and tissue degradation during the wound healing process, resulting in excessive collagen production and fibroblast proliferation [222]. Although contraction is part of the regular wound healing process [222], the contraction of healing burn wounds, grafts and scar tissue results in abnormal scar formation [223,224]. In addition, prolonged wound-healing and the inflammatory nature of burn wounds lead to hypertrophic scarring [225], followed by pigment alteration due to a dysbalanced amount of melanin or erythema [226,227]. Laser treatment may serve as a useful modality for the treatment of hypertrophic and keloid scars [228] that have shown very encouraging results [207,229]. Over the last decade, laser therapy has become increasingly popular and is increasingly a crucial part in reconstructive burn surgery [224,230].

5.3.3. Pulsed dye lasers (PDL) & neodymium-doped yttrium-aluminium-garnet (Nd:YAG) lasers

Wavelength-specific lasers, such as the PDL and Nd:YAG laser, that selectively absorb oxyhaemoglobin and thus ablate blood vessels, have been widely analysed for the treatment of hypertrophic burn scars [151,207,231]. The mechanism of these vascular lasers still remains unclear, however, it has been postulated that selective photothermolysis by targeted vascular destruction leads to tissue hypoxia, collagen fibre heating, dissociation of disulfide bonds, catabolism and decreased cellular function, which consequently prevents excessive collagen deposition, and results in collagen fibre realignment and remodelling [223,232]. The relative hypoxia of fetal skin leads to an upregulation of hypoxia-inducible factor I, which subsequently upregulates oxygen-dependent genes such as VEGF and TGF-β3, that results in a decrease in fibroblast activity [233]. Histological analysis of scars treated with a 585-nm PDL revealed that thick hyalinised dermal collagen with haphazardly arranged fibroblasts became looser, with less coarse collagen fibres and a normal number of fibroblasts [234]. A meta-analysis including 28 well-designed clinical trials [232] showed that the 585/595-nm PDL is effective in improving overall scar appearance and reducing both scar height and degree of erythema of hypertrophic scars. It was also found that to 585/595-nm PDL decrease scar pruritus [224,235], and may result in a synergistic action when combined with intralesional steroid or 5-fluorouracil injections [236].

5.3.4. Non-ablative and ablative fractional lasers

Novel techniques such as non-ablative and ablative fractional resurfacing techniques are also developed to rehabilitate burn scars [224,230,237]. Fractional lasers affect the scars only in small areas leaving the surrounding skin uninjured, which serve as a reservoir of viable tissue to stimulate neocollagenesis and tissue remodelling [229,237]. Non-ablative fractional lasers (NAFL) are particularly effective for the treatment of atrophic, flat or mature scars [237]. A clinical trial demonstrated that treatment of burn scars with NAFLs significantly improved scar quality over a 6-month follow-up, and through histological analysis collagen resembled normal skin [238]. However, it seems that treatment of burn scars with an ablative fractional laser (AFL) triggers a more vigorous reaction of neocollagenesis and tissue-rearrangement when compared to NAFL [237,239].

Histological analysis demonstrates that the distinct AFL injury promotes a cascade of heat shock proteins, matrix metalloproteinases, and inflammatory processes, which result in a rapid wound healing response with prolonged neocollagenesis and ensuing collagen remodelling [240–243]. Tension of the scar is released and the dermal architecture is rearranged by this remodelling process, leading to improved pliability, decreased thickness, and better function [243–249]. Several groups reported a significant decrease in scar assessment scores and a significant decrease in scar thickness when measured by ultrasound [230,240,242–244,250,251]. Recent reports demonstrate that even one treatment with the AFL can lead to significant improvements in scar quality (Fig. 3) and symptoms (such as pruritus and neuropathic pain), heat-sensitivity, and a measured decrease in scar thickness, irrespective of the scar maturation status [230,244].

Laser-facilitated drug delivery combined with fractional resurfacing is another advanced technique to further enhance pliability and reduce thickness [252,253]. This combination can help to reduce adverse effects from the local accumulation of intralesional injected steroids or 5-fluorouracil by assisting the even distribution of the drug in the dermis [252,254–256]. Laser treatment represents a therapy that has the potential to

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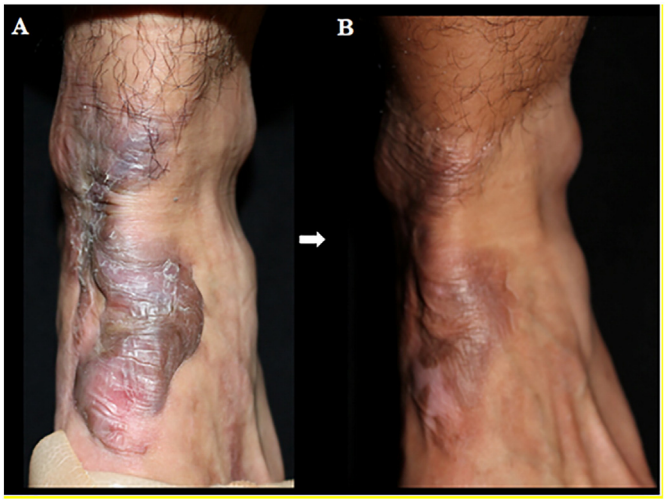

Fig. 3. (A) A 19 year old patient with hypertrophic scarring on his left ankle 7 months following a burn injury with hot oil. The scar was unstable and led to frequent wound breakdown depending on the footwear. (B) 6 weeks following one treatment with the ablative fractional Ultrapulse® CO_2 laser and laser facilitated steroid infiltration, the scar has flattened, became more pliable, pain and itchiness improved, and wound breakdown subsided.

fill the gap between non-surgical treatment options and surgical interventions for scar management [237]. It can also be used before surgery to make scars more pliable, to potentially improve surgical outcomes [230] or in scar rehabilitation to limit the development of contractures, promoting early mobility and thus accelerating the entire rehabilitative process [237,249]. However, the exact mechanisms by which lasers can achieve beneficial scar modulation remain unclear. Most data supporting its clinical application stem from retrospective series, thus being prone to selection bias and similar. Therefore, more prospective studies using in depth molecular analyses to explain treatment effects and patient outcomes are required to determine the exact role for this novel, promising therapeutic strategy for burn scars.

6. Skin tissue engineering in treatment of burn injury

Skin tissue engineering provides a new tool in treatment of burn injury, aiming to enhance wound healing, trigger skin regeneration and reduce the long term consequences of scarring [257]. The ultimate goal of skin tissue engineering is to produce a 'living skin' which offers completely functional skin, including all skin appendages to replaces human skin in its entirety. Challenges and problems in skin tissue engineering include poor vascularization; delayed cell infiltration and migration due to undesirable surface structure or lack of cell-recognition signals or poor mechanical strengths. Researchers therefore pay their attentions into developing innovative biomaterials, advanced formulation technologies or new methods to incorporate autologous cells (e.g. keratinocytes, dermal fibroblasts, melanocytes) in order to increase the complexity of the skin substitutes. The applications of skin tissue engineering are broad, ranging from basic scaffolds to aid the growth of the neodermis, to the delivery of biomolecules such as growth factors, and stem cells to enhance wound healing and skin regeneration with full functional skin.

6.1. Biomaterials in skin tissue engineering

Both natural polymers and synthetic polymers have been widely investigated in skin tissue engineering. Natural polymers are isolated from a variety of sources including animal (collagen, hyaluronic acid), seaweed (agarose, alginate) or bacteria. They are soluble in aqueous or buffer solutions and are biodegradable in vivo. Collagen and hyaluronic acid (HA) are two major components for skin regeneration and have been fabricated as sponges, films, matrices and gels to facilitate wound healing utilising the biodegradability and biocompatibility properties that make these polymers favourable [258–262]. Collagen scaffolds promote the strong attachment and proliferation of keratinocytes and dermal fibroblasts with various collagen based skin templates such as Biobrane™, MatriDerm®, Apligraf® and Integra® currently used in burn injury wound care. Hyaluronic acid (HA) is a natural polysaccharide composed of *N*-acetylglucosamine and glucoronic acid sugar units. HA is a structural component of skin ECM and due to its low immunogenicity, it has been considered as an ideal biomaterial for wound repair [260–262]. However, poor physical properties of HA represent serious limitations for its medical application. Chemical modification with enhanced resistance to degradation has significantly improved physical properties of HA, resulting in two commercial products: Hyalomatrix and Hyalosafe that are currently used in burn treatment as dermal substitutes.

6.1.1. Elastin

Elastin is an essential component of native human skin, providing structural and cell mediating functions [263]. Recent studies demonstrated that incorporation of elastin in skin substitutes can improve scar quality and enhances angiogenesis [264,265]. In a clinical study, collagen-elastin scaffolds were found to reduce wound contraction and improve scar tissue architecture [265]. Reduced wound contraction was attributed to a decrease in the number of fibroblast differentiating into myofibroblasts [263,266]. The ability of elastin to enhance angiogenesis has led to the introduction of one-step procedures in burn surgery. Currently, many dermal skin substitutes involve two-step procedures as skin substitutes need time to be fully integrated with the wound bed and vascularized, prior to a secondary surgical step of split-thickness skin grafting. Otherwise, skin grafting will fail and result in skin graft loss and poor take. MatriDerm® is the first commercialized skin substitute containing elastin. MatriDerm® has been proven to be applicable in one-step procedures without a reduction in skin graft taken rate [267–271] and it was also found effective in a range of acute and reconstructive burn wounds.

6.1.2. Silk

Silk is composed of two proteins, fibroin and sericin. The favourable characteristics of silk make it as an optimal biomaterial in skin tissue engineering to enhance biocompatibility, mechanical structure with controllable biodegradability [272,273]. Silk are widely investigated in tissue engineering studies, including hard tissue, e.g. bone/cartilage and soft tissue, e.g. eye and neuron regeneration. In skin tissue engineering, silk was found to promote collagen synthesis from dermal fibroblasts [274] and 3D silk scaffolds are being optimized as a new generation of skin substitutes. A recent study showed that scaffold incorporation of silk and hair-derived keratin as a dermal substitute, resulted in better cell adhesion and proliferation of fibroblasts, and increased collagen protein expression [275]. The advantages of using silk in skin tissue engineering are further expanded in combination with keratin, collagen, elastin, chitosan, fibronectin and synthetic materials [272–274].

6.2. Advanced technologies in skin tissue engineering

6.2.1. Recombinant proteins

In addition to advancements in biomaterials, artificial ECM proteins are being produced to diminish the risk of disease transmission and to reduce host immunological responses, yet maintain a high bioactivity for wound healing [17]. Typically using *E. coli* or yeast systems, recombinant proteins with designed structures and functions can be produced by genetic manipulation. A variety of recombinant proteins are currently being investigated, such as tropoelastin, a precursor to elastin. Our research team recently investigated the effects of tropoelastin incorporated into Integra®, and found that tropoelastin has a comparable

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function to bovine derived elastin [264]. Tropoelastin incorporated Integra® significantly increased angiogenesis in both mouse and porcine wound repair models compared to skin grafting only [264]. In contrast, injection of tropoelastin into a porcine hypertrophic burn scar showed no changes in scar flexibility [276]. Research into recombinant collagen is also under taking, but the complex structure of collagen makes it more challenging in tissue engineering. The production of recombinant collagen is limited by the lack of an animal-cell-specific, post- translational enzyme system. Although the gram-positive bacterium, *Streptococcus pyogenes*, has been found to produce a stable and thermal resistant collagen, it lacks specific binding sites native to human collagen [277,278]. This represents the framework for recombinant collagen engineering and further studies aim to improve its complexity in comparing to native human collagen. Recombinant proteins as building blocks for skin substitution is progressing, limitations including the lack of production in commercially required quantities and insufficient knowledge regarding protein structure-function relationships needs to be overcome [278].

6.2.2. Electrospinning

Electrospinning was developed over 30 years ago but has attracted new interest in the last decade [279]. Using this technique, nano-scale fibers can be produced to mimic ECM in native human skin. A major advantage of electrospinning technology is the ability to spin both natural polymer such as silk, chitosan, gelatin, fibrinogen and synthetic materials such as Poly (ε-caprolactone (PCL), polyurethane (PU), poly (glycolic acid) (PGA) and poly (L-lactide) PLLA [280–282] or copolymer together. Research attempts to combine various natural and synthetic materials to enhance the biocompatibility as well as the mechanical strength of scaffolds [282]. In order to overcome poor infiltration of cells into electrospun scaffolds due to low porosity and small pore size, many advanced methods have been developed, including leaching of selective water-soluble fibers [283] and cell-nanofiber fabrication. A successful approach involved repeatedly seeding fibroblasts layer-by-layer into electrospun scaffolds until the desired number of cell-nanofiber layers were achieved [284]. Adoption of coaxial electrospinning system has also shown excellent results in cell infiltration and proliferation [285]. Additionally, the unique properties of coaxial electrospinning system has been utilised in drug and bioactive molecule delivery as it can protect the bioactivity of bioactive molecules by spinning two separate layers of nanoscale fibers that contain both polymer solution and bioactive molecules [281].

6.2.3. Three-dimensional (3D) bioprinting

3D bioprinting is an advanced manufacturing platform that enables the predefined deposition of living cells, biomaterials and growth factors using computer-aided design (CAD) technology. Bioprinting technology has the potential to directly create graded macroscale architectures to better mimic the natural ECM, thereby augmenting cell attachment and proliferation [286]. Bioprinting is also to produce microfeatures, such as ridges and modulated surfaces by using multiple material platforms with various dispensing mechanisms [287]. There are three important steps in 3D bioprinting, including pre-processing (3D model generation and bio-ink preparation); 3D bioprinting and post-processing (using a bioreactor for tissue regeneration). 3D bioprinting of skin is receiving great attention as it can rapidly produce an even landscape by allowing an increasingly controlled and precise deposition of cells into a predefined tissue structure. Various biomaterials have been evaluated for bioprinting skin such as collagen [288], bovine gelatin [289], chitosan and silk fibrin [290], also synthetic biopolymers being PCL, poly (lactic acid) PLA, poly (lactide-*co*-glycolide) PLGA and PLLA [291] or human plasma [292]. Additionally, keratinocytes and fibroblasts are two widely studied cell types in 3D bioprinting skin [289]. A recent study successfully demonstrated the deposition of 20 layers of fibroblasts and 20 layers of keratinocytes, respectively, in collagen using laser-based bioprinting. The results showed the presence of cadherin and connexin 43 in the epidermis, which are fundamental for tissue morphogenesis and cohesion [293]. Furthermore, a 3D bioprinted skin using keratinocytes and fibroblasts in collagen showed good graft take, and blood vessel formation/growth in the surrounding wound area in nude mice at 11 days post transplantation [294]. In order to regenerate fully functional skin, co-bioprinting melanocytes with keratinocyte; or incorporating endothelial cells to facilitate angiogenesis should be evaluated in future studies [291]. The integration of pilosebaceous units, with hair follicles and sebaceous glands in skin substitutes remains an unsolved challenge.

Skin tissue engineering has evolved from two dimensional supports to multifunctional complex systems, providing platforms for support, drug delivery, and the foundation for tissue regeneration. Limitations in current available products have led to developments in the use and applications of new materials and techniques. These advancements aim to optimize skin substitutes and ultimately improve patient quality of life.

7. Conclusion

Significant advancements have been made in burn injury management and research in the past decade, including developments in novel skin substitutes; application of new antimicrobial wound dressings and enhanced systemic drug delivery for wound infection; testing new pharmacological interventions and finding new targets for wound pain control; together with advanced surgical approaches such as laser therapy, fat grafting, skin grafting and coverage options. As a result, the survival rate of severe burn injury patients has been improved with significantly reduced hospital stay, resulting in decreased costs to patients and medical providers. However, several challenges still need to be solved to continue to improve current burn care. In particular, investigating how to accelerate wound healing, attenuate burn induced hypermetabolic-catabolic conditions, control systemic infection and reduce the overall time for functional recovery, should be prioritized. Further research will continue to optimize current treatment paradigms and identify novel targets in burn care to ultimately enhance the outcome for severe burn injury patients.

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