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Review

Advance in topical biomaterials and mechanisms for the intervention of pressure injury

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SUMMARY

Pressure injuries (PIs) are localized tissue damage resulting from prolonged compression or shear forces on the skin or underlying tissue, or both. Different stages of PIs share common features include intense oxidative stress, abnormal inflammatory response, cell death, and subdued tissue remodeling. Despite various clinical interventions, stage 1 or stage 2 PIs are hard to monitor for the changes of skin or identify from other disease, whereas stage 3 or stage 4 PIs are challenging to heal, painful, expensive to manage, and have a negative impact on quality of life. Here, we review the underlying pathogenesis and the current advances of biochemicals in PIs. We first discuss the crucial events involved in the pathogenesis of PIs and key biochemical pathways lead to wound delay. Then, we examine the recent progress of biomaterials-assisted wound prevention and healing and their prospects.

INTRODUCTION

Pressure injury (PI), also named pressure ulcer (PU) before 2016,[1] is defined as "localized damage to the skin and/or underlying tissue, as a result of pressure or pressure in combination with shear; PUs/PIs usually occur over a bony prominence but may also be related to a medical device or other object".[2] Prolonged or intense mechanical pressure on skin and soft tissue impairs internal tissue, ultimately producing distorted metabolisms and skin ulcers. Epidemiological data indicates that PIs occur across all health care settings and age groups, and particularly affect the elderly.[1,2] The most prevalent sites of PIs are sacrum, heel trochanter, and ischial tuberosity in adult patients, whereas it is occipitalia and auricle in children, which is mainly associated with medical device. Several different health conditions affect the tolerance of soft tissues to topical loading, such as chronic disease, microclimate, age, and malnutrition.[3] Individuals with limited mobility and impaired sensation are highly susceptible to PIs. Around 30% of spinal cord injured patients develop a PI during their acute and rehabilitation phases.[4] In intensive care units, 22–49% of critically ill patients are affected.[5] Despite ongoing research over the last decades, the prevention and treatment of PI are still tricky in the clinic, and the prevalence of PI has been unchanged primarily from 0.3 to 46%.[6,7] PIs can burden health care system because of increased pain and infection, impaired life quality, extended hospital stay and even rapid death, leading to additional costs.[8] The annual expenditure on treating PIs has been estimated at $26.8 billion.[9] About 60,000 patients die as a direct result of PIs per year in the US.[10] Aging population is driving the worldwide epidemic of chronic illness and disability accompanied by high care dependency, PI has become a worldwide health challenge.

Despite various establishments and implementation of the guideline for PIs, the current treatment of PI depends mainly on clinical experience or refers to other chronic wounds especially diabetic foot ulcers (DFUs).[11] Although PIs are deemed to have similar pathologies to DFUs, the effective therapeutics for PI patients are still a difficult problem to be solved at present. For example, once daily treatment of 100 μg/g becaplermin (a topical gel approved by FDA for DFUs) increased the incidence of complete healing of advanced stage PIs by 23% (23% vs. 0%),[12] which was 43% (50% versus 35%) in DFUs compared to placebo.[13] In addition, the Wound Healing Society proposed that ideal healing should come with sustained anatomical and functional integrity rather than just the acceleration of wound closure during the active treatment period.[14] In that case, some growth factors speeded PIs during the first 35 days but failed to reach statistical significance in the one-year follow-up phase.[15] The mechanism of PIs has peculiar elements that refer to more refined

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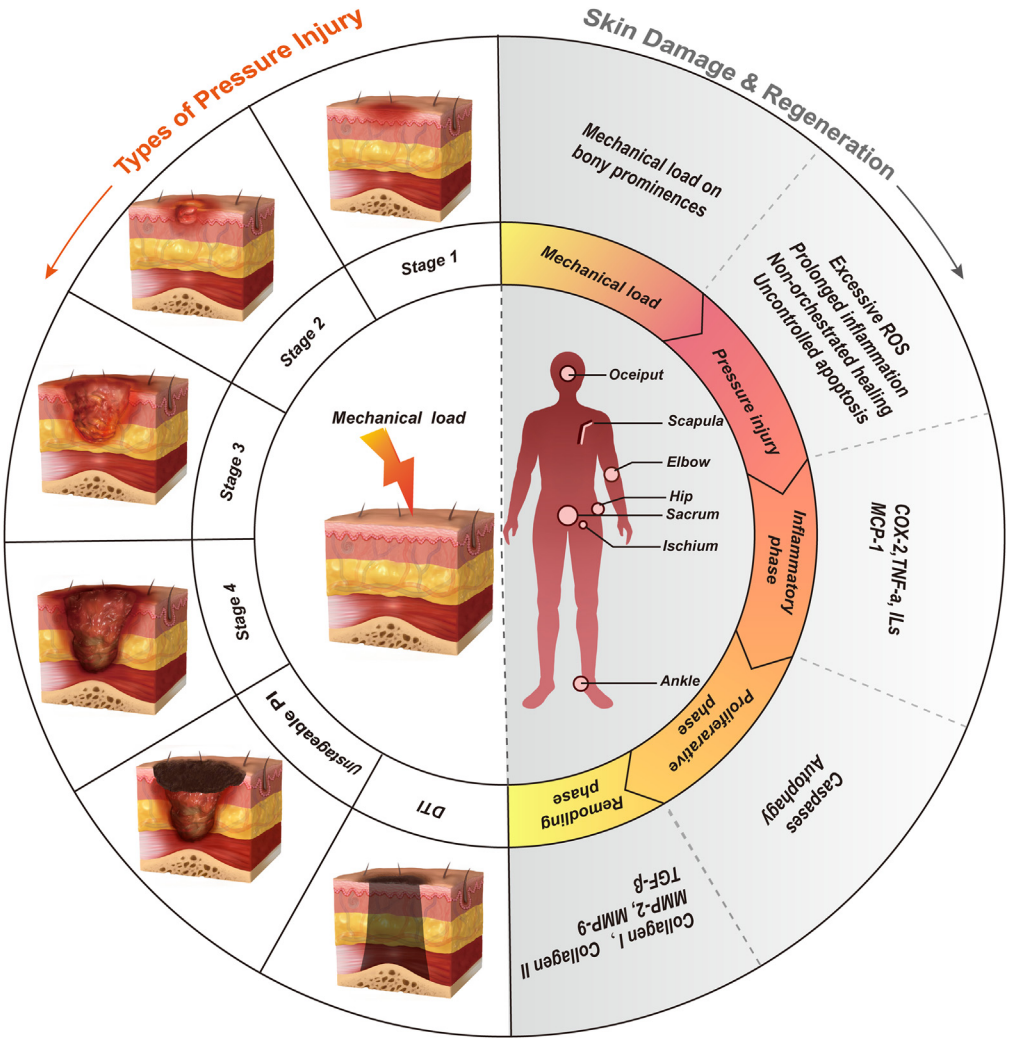

Figure 1. Stages of PIs and different endogenous factors involved in various stages of wound healing as well as in PI formations

intervention. Regarding PIs care limitations, further basic scientific research is still needed to delve into the molecular pathways involved.

Classification of pressure injuries

Currently, the widely adopted staging system is from National Pressure Ulcer Advisory Panel (NPUAP),[1] classifying PIs into six stages depending on the depth of pathophysiologic changes and skin discoloration (Figure 1).

Stage 1 PI belongs to the early stage. Local skin is intact with non-blanchable erythema, mainly injuring the epidermal layer.[16] Regarding that stage 1 PIs are primarily judged by the visual change in the skin, it will be difficult to detect if the patient has darkly pigmented skin. Besides, one of the most common locations is the sacrum, and stage 1 PI can be easily misdiagnosed as incontinence dermatitis, leading to different treatments, and affecting timely intervention. Once the prevention is delayed, the damage will invade deeper tissues and develop into stage 2 PI.

Stage 2 PI presents as a partial-thickness skin loss with dermal tissue exposed.[1] The ulcer remains superficial, appearing as an abrasion, blister, or shallow crater.[17] Without prompt treatment, it may progress to stage 3 and stage 4, subsequently requiring additional treatment and a longer time to heal. Thus, rapid intervention and fast healing is the focal point of treatment at this stage.

Stage 3 PI involves full-thickness skin. At this stage, mostly fat tissue is exposed in the wound bed, whereas muscle, tendon, ligament, cartilage, or bone are not involved. Although stage 3 PIs appear to only develop in areas with subcutaneous tissue, the updating guidelines do not agree with that.

Stage 4 PI aggravates by tissue loss with muscle, tendon, or bone exposed in the wound bed, often including undermining and tunneling. It is reported that in the lifetime of spinal cord injury (SCI) patients, up to 95% may develop advanced stages 3 or 4 PIs.[18]

Unstageable PI is characterized by slough (yellow, tan, gray, green, or brown) and/or eschar (tan, brown, or black), under which is extensive and full-thickness tissue damage in the wound bed,[1] making it difficult to verify the extent of tissue damage within the ulcer. Clinical examination often underestimates the degree of deep-tissue involvement, and its findings are inadequate for the detection of associated osteomyelitis.

Besides unstageable, deep tissue pressure injury (DTI) can also be difficult to diagnose. It can remain undetectable for days or weeks until a local purple or maroon discoloration develops with intact or non-intact skin. It has been suggested that DTI is a second way to develop severe PIs starting from the damaged muscle rather than the skin.[19] Subcutaneous tissue is injured earlier than it can observed visually, making the detection and prevention of DTI challenging. Histological analysis of DTI muscle tissues showed degeneration characteristics such as rounding-shaped myofibers, massive muscular necrosis, muscle fiber dissolution, and increased endomysium distance.[20–22] Thus, this deep injury eventually leads to the destruction of the superficial layers.

It should be noted that PI does not evolve sequentially following the numerical staging. That is, PIs do not always commence as stage 1 and then progress toward a higher stage. PIs can initiate from superficial or deep soft tissues. Similarly, the scale does not imply that repair necessarily progress from stage 4 to stage 1.

PATHOPHYSIOLOGY OF PRESSURE INJURIES

The formation of PIs is believed to be multifactorial. Among all hypotheses, ischemia-reperfusion (IR) injury, cell deformation, and cell death and lymphatic blockage are widely accepted and supported by laboratory evidence. In most cases, the onset of damage development is the result of the interaction of multiple factors.[23]

Ischemia-reperfusion injury

According to the IR hypothesis, excessive oxidative stress is the sole initiating factor resulting in PI. When the compressed tissue is released because of repositioning, reactive oxygen species (ROS) will injure cells following the restoration of blood flow, which further attracts immune cells to infiltrate and induce more ROS, thus aggravating the wound.[24,25] During the process, external load stimulates anti-oxidative defense to remove the oxidative species. Serum protein carbonylation is reported upregulated in PI patients, which is the result of secondary reaction of oxidative stress.[26] Li-ping Jiang et al. demonstrated that malondialdehyde (MDA), nitric oxide (NO), and endothelin-1 levels were significantly higher in the IR than in the control and ischemia groups.[27] Histological examination showed significant leukocyte infiltration and edema in epidermal which was a result of microvascular dysfunction. These two factors combined can induce "no-reflow phenomenon" happen, featured as failure to reestablish restorative local perfusion despite decompression and following reperfusion.[28] In addition, enzymatic antioxidants such as catalase (CAT), glutathione peroxidase (Gpx), and superoxide dismutase (SOD) were activated to help ROS clearance in the compressed area.[29] SODs dismutation is the primary defense against superoxide radicals, which convert superoxides to peroxides. CAT and Gpx further degrade the peroxides into non-toxic molecules. These enzymes are under the regulation of peroxisome proliferator-activated receptor gamma coactivator1-alpha. Previous studies using PI murine models have demonstrated ROS production in the compressed area correlated with skin necrosis, which consequently causes the accumulation of 8-hydroxy-20-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage.[30] The expression of 8-OHdG was found to persist for eight days after being released in epidermal and adipose tissue,[29] indicating that sequential injury induced by ROS is prolonged. When exposed to prolonged oxidative stress, excessive ROS eventually cause damage to lipids, proteins, and nucleic acid, leading to tissue injury.[31,32] This is supported by a study showing that serum MDA of patients with PIs significantly decreased, indicating that PIs patients

consumed antioxidants.[26] The imbalance of tissue redox balance will eventually result in delayed wound repair.

Cell deformation and cell death

Mechanical loading on the skin and deeper soft tissues are experienced as localized strain and stress, leading to regional tissue distortion and deformation. Normal skin tissues can withstand a pressure of around 30–32 mm Hg on the arterial side over a short period.[33] An analysis based on 980 medical cases indicated that high interface pressure over a short time (<2 h) or low pressure over a long period (>4 h) may result in PIs.[34] At the cellular level, mechanical deforms the cells at the stress-focusing sites, causing a sublethal stretch of the plasma membrane and subsequently membrane poration.[35,36] Within less than 1 h, the loss of membrane integrity disturbs cellular homeostasis, leading to cell death starting with apoptosis, followed by inflammatory damage triggered by apoptotic cells. It is reported that it is a process of tens of minutes, which is much faster than ischemic damage that takes hours.[37] This injury mechanism is more common in the process of DTI. One reason is that an external pressure of 50 mm Hg may rise to over 200 mm Hg at a bony prominence which is usually at the muscle/bone interface.[38] Besides, skeletal muscle is particularly susceptible to compressive loading, where a denser capillary network was found,[39] which means greater metabolic demand and lower tolerance for lateral mechanical compression compared with skin. Hypoxia-inducible factor 1 (HIF-1α) can be activated in response to the hypoxia environment.[40] Several studies revealed higher density of HIF-1α positive cells in fat and muscle cells, suggesting more severe hypoxic conditions in subcutaneous tissue[41,42] These results supported that skeletal muscle change its metabolism from aerobic to anaerobic.

Parco M. Siu et al. demonstrated that apoptosis was triggered in the compressed muscle tissue under 6 h-ischemia, which is in the early stage of DTI,[43] when there is still no visual change in the skin. During the process, pro-apoptotic proteins such as Bax, cysteine-containing aspartate proteolytic enzyme (caspase) $^{3}/_{8}$/9,[44] and anti-apoptotic factor B lymphoma-2 (Bcl-2) were activated.[43] Z-Val-Ala-DL-Aspfluoromethylketone (a caspase inhibitor)-treated rats displayed normal muscular structure with an angular shape and tight arrangement under prolonged compression, owing to the effects of negating activation of pro-apoptotic regulators including Bax, p53, and endonuclease G.[21] Similarly, the muscle-specific ablation of Bax also helps maintain muscle structural integrity and reduces muscular death under mechanical load.[45] Significantly, Bax-mediated apoptosis is a prerequisite for pressure-induced inflammation in muscle.[45] In addition, endoplasmic reticulum (ER) stress was also reportedly involved.[20,46] PI muscle displayed mitochondrial swelling and vascular degeneration under transmission electron microscopy.[46] C/EBP homologous protein (CHOP) was significantly elevated in C2C12 myoblast cells suffering oxygen-glucose deprivation and reoxygenation.[46] The decrease in Akt phosphorylation was found to contribute to increased activities of ER stress-related protein glucose-regulated protein 78 (GRP78), CHOP, and caspase-12.[20]

Besides apoptosis, the over-activation of autophagy also contributes to cell death in PI. At first, autophagy is activated to adapt to mechanical stimulation, and proper autophagy is essential to maintain muscular survival.[47] Autophagosomes increased in muscle tissues of deep PI patients compared with normal muscle.[46] Beclin1 and autophagy-related protein 5, autophagic markers for induction and formation of a pre-autophagosome structure, with microtubule-associated protein light chain 3 (LC3) II, were significantly increased. Whereas P62 (an autophagy protein receptor), a substrate that drives LC3 and ubiquitinated proteins to degradation during autophagy, was enormously decreased in PI muscle.[45,46] Compression led to Bcl-2 and Beclin-1 dissociation, although their abundances remained unchanged.[45] Bjorn T. Tam et al. demonstrated the myoprotective effects of ablation of Bax against mechanical compression conferred by the Akt-mTOR pathway, which alleviated autophagic cell death.[45] Their study showed that the LC3-II to LC3-I ratio and the LC3-II and total LC3 abundance increased after compression.

Lymphatic blockage

Aberrant mechanical loading compress blood and lymphatic vessels, which might cause the failure of lymphatic drainage.[48] It has been reported impaired lymphatic clearance at an interface pressure between 60 mmHg (8 kPa) and 75 mmHg (10 kPa) based on a canine model.[49] The authors conducted another study and noted the recovery of lymphatic clearance following 30 min of 75 mmHg occlusive pressure and post-occlusive pressure is not a linear correlation. The postocclusive clearance was moderate at 0 mmHg, maximal at 30 mmHg, and virtually zero at 45 mmHg.[50] They also demonstrated that the recovery time required is at least 1 h. A study done on healthy volunteers reported that it takes at least 40 min to return

to normal in healthy volunteers following compression (60 mmHg for 40 min).[51] Considering that the average pressures of bony prominences in different lying positions were all above 60 mmHg.[52] More clinical research is needed to explore the effect of higher pressure on recovery time and lymphatic clearance rate. Recently, Kasuya et al. reported that lymphatic ducts are more susceptible to ROS-induced cell damage compared with blood vessels.[53] Lower activity of SOD in lymphatic endothelial cells (LEC) was found than vascular endothelial cells (VEC) when under IR mimic *in vitro* system.[53] Lymphatic vessels serve as a crucial part of the immune system, responsible to remove waste metabolites and toxic bacterial substances, and carry extracellular fluid from interstitial space back to the circulation.[54] Hence lymphatic dysfunction will inevitably result in the accumulation of those factors which exacerbate inflammation and cell death.[55] Besides, elevated extravascular tissue pressure caused by interstitial edema formation leads to additional cell deformation.[56] When the stepwise increase of interstitial pressure reaches a certain level that in turn obstructs the vasculature itself, the ischemic cascades induce a higher level of damage, where the poor blood perfusion into the affected tissues aggravates hypoxia and ischemia. These three main contributors, namely cell deformation, inflammatory edema, and IR damage are therefore activated sequentially and worsen the situation of tissues altogether, with a combined effect.[56,57] Although the difference between post-occlusive pressure remains unclear, it may be associated with ROS damage.

ABERRATIONS IN A PRESSURE INJURY HEALING PROCESS

Wound healing is a highly regulated and complex process, which involves four continuous and spatiotemporal overlapping stages: hemostasis, inflammation, proliferation, and remodeling.[58] Acute wounds heal in an orderly and timely fashion through all the phases. However, the repair of PIs is slower and different from that of acute wounds.

After an injury, platelets accumulate immediately at the sites of injury and release multiple growth factors, resulting in the formation of a hemostatic plug to halt bleeding.[59] During the following inflammation stage, vascular permeability is increased, allowing enzymes and immune cells to reach the wound site.[60] In the first three days, circulating neutrophils are the principal effector cells, then decline four days later and are replaced by macrophages. Neutrophils could produce more chemokines to continue neutrophil recruitment,[61] as well as ROS and antibacterial proteins to remove bacteria, damaged cells, and debris from the wound bed.[62] Of interest, Madeleine J. Gust et al. found up-regulation of neutrophils infiltrated in adipose tissue with inflammatory cytokines in the murine IR model compared with dermal tissue, suggesting that adipose is more susceptible to IR injury.[63] Several pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1-alpha (IL-1α) were rapidly secreted upon sustained epidermal loading, even though the EpiDerm$^{@}$ cultures (an *in vitro* model of human epidermis) were subjected to a relatively low pressure of 75 mmHg with slightly microscopic damage.[64] It is recently confirmed that upregulated leucine-rich repeat-containing protein 19 in the compressed epidermis promotes infiltration of neutrophils and macrophages through the nuclear factor kappa-light-chain-enhancer of activated B (NF-κB) pathway.[65] Thus, although it appears visually unchanged, the histological examination showed dermal edema and infiltrating cells in the IR area immediately after release,[66] even with compression for only 1 h [43]

Although the circulating monocytes originating from bone marrow, are attracted to the wound by several chemoattractants such as monocyte chemotactic protein-1 (MCP-1) and transforming growth factor β (TGF-β).[67] This has been proven by cutaneous IR injury MCP-1$^{-/-}$ mice, which represented reduced infiltrating macrophages rather than neutrophils during and following IR cycles.[68] Once inside, the monocytes differentiate into diverse macrophages in response to the microenvironment.[69] Macrophages exhibit a marked heterogeneity.[70] Two main macrophage subtypes are extensively studied: M1, the classically activated state and M2, the alternatively activated state. Interferon gamma (IFNγ), TNF-α and Milk fat globule-EGF factor 8 could activate macrophages toward inflammatory phenotype (M1) with similar functions as neutrophils,[68,70] secreting more ROS, IL-1, IL-6, TNF-α, matrix metalloproteinase (MMP)-2 and MMP-9.[71] When exposed to prolonged oxidative stress, excessive ROS eventually cause damage to lipids, proteins, and nucleic acid, leading to tissue injury.[31,32] The expression of 8-OHdG (a sensitive biomarker of oxidative DNA damage) was found to persist for eight days after release in epidermal and adipose tissue,[29] indicating prolonged sequential injury induced by ROS. Although the serum MDA (antioxidant system markers) of patients with PI were significantly decreased compared with healthy controls, showed greater consumption antioxidants in PI patients.[26] Several molecules have been confirmed involved in the downstream transduction of oxidative load such as nuclear factor erythroid-2–related factor-2 (Nrf2), heme oxygenase-1 (HO-1), and NADPH oxidase 2.[29,72,73] Based on that, apelin, hydrogen gas, dimethyl fumarate and botulinum toxin B

were validated to reduce hypoxia area and accelerated wound closure against oxidative stress.[29,72–74] In addition, under the influence of ROS, immune cells such as macrophages can continuously produce high amounts of inflammatory cytokines to sustain inflammatory responses and impede healing process. The cytotoxic ROS level is responsible for the generation of iNOS, which promotes the production of COX-2 and contributes to chronic inflammation in PI mice.[30,75] The fact that the levels of IL-1β and TNF-α in the wound edge,[76] and myeloperoxidase (MPO) levels in wound exudate of full-thickness loss PI patients are elevated also suggests robust inflammatory responses in PIs wound.[77]

Generally, during the resolution of inflammation, interleukin (IL)-4, IL13 glucocorticoids stimulate M2 polarization of macrophages,[78,79] which then secrete high levels of IL-10 and or transforming growth factor β (TGF-β), serving as "stop signals" to restrain inflammation leading to transition to the proliferative phase.[80] However, PIs exhibit a derangement of the inflammatory and anti-inflammatory cytokines. It had been reported that the upregulation of IL-10 was relatively low compared with that of inflammatory cytokines in the subcutaneous tissue following 4h-loading.[66] Thus, the M1/M2 macrophage imbalance combined with factors mentioned above making PIs remain in a pathological inflammatory stage. Application of phosphatidylserine-containing liposomes on the first day after wound attenuated macrophage infiltration and, more importantly, induced M1 to M2 polarization during inflammation phase (days 4) to promote wound healing on PI in young and middle-aged mice, indicating that targeting macrophages can be a potential strategy for overcoming failed wound repair.[81] Of note, only a proper switch favors wound care. Given that M1 function to clear out debris and foreign materials, the time point of controlling M2 activation is critical.

At the same time, during the initial 2–3 days post-injury, the growth factors such as fibroblast growth factor (FGF) produced by macrophages recruit fibroblasts and endothelial cells to proliferate and migrate into the wound site.[67] Part of fibroblasts further differentiate into myofibroblasts, which then produce new and disorganized collagen III to support other cells ingrowth.[82] Proliferative fibroblasts, endothelial cells, new blood capillaries, and fibrin interact to form granulation tissue filling the wound defect. Collagen deposition in PI skin was revealed to be much less than in acute wound or normal skin by Trichrome staining,[76] making keratinocyte and fibroblast hard to infiltrate from wound edge to center. Although growth factors are critical for wound healing, the wound centers of PIs are deficient in growth factor such as basic fibroblast growth factor (bFGF), platelet-rich growth factor (PDGF), vascular endothelial growth factor (VEGF) and TGF-β compared with that in acute wounds.[76,83,84] Of greater importance, levels of receptors such as VEGF receptor 2 and FGF receptor 1 were also decreased compared with acute wound,[76] leading to impaired GF effects in cell proliferation, migration and angiogenesis. Indeed, excessive apoptosis were detected in wounded tissue,[76,85] which may be related to the decreased level of phosphorylation Akt.[86,87] In addition, PIs wound also exhibited angiogenic dysfunction,[77] which contributes to the poor healing response of PIs. Despite that, administration of bFGF or autologous PRGF combined with a wound dressing exhibited accelerated wound healing.[15,88,89]

As wound healing progresses, fibroblasts undergo apoptosis with macrophages, keratinocytes and myofibroblasts, whereas collagen is deposited and collagen type III is gradually replaced with collagen type I.[90] Collagen synthetic rate reaches peak levels three weeks after injury and starts to decline thereafter and maintains balanced with its degradation rate. Matrix metalloproteinases (MMPs) secreted from fibroblasts, neutrophils, and macrophages mediate collagen degradation. Elevated levels of MMPs, particularly MMP-9, MMP-2, MMP-8, both in serum, tissue, and wound exudates of PIs patients were reported.[91–93] The ratio of MMP-9 and tissue inhibitor of metalloproteinase 1 (TIMP-1) in wound exudates is positively related to the severity of PI.[93] The ratio decreases gradually as the wound is healed, suggesting that the MMP-9/TIMP-1 ratio can be a predictive biomarker. Meanwhile, high expression of MMP-2 in compressed skin was found to be positively associated with inflammatory factor TNF-α and the reduction of collagen IV.[94] As one of the main components of ECM, loss of collagen reduces ECM deposition. The pathways involved in the pathogenesis of PI are shown below (Figure 2).

NEW BIOMATERIALS IN THE PREVENTION AND TREATMENT OF PIS

Topical dressings, especially silicone foam dressing, are strongly recommended for prevention according to the current clinical practice guidelines.[1] Mostly the commercial dressings for prevention are mutilayered to reduce the incidence of PI formation via alleviating the local pressure.[95] However, the use of dressing varied depending on personal experience, and the effects cannot be quantified. Even same kinds of dressing from different manufacturers could result in different changes in skin temperature and the profile of IL-1α.[96]

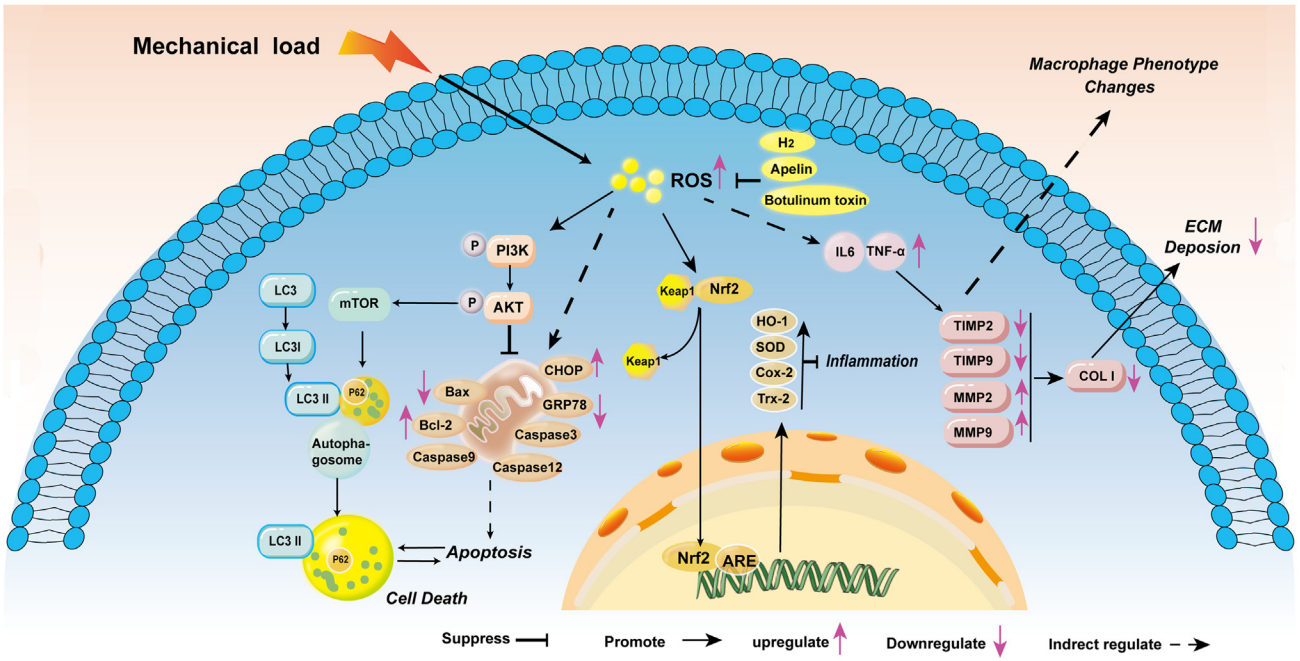

Figure 2. Schematic diagram of intracellular signal transduction pathways related to pressure injury

Various stimuli *in vivo* and *in vitro* will result in elevated oxidative stress, inflammation, apoptosis and autophagy, decreased ECM deposition, which contribute to protective response dysregulation and impaired wound healing.

Stage 2 PIs with an average wound size of 5.14 cm^2 healed (complete re-epithelialization) on an average of 22.9 days[97] Although most stage 3 or 4 PIs have become hard-healing wounds with a significant amount of necrotic tissue. Clinicians and researchers often try to accelerate wound closure through granulation formation. Compared with traditional gauze dressings, advanced wound dressings have become a preferred solution and have been widely utilized to absorb wound drainage, reduce pressure, or release antimicrobial silver ions into the wound bed. In addition, modern wound dressings could provide a moisture microenvironment for the wound to promote the formation of capillaries, collagen deposition, epithelization, as well as the dissolution of necrotic tissue and fibrin,[98] which comply with the wet healing theory. However, it takes quite a long time to achieve wound closure in advanced stage PIs. Previous research has indicated that the wound closure in stage 3 and 4 PIs with an average wound surface area of 4.1 cm^2 treated with standard and moisture-retentive dressings took around 151 days, which healed by a rate of 0.25 cm^2 per week.[99] Although surgical intervention contributes to faster healing, there is still around six weeks of bed rest required,[100] and remains a high recurrence rate.[101] A 20-year review study involving 598 SCI patients reported a recurrence rate of 33% at the same site during a 2 months to 3 years follow-up period, with average 136.6 in-hospital days per person.[102] Therefore, it is desirable to develop more effective biomaterial scaffolds in terms of reduced treatment costs and reduced patient morbidity.

Biomaterials for timely assessment

Although pressure ulcers can develop in 24 h, they may not present until a week later.[103] Identifying the early stage of PIs is vital for prompt intervention and prevention of irreversible skin damage. Braden scale is the most widely used to assess and predict the early stage of PI.[104] However, Braden scale was found not associated with the occurrence of PIs in ICU adult patients.[105] In fact, the Braden scale contains six subscales evaluating potential risk factors, but still lacks other specific risk factors of PIs, making risk assessment scales high sensitivity but low specificity for identification of PIs in adult ICU or surgical patients.[106] Besides, regarding the subjectivity of nurses, especially the level of knowledge about PI, the accuracy of risk score is unavoidable and a problem.

For that, several research groups try to identify objective markers reflecting PIs status. It was reported that subepidermal moisture (measured by a subepidermal moisture scanner) and wound temperature

(measured by infrared thermography) might be potential indicators of tissue damage before changes become visible.[16,107] Although there was a significant difference of subepidermal moisture in stage 1 PI.[16] Patients with edema and high-level cervical injury showed similar patterns.[108] Thus, it put forward higher requirements on clinical differential identification. IL-1α/TP-ratio increased following pressure and shear force on the skin.[109] In addition, a transient elevated circulating level of pro-inflammatory factor interferon-γ-induced protein of 10kd in spinal cord injury patients with PIs was observed, compared with their controls.[110] The results indicating inflammatory factors may be able to characterize early PI require a larger sample size to confirm it. Although ultrasonographic image and magnetic resonance elastography also help the early detection of DTI,[111,112] these technologies are limited as time-consuming and costly to be workable assessments.

Despite various methods to assess PI, manual repositioning is still the fundamental and preferred prevention strategy to redistribute pressure. Although it is recommended by the guidelines of NPUAP, 2-hourly repositioning may induce some negative impacts (distortion of sleep and hemodynamic instability). More importantly, there is little empirical evidence to support the effectiveness of repositioning at 2–3 or 4-h intervals.[8] Because different individual has different healthcare setting, patient-tailored systematic repositioning is needed. Weiwang Qiu et al. prepared a 3D hydrogel with Al^{3+} embedded, thus endowing the hydrogel with great conductivity property, serving as a strain sensor in monitoring the variations of pressure on the wounds.[113] The analog-to-digital convertor was used for digital signal processing to convert the change in pressure into digital. It is reasonable to assume that once the pressure of the target sites exceeds the set threshold range, the monitor will trigger an alarm and send out a turning request to the healthcare workers. In addition, PAIL hydrogel based on imidazolium-based ionic liquids endows PAIL with hydrogel excellent pressure sensitivity, reaching 9.19 kPa^{-1}.[114] Hence, the PAIL hydrogels exhibited extremely high sensitive sensing performance at low-pressure stress, which allowed monitoring even slight movement of palsy patients. Xinmeng Liu et al. further developed organosilicon nanoparticles-contained zwitterionic hydrogel (CH-OSNP) as a smart skin sensor (Figure 3).[115] This skin dressing exhibited continuous real-time monitoring of the pressure, temperature, exudate, swelling, and infection of PI under persistent stress stimuli. This property could indicate the biochemical changes of early PI (stage 1 or stage 2 PI) which has the potential for PI prevention. As discussed above, excessive production of ROS can change the microenvironment of wound site by expanding blood vessels, increasing capillary permeability and recruiting inflammatory cells. The skin temperature has been confirmed to increase by 1–2°C during PI formation.[116] However, the studies above focused on absolute temperature change which may be affected by room or body temperature. Recently, relative temperature between a high PI risk position and a remote region (at least 10 cm away) has been proposed to monitor the process of PI.[107] Skin relative temperature less than −0.1°C in the sacral area indicating a high risk of PIs.[107] Regarding that, the biomaterials should be designed to cover more skin surface or enable at least two independent dressings to deliver diagnostic messages in an easy way.

Drug delivery system

Taking ointments or antibiotics is one of the common treatments for PI.[11] Many potent biologic agents were found effective in wound healing. But most of them are fragile and/or susceptible to various *in vivo* conditions. Numerous promising drug delivery systems based on biomaterials are developed to enhance drug therapeutic efficacy in PI treatment owing to their capability of sustaining drug release and preventing therapeutic agent degradation.

Controlled-release wound healing formulations are highly efficient in promoting the stability and bioavailability of sensitive drugs such as growth factors.[117] It has been demonstrated that bFGF can accelerate wound healing in PI animal studies.[86,118] bFGF has been marketed and used for wound healing applications.[119] But because of its low stability *in vivo*, recombinant bFGF solution has to be topically applied on the wound surface once or twice a day.[120,121] Besides, once injected, bFGF in soluble forms can rapidly diffuse away from the injection site, causing undesirable side effects. Therefore, it is imperative to develop an applicable system to stabilize growth factors to enhance the clinical efficacy. A PI patient treated with collagen/gelatin hydrogel impregnated with bFGF displayed significant epithelization after 14 days[122] Wei Jiang et al. designed a gelatin sponge dressing containing bFGF-loaded gelatin microspheres which could continuously release bFGF for seven days and significantly accelerated wound healing rate compared with control groups.[123] A shape-memorable methacrylated gelatin cryogel incorporated with endothelial progenitor cells (EPCs) and acid fibroblast growth factor

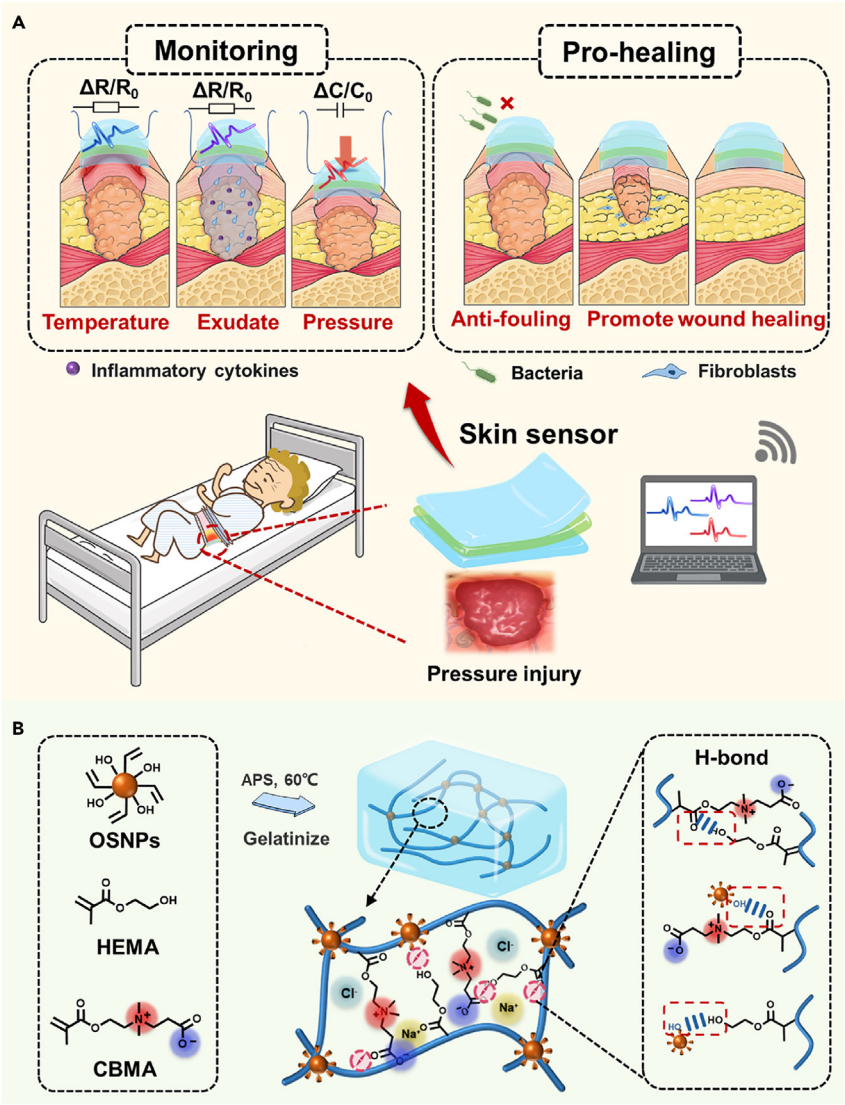

Figure 3. Design of CH-OSNP skin sensor.[115]

(A) The CH-OSNP skin sensor for real-time monitoring and pro-healing of PI.

(B) Synthesis procedures of pressure-resistant CH-OSNP skin sensor based on multiple H-bond interactions. Copyright 2023, Elsevier.

(aFGF) (EPCs/aFGF@GelMA) was also applied in a mouse PI model.[124] According to *in vitro* results, this cryogel provided a steady release of aFGF for six days. In PI mice, EPCs/aFGF@GelMA promoted epithelialization compared to free EPCs/aFGF. Among biomaterials, Chitosan (CS) is a promising candidate for preventing protein agents' degradation. Park et al. applied abFGF-loaded chitosan scaffold in an aged mouse PI model.[125] Chitosan inhibited elastase activity, which contributes to the degradation of bFGF, thus remaining higher and functional bFGF level compared with conventional dressing. This bFGF-loaded chitosan scaffold showed a capillary density when used to treat PI created on the backs of mice. Chitosan also acted as the base material for hydrogels to protect LL-37 peptide activity.[126] This chitosan hydrogel was injected deep into the wound induced by pressure. Findings indicated that LL-37-loaded CS hydrogel induced HIF-1α, which then upregulated pro-angiogenic growth factor VEGF-A expression to promote angiogenesis of wounds. Calcium-releasing particle has been found to stimulate endothelial progenitor cell and mesenchymal stromal cells.[127] Soledad et al. further examined the use of poly (lactic acid) (PLA) fiber matrices loaded with calcium-releasing nanoparticles (SG5) (PLA-SG5) to increase the vascularization of PI.[128]

Apart from macromolecule drugs such as growth factor and peptide, extracellular vesicle (e.g., exosomes) is another promising drug to be loaded. Exosomes (Exos) derived from human umbilical cord mesenchymal stem cells (hucMSC) or human embryonic stem cells (ESC) accelerated wound healing through different pathways. *In vitro* experiment demonstrated that hucMSC-Exos could be taken up by fibroblasts.[129] The animal study also showed improved collagen organization and revascularization after hucMSC-Exos treatment. ESC-Exos behaved differently that rejuvenated senescent endothelial senescence by an Nrf2-dependent manner which was owing to the restoration of Nrf2 downstream genes that act as antioxidants.[130] Because mRNA levels of VEGF and bFGF growth factor receptor 1 (KDR and FGFR1, respectively) in the wound center and margin of advanced stage PI patients were dramatically decreased compared with normal skin or acute wound.[76] Activation fibroblast and endothelial cells or restoring cells' function may be a more effective way than external supplication of growth factors. Besides that, deliver fibroblast is another choice. Kuroyanagi et al. used a dermal substitute by plating fibroblasts on spongy collagen and treated 145 patients with various wounds including 5 PI patients.[131] It was reported to have a 100% coverage in PI patients. Considering that active fibroblasts are the mainly resource of ECMs, biomaterials combined with fibroblasts benefit the treatment of deeper wounds.

Although various topical advanced dressings have been developed for chronic open PI wounds, dressings on the market are mostly for superficial or open skin wounds. When it comes to some special stages of PIs especially DTI and unstageable PI, which is injured deep beneath the intact skin or covered with eschar, drugs that are applied for local action need to scatter into the target site instead of on the surface of the skin. Transdermal drug delivery systems have been developed for drugs with low solubility and penetration. Liu et al. developed (lactic-*co*-glycolic acid) (PLGA) nanoparticles to encapsulate Tazarotene (Ta), a receptor-selective topical tretinoin with identified protective effects of vascularization and tissue regeneration as well as limitations in low skin penetration and rapid metabolism.[132] They found that the particle size is a key factor in the skin penetrating efficiency for nanoparticles. As PLGA particle sizes with 200 nm have been reported effectively in drug delivery to wounds[133] and smaller size nanoparticles enable enhanced penetration ability.[134] The authors then precisely controlled diameters around 149.2 nm, which was small enough to pass through the skin. They further tested this nanoparticle on a deep tissue injury mice model and found a 2-fold faster healing rate compared with mice treated with Ta on day 15 past injury. Similarly, the hydrophilic deferoxamine (DFO) with a molecular weight of 560 Da and low lipid solubility has difficulty in penetrating the hydrophobic epidermis. To solve that problem, Clark A et al. encapsulated DFO into nonionic surfactants and polymers, making DFO enclosed by nanoscale reverse-micelles to be constantly released.[135,136] After modification, DFO can be delivered into the deep dermis in excised full-thickness human skin. The research group further proved that transdermal DFO could accelerate and prevent PI in diabetic mice via improving neovascularization as an HIF-α stabilizer.[135] Given the hypoxic exposure in muscle, it will help to solve that problem if other system could deliver DFO to muscle tissue successfully. Overall, transdermal medication conveyance seems to be a less invasive, non-obtrusive, and effortless method for treating DTI and unstageable PI. Recently, it has been proved that microneedles are able to penetrate the dermis in a rabbit ear hypertrophic scar model.[137] However, a hypertrophic scar in rabbit model is 0.5–2 mm which may not be deep enough.[137] In addition, human skin is much thicker than the mouse or rat. Future research should consider improving the penetration property such as updating needle strength and stiffness.

Scaffold system

Considering that non-healing PIs exhibit impaired ECM deposition, which is central for cell migration and proliferation in the wound bed, developing a degradable regenerative scaffold system to provide a temporary platform to facilitate a more rapid cell migration from the wound margins into the center is a potential treatment. This is an essential step following debridement in stage 3, stage 4 and unstageable PIs. An ideal porous scaffold in skin tissue engineering should also allow cell infiltration and exchange of nutrient and oxygen.[138] However, for PIs treatment, it should possess the specific property to withstand mechanical force.[139] In fact, most biomaterials serve as scaffolds. Here we focus on several examples of which biomaterial designed for PI to illustrate how it promotes ECM reconstruction. Weiwang Qiu et al. encapsulated nanofiber yarns (NFY) network into the injectable hydrogel.[113] Although the hydrogel serves as a natural ECM to create an appropriate 3D microenvironment for cell growth and arrangement, the aligned NFY also helped to guide cellular elongation and alignment. This cell movement resembles the re-epithelialization process seen in superficial wound closure.[140] Vaibhav Sharma et al. fabricated a fibrin based dermal scaffold with an open and interconnected pore structure, which supported dermal fibroblasts proliferation and infiltration throughout the scaffolds.[141] To be noted, the scaffold also combined with silicone

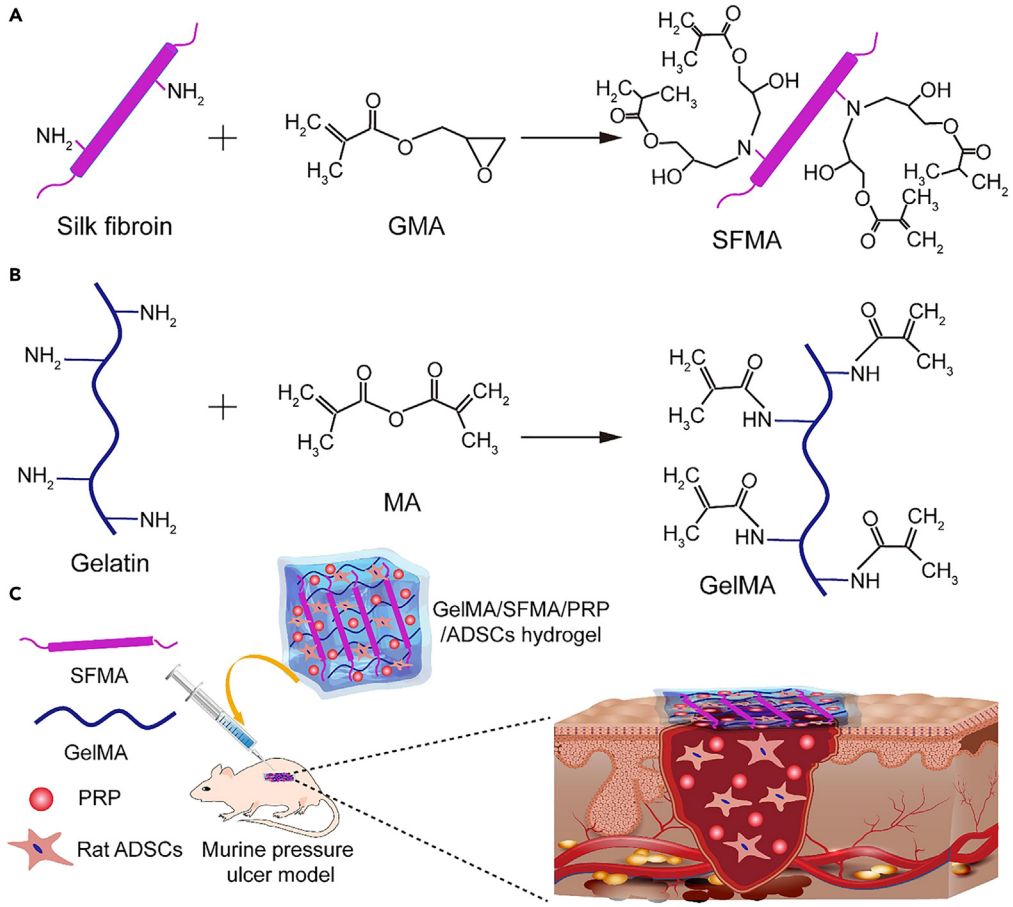

Figure 4. A high-strength hydrogel served as a promising multifunctional dressing for healing of pressure injuries

(A) Modification of SF molecule with glycidyl methacrylate (GMA).

(B) Modification of gelatin molecule with methacrylic acid (MA).

(C) ADSCs are encapsulated in GelMA/SFMA/PRP hydrogel and the hydrogel system is applied onto a murine pressure ulcer model.[142] Copyright 2023, Elsevier.

membrane to enhance the strength to against high pressure, which is common in PIs. Methacrylate gelatin (GelMA) is another ideal material to mimic the native ECM, though lacking mechanical strength. Kui Lu et al. doped methacrylated silk fibroin (SFMA) to construct a high-strength hydrogel (Figure 4).[142] The prepared hydrogels could support the proliferation of adipose-derived stem cells (ADSCs) loaded within the interior of hydrogels, prolonging the retention of ADSCs in the wound, thus improving PI wound. Sulfobetaine methacrylate hydrogels were also capable to accelerate collagen deposition and maturation (higher collagen I/III ratio) to treat PI wounds via the reduction of MMP-2 regulated by PI3K/Akt/mTOR axis.[143] There was another interesting finding that increased biomaterial (electrospun scaffolds) fiber and pore size could induce M2 macrophage conversion which contributes to fibroblast proliferation.[144] However, the authors detected cellular infiltration and VEGF release, which is one of factors that M2 macrophages produce, rather than the specific markers of M2 phenotype to confirm their hypothesis. In addition, the additive of chondroitin sulfate at a concentration ranging from 100 to 1000 μg/mL induced the production of ROS and proinflammatory cytokines.[145] The studies remind us that future work should pay more attention to the structure and material of porous scaffolds.

Functional wound dressings with anti-bacterial or other properties

The loss of skin barrier function may result in an increased risk of bacterial colonization, thereby disturbing the healing process. Pressure injuries are commonly infected by *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus*.[146] It is necessary to reduce the bacterial burden in wounds when treating

pressure ulcers. Chitosan is a natural macromolecule with inherent bacteriostatic ability and is widely used in wound treatment. Biomaterials composed of chitosan showed bacteriostatic activity.[147] A clinical study enrolled 90 chronic infected wound patients, six of which were PI. The healing rate of the group with chitosan was 43%, much higher than the control group (11.7%).[147] Zwitterionic materials were emerged as a new dressing for repelling bacteria, because of their strong hydration via ionic solvation.[148] The zwitterionic conductive hydrogels developed by Xinmeng Liu et al. showed a strong reduction (at least 90%) in bacterial adhesion compared to the commercial dressing Duoderm.[115] There are also different kinds of antimicrobial agents incorporated with hydrogels. Alginate and chitosan were mixed in poly (vinyl pyrrolidone) (PVP) hydrogel to improve its mechanical properties and biocompatibility, which were further loaded with 10 mM silver nitrate.[149] The authors noticed non-cytotoxicity and effective antibacterial capability against *E. coli*, VRE, *P. aeruginosa*, and *Staphylococcus epidermidis*. Ionic liquids are another type of cationic organic molecules that demonstrated excellent antibacterial effects against *E. coli*, *S. aureus* and *Candida albicans*, and fungi after being incorporated into acrylamide and polyvinyl alcohol (PVA).[114] The cationic group adheres to negative charges on the microbial cell membranes, whereas the alkyl chain inserts into the lipid bilayer, resulting in membrane rupture and subsequent cell death. The authors also noticed that the antibacterial property of alcohol/acrylamide-ionic liquid hydrogels depends on the length of alkyl chain of ionic liquids. Similarly, the addition of quaternary ammonium salt groups endowed the injectable hydrogel containing quaternized carboxymethyl chitosan with outstanding antibacterial ability against *S. aurens* and *E. coli*.[113] PVA hydrogels containing ciprofloxacin hydrochloride-loaded PLGA nanoparticles were also capable of treating infected PI wounds.[150]

In addition to bacteria itself, the aggregation of bacteria on the wound bed leads to the formation of bacterial biofilms. Some factors such as increased shear and pH could facilitate biofilms development.[151] When it comes to the irreversible attachment or colonization phase, gentle rinsing can only partially remove biofilms,[152] where the microbial cells inside developed increased resistance to antimicrobials.[153] Biofilms may also result in incomplete or slow penetration of anti-microbial agents.[153] To address that problem, microneedles have been applied because of the capability to easily break that barrier, contributing to deeper penetration of drugs.[154] However, the number of studies about the PIs microbiome is few.[155] Research on microbial profile at the various stages of PIs development may help to control bioburden.

Moreover, some biomaterials have immuno-regulatory activities. Chitooligosaccharide (COS), the degradation product of chitosan, can promote M2 macrophage polarization,[156] which is central for tissue remodeling.[81] Based on its immunomodulatory effects, Xiuhong Huang et al. developed the effect of composite material COS-Eu and applied it in PI mice model.[157] With the application of COS-Eu powder at the wound site, more expression of anti-inflammatory factor IL-10 was observed on day 3 and 7, which is in the inflammatory stage. In addition, as Eu emits red fluorescence, the complex was easy to achieve objectively and visually monitoring pH variation.

CONCLUSION AND OUTLOOK

Undergoing PI discomforts people with pain and prolongs their hospitalization time. To a certain extent, Current therapeutic strategies have served as guides to cure but still lack of topical treatments available to PI patients. Much scientific progress has been achieved in stimulating the understanding of the pathogenesis and molecular biomarkers of PIs in recent years. We still need to further explore the dynamic changes of the biomarkers to develop effective drugs targeting the signaling. In fact, pathophysiologic events responsible for different stages of PI are dominated by a peculiar combination of molecular signals. Agents focusing on single factor may achieve limited success in clinical trials. For instance, 5% dimethyl sulfoxide (DMSO) cream, a hydroxyl antioxidant, did not show preventative effects on stage 1 and stage 2 PI formation when put to the test in clinical trials.[158] One reason may probably be that DMSO is a relatively non-specific antioxidant. And antioxidant agents work in a concentration-dependent way. Additional studies are warranted to explore the multifaceted nature of the pathologic process in PIs. Apart from that, the proper concentration and timepoint to apply drugs is also crucial for wound healing. Hopefully, future research will determine reliable biomarkers and, more importantly, support innovation in the treatment of PIs.

Recently, a wide range of new materials for PIs is emerging. Biomaterials combined with small-molecule drugs as well as bioactive agents including proteins and peptides have emerged as a promising strategy for managing and promoting the healing of PIs. But we still have a long way to go to make the biomaterials applied in the clinic in the end. The tricky problems in skin regeneration involve highly variable wound

characteristics. The dynamic healing process requires different drugs in order. In addition, the wound patterns in patients vary dramatically. Therefore, the property of biomaterials should consider the location, size of the wound, wound bed tissue type, and exudate amount. This proposed some requirements for further development of new materials. Considering the complicated microenvironment of PI wounds, topical biomaterial should be smart and highly sensitive to the changes of several biochemical markers such as local pressure, temperature, pH, and ROS to assess more accurately for different stages of PIs, as well as wound phases. The property of identifying microenvironmental changes is essential for adaptive response to skin injury. Based on that, biomaterials loaded with single or multiple drugs can deliver the specific one in a spatiotemporal manner. There is another requirement that wound dressing should be easy to apply and dispose. As dressing is usually a kind of conventional treatment, which was treated more often at home or nursing home than in a hospital. As for the test of new biomaterials in clinical trials, it is necessary to track the complete wound closure time and percentage, wound rate, and recurrence rate with multicenter and large sample size to give robust evidence to guide the clinical. Last, we should expect to develop effective and adaptive wound dressings based on the unique pathological changes of PI and achieve customized treatment ultimately.

Limitations of the study

Significant work has been done in the understanding of the pathophysiology of PIs as well as the development of preparation strategies and the application of biomaterials for PIs. However, most current findings are based on animal or *in vitro* studies with limited pre-clinical or clinical reports. Regarding more complicated wound environment in patients, biomaterials against different stages and statuses of PIs remain to be fully explored. In addition, spatiotemporal dynamic modification of the wound environment needs to be considered.

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AUTHOR CONTRIBUTIONS

Conceptualization: Y.L., H.L., D.Y., and Y.P. Investigation, interpretation, and compilation: M.Z., L.H., and Y.W. Visualization: M.Z., J.P., and D.Y. Supervision: H.L. and Y.L. Writing-Original Draft: D.Y. and Y.P. Writing-Review and Editing: H.L., D.Y., and Y.P.

DECLARATION OF INTERESTS

The authors declare no competing interests.

INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

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