Current advances in modern wound healing

Under normal circumstances, wounds are expected to heal within a reasonable period of time through a series of a regulated cascade of events. However, when the cascade becomes interrupted, wounds fail to heal in a timely manner, resulting in chronic non-healing wounds (ulcers). Over the years, a variety of measures have been attempted in the treatment of non-healing wounds, including a range of different dressing products, drugs and devices. However, not all wounds respond to the above modalities of treatment and, consequently, non-healing, refractory wounds continue to be a significant burden in the hospital as well as the community.

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Recent advances in molecular biology, nanotechnology and functional genomics, coupled with an increased understanding of the pathophysiology of chronic wounds have resulted in the development of novel therapies such as tissue engineered substitutes and growth factors. In addition, promising developments in the areas of stem cells and gene therapy have given rise to new hope in modulating non-healing wounds. This article discusses some of the aetiological factors of non-healing wounds, the essential scientific aspects, the current treatment options and the potential future advances in the management of chronic wounds.

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A systematic approach to research, a multiprofessional approach to management and a willingness to consider the patient's perspective are some of the important changes that have paralleled technological advances and expertise, which, as ever, have been the prime drivers of progress.

Acute wound healing, triggered by tissue injury, comprises a complex systemic cascade of events that includes inflammation, neovascularisation, collagen synthesis, granulation tissue formation, epithelialisation and wound remodelling (Clark, 1996). Normally, wounds are expected to heal within a reasonable period of time that ranges from about 7–14 days. However, when the above cascade becomes interrupted at any of the stages of the healing process, the wounds will fail to heal in a timely manner, resulting in chronic non-healing wounds (Lazarus et al, 1994). A chronic wound may be defined as one that has not adequately re-epithelialised within 6–8 weeks (Enoch and Price, 2004). Although a variety of measures have been attempted in the treatment of non-healing wounds, some wounds are refractory to all forms of treatment and result in chronic wounds.

Scientific enquiry into the many aspects of chronic wound healing is far from complete, and, consequently, the knowledge base is continually being enriched by input from clinicians and researchers. A systematic approach to research, a multiprofessional approach to management and a willingness to consider the patient's perspective are some of the important changes that have paralleled technological advances and expertise, which, as ever, have been the prime drivers of progress. In addition to providing an overview of the different types of common ulcers and types of wounds healing, this article discusses some of the recent developments in the management of chronic wounds and the potential future advances.

Common types of chronic wounds

Common types of chronic wounds arise from one of the following aetiologies: venous, arterial, neuropathic or pressure. The other important causes include malignancy,

Table 1
Important characteristics of some common types of ulcers

Type of ulcer	Aetiology	Site	Salient features
Venous	›› Incompetent valves in perforating veins ›› Venous hypertension ›› May be secondary to DVT and/or varicose veins	›› Medial gaiter area of the leg	›› May be painful; particularly if long-standing and with atrophie blanche ›› Usually shallow ›› Irregular, sloping edges ›› Characterised by pigmentation in the surrounding skin
Arterial	›› Tissue hypoxia and damage secondary to arterial insufficiency ›› Atherosclerosis	›› Dorsum of foot, toes, heel and bony prominences of foot	›› Painful ›› Punched out appearance ›› The affected limb may be painful, cool to touch and hairless ›› The skin may be dusky, thin and shiny ›› Nail(s) may be brittle or lost in the affected limb
Neuropathic	›› Diabetes, spinal cord injury, peripheral nerve injury	›› Usually on plantar surface of the foot under the metatarsal heads or toes	›› Painless ›› Surrounding calluses ›› Warm limb; good peripheral pulses ›› Surrounding skin may be dry and fissured due to decreased sweating
Pressure	›› Tissue compression between a bony prominence and an external force	›› Most develop on the lower half of the torso with heel ulceration becoming the most common	›› Painful or painless ›› Surrounding skin may appear inflamed or blistered ›› May go very deep extending to bone

drug-induced ulcers and vasculitis. Some of the salient features of the common types of ulcers are shown in *Table 1*.

How do normal wounds heal?

Normal wounds heal by a systemic cascade of events that includes four overlapping, but regulated phases (*Table 2*).

Types of wound healing

The salient features of the four recognised types of wound healing are summarised in *Table 3*.

With great strides in technological innovations and increased understanding of the pathophysiology of wound healing, various devices (physical modalities) have been developed to aid the management of chronic wounds.

Why don't some wounds heal?

Some wounds fail to follow the regulated cascade of events, as happens in acute wound healing, and thus become recalcitrant or chronic wounds. In most chronic wounds, the healing process seems to be halted during the inflammatory or proliferative phases (Lazarus et al, 1994). Disturbance in the action and balance between components such as growth factors, cellular and extracellular elements contribute towards a non-healing wound (*Table 4*). Additionally, accumulation of necrotic tissue or slough promotes colonisation of bacteria, which prevents complete repair of the wound. Finally, condition-specific factors, such as peripheral oedema in sustained venous hypertension, ischaemia in peripheral vascular disease or neuropathy in diabetes, as well as intake of certain drugs (e.g. non-steroidal anti-inflammatories and steroids), smoking, poor dietary intake and malnutrition also contribute to impaired healing (*Table 5*) (Edmonds and Foster, 2006; Grey et al, 2006a).

Conventional management of difficult-to-heal wounds

There are some established treatment modalities in the treatment of difficult-to-heal wounds (Humpherys et al, 2007). Some of the commonly used management options for such wounds are shown in *Table 6*.

Current advances/novel therapies

With great strides in technological innovations and increased understanding of the pathophysiology of wound healing, various devices (physical modalities) have been developed to aid the management of chronic wounds.

Intermittent pneumatic compression (IPC)

Intermittent pneumatic compression (IPC) is effective for managing chronic venous ulcers with severe oedema that are resistant to simple compression therapy (Enoch et al, 2006a). A compression pressure of 20–120mmHg is provided at preset intervals to improve venous and lymphatic flow. It is generally used two hours a day for up to six weeks.

Table 2
Phases of acute wound healing

Stages	Time after injury	Cell type	Important features
Haemostasis	Immediate	Coagulation cascade, platelets and inflammatory mediators	Loss of structural integrity triggers the coagulation cascade and constriction of the vessels, which further limits blood loss Major initial stimulation for inflammation
Inflammatory phase	24–72 hours	Neutrophils and macrophages	Neutrophils phagocytose bacteria and other foreign particles. Macrophages transformed from monocytes appear to act as the key regular cell for repair and stimulate fibroblast division, collagen synthesis and angiogenesis
Neuropathic	3 days–2 weeks	Fibroblasts	Fibroblast migration, extracellular matrix deposition, formation of granulation tissue and epithelisation Fibrin/fibronectin matrix will be replaced by the newly formed granulation tissue
Remodelling and scar maturation	1 week–several weeks	Fibroblasts Myofibroblasts Extracellular matrix and collagen Balance between MMP and TIMP profiles	Further development of granulation tissue Reorganisation of collagen Protease activity

This method is ideal for patients with limited mobility, and should be used as an additional therapy to simple compression, not as a substitute (Enoch et al, 2006a).

Topical negative pressure therapy (TNPT)

The wound is compartmentalised by an airtight seal around it. Through a dressing interface the compartment is connected to an external suction apparatus creating a negative pressure to allow removal of excess fluid (Kumar et al, 2004).

TNPT improves local dermal perfusion, promotes angiogenesis, stimulates granulation tissue, decreases interstitial fluid control, wound exudate and bacterial load (Enoch et al, 2006a). These effects have clinically translated into faster healing rates of wounds (Wong et al, 2010). Problems with this method include pain, fluid loss, especially in large wounds, and risk of bleeding. It is contraindicated in patients with frail, thin or easily bruised skin, and in those with neoplasms forming part of the wound floor (Hurd et al, 2010).

Hyperbaric oxygen

Hyperbaric oxygen may be a useful adjunct in the management of non-healing wounds. As most non-healing tissues are hypoxic, 100% oxygen given in a pressurised chamber may hasten the healing process (Thackham et al, 2008). A systematic review (Wang et al, 2003) on the use of hyperbaric oxygen in wounds identified six controlled trials involving diabetic ulcers and chronic non-healing wounds showing positive results. However, its use is restricted as special equipment and expertise is required.

Biosurgery

The use of sterile maggots, also known as biosurgery, has a selective technique of slough and necrotic tissue digestion from wounds without damaging the surrounding healthy tissue (Kumar et al, 2004). Along with its antimicrobial effect, biosurgery is best suited for wounds with slough and infection. It is cost-effective and tolerance is excellent (Wollina et al, 2002). Apart from the presence of fistulas and the proximity of the wound to major blood vessels or vital organs, there appear to be no contraindications. Limitations are the lack of aesthetic appeal, short shelf-life of maggots and increased pain at the wound site which is found in some patients.

Others

Other non-surgical methods include; laser therapy, hydrotherapy, electrotherapy, psoralen combined with ultraviolet A (PUVA) therapy, radiant heat dressing and ultrasound therapy (Enoch et al, 2006a). However, to date, limited evidence is available to prove their effectiveness.

Drugs

Some drug therapy has been proven to aid healing of chronic ulcers (D'Hemecourt et al, 1998; Falanga et al, 1999). They are all based on the concept of increasing peripheral blood flow to the wound area through vasodilation. Drugs of this type include calcium antagonists such as diltiazem and nifedipine, glyceryl trinitrate, Iloprost and pentoxifylline (Falanga et al, 1999).

Table 3
Types of wound healing

Type of wound healing	Features
Primary wound healing	›› Ideal, seen in wounds such as clean surgical incisions ›› Wound edges closed directly by mechanical means such as sutures, glue, tapes or staples
Delayed primary wound healing	›› Ideal in contaminated wounds such as animal and human bites ›› Wound is left open for a few days and closed later
Secondary wound healing	›› Preferred in large cavity wounds in difficult anatomical positions where closure is not feasible, such as in grade 3 or 4 sacral pressure ulcers ›› After appropriate debridement and control of infection, the wound is left open to heal by contraction
Healing by epithelialisation	›› Found in wounds caused by split-thickness skin graft, superficial burns and abrasions ›› As only the superficial layer of skin is involved, the 'new' skin will retain all the normal characteristics ›› Scarring is minimal

Table 4
Important molecular and cellular changes in chronic wounds

1. Molecular changes
›› Increased activity of collagenases (MMP — 1, 8 & 13), gelatinases A (MMP 2) and B (MMP 9), stromelysins — MMP 3, 10 and 11, and serine proteases (Cathepsin G, neutrophil elastase)
›› Decreased activity of TIMPs, a1- protease inhibitor and a2 – macroglobulin
›› Increased degradation of fibronectin, vitronectin and tenascin
2. Cellular changes
›› Reduced mitotic activity
›› Impaired keratinocyte migration
›› Altered fibroblast phenotype
›› Decreased fibroblast proliferation and migration
›› Decreased response of fibroblasts to growth factors
›› Presence of increased proportion of senescent cells

Medicated paste and bandages are also available for the management of infected wounds. These include; iodine-based preparations, silver-releasing agents, zinc, phenytoin and vitamin A (Enoch et al, 2006a), along with systemic oral antibiotics depending on the extent of infection.

Simple pain is treated with appropriate analgesia based on the World Health Organization (WHO) analgesic ladder (6. www.who.int/cancer/palliative/painladder/en/). Neuropathic pain may need certain tricyclic antidepressants such as amitriptyline, or antiepileptic drugs such as gabapentin.

Natural products

Natural products include honey, yoghurt, tea tree oil and potato peeling, which have been used in various parts of the world to treat chronic wounds (Enoch et al, 2006a). However, evidence of success is lacking.

Tissue engineered skin substitutes

A variety of skin substitutes are now available to treat non-healing wounds and burns (Bello and Phillips, 2000; Hrabchak et al, 2006). Some of the characteristics and indications for using the recently developed products are highlighted in *Table 7*. Despite the availability of a fairly large range of products, randomised controlled trials (RCTs) are currently limited and there is little evidence to justify their use. Furthermore, the cost-effectiveness of their usage has not been well established.

Growth factors

Normal wound healing is dependent on a range of growth factors and cytokines that interact with cells and the matrix at different stages (Brown et al, 1991; Barrientos et al, 2008). Use of growth factors produced by recombinant DNA technology increase the wound's capacity to heal by causing cells to grow and attract new cells to the wound (Barrientos et al, 2008). Growth factors are designed to target the individual phases of wound healing (*Table 8*). They should ideally be resistant to rapid degradation from the proteolytic environment of the wounds and their release has to be sustained. Platelet derived growth factor-BB (PDGF-BB) is the only growth factor that has currently been approved in the treatment of chronic ulcers (Barrientos et al, 2008), although others such as vascular endothelial growth factor (VEGF),

Table 5
Local and systemic factors that impede wound healing

Local
Inadequate blood supply
Poor venous drainage
Presence of foreign body and foreign body reactions
Continued presence of microorganisms
Sustained wound infection (sub-acute)
Excess local mobility
Underlying osteomyelitis
Malignant transformation (Marjolin's ulcer)
Systemic
General malnutrition
Deficiency of protein, vitamin (particularly A and C) and/or trace elements such as zinc
Peripheral vascular disease and vasculitis
Venous oedema or lymphoedema
Neuropathy secondary to congenital or acquired spinal cord pathology, leprosy (Hansen's disease)
Systemic diseases such as diabetes mellitus, rheumatoid arthritis, connective tissue diseases and metabolic diseases
Systemic malignancy and terminal illness
Chemotherapy and whole body radiation
Immunosuppressant drugs and corticosteroids
Advancing age and immobility
Obesity
Anticoagulants
Marfan's syndrome
Inherited neutrophil disorders such as leucocyte adhesion deficiency
Impaired macrophage activity (malacoplakia)

basic fibroblast growth factor (bFGF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) have shown some promising initial results (Daniele et al, 1979; Greenhalgh and Rieman, 1994; Smiell et al, 1999; Robson et al, 2000; Tsang et al, 2003).

Future advances

Stem cell therapy

Stem cells have been identified in various tissues including bone marrow, blood, muscle and cartilage. Although embryonic stem cells and induced pluripotent stem cells are theoretically highly beneficial, there are considerable limitations to their use. In addition to the strong ethical disagreements, studies have shown that they yield a low number of harvesting cells and bone marrow biopsies can be painful (Mizuno, 2009). Therefore, stem cells from adults have been the subject of targeted clinical research (Charruyer, 2009). Adult stem cells are multipotent cells with the ability to renew themselves and to differentiate into a diverse range of specialised cell types such as fibroblasts, endothelial cells and keratinocytes (Hanson et al, 2010). Early reports from case series on the application of bone marrow-derived cells on the chronic wound were promising (Badavias and Falanga, 2003; Dash et al, 2009), but further research is necessary. Another study by Wu et al (2007) showed bone marrow-derived mesenchymal stem cells to demonstrate the beneficial effect in cutaneous regeneration and wound healing in non-diabetic and diabetic mice through differentiation and paracrine effects.

Recent studies have looked at the potential of skeletal muscle (Kumar et al, 2004; Jackson et al, 2010) and adipose-derived stem cells. They are found to be capable of equally differentiating into cells and tissues of mesodermal origin compared to bone marrow-derived mesenchymal stem cells. Since fat can be obtained (harvested) relatively easily in most people, adipose-derived stem cells have become the ideal large-scale source in practical regenerative medicine. They have an advantage over other stem cell sources, as they have neither ethical nor immunoreactive considerations, as long as they are of autologous tissue origin. Additionally, adipose tissue can be obtained under local anaesthetic with minimal patient discomfort (Mizuno, 2009). Adipose-derived stems cells have been found to accelerate wound healing and exhibit antioxidant effects under various experimental conditions (Kim, 2009). The wound-healing and antioxidant effects are mainly regulated by the activation of dermal fibroblasts and keratinocytes via the paracrine mechanism. Administration of allogeneic adipose-derived stem cells may provide an alternative source for mesenchymal tissue regeneration and engineering.

Gene therapy

Gene therapy aims for the provision

Key points

- Tissue-engineered skin substitutes and other biological wound manipulations are seldom effective in sloughy and exudative wounds with unhealthy wound beds.
- The novel treatment modalities and biological-based therapies should complement rather than replace the tenets of good, basic wound care.
- Cutaneous wound healing is a multi-step process requiring the collaboration and coordination of many different cell types and molecules.
- Given the multiple molecular mechanisms involved, it is unlikely that any one single mediator or growth factor will be successful in accelerating healing.
- Identification of the cellular and molecular dysfunction in individual wounds and targeting or supplementing them is one of the goals for the future.

Table 6
Commonly used management options for difficult-to-heal wounds

Type of ulcer	Conservative	Indication for surgery	Surgical procedure
Venous	▸▸ Compression therapy remains the mainstay. Examples include compression stockings, hosiery, Unna's boots, elastic wraps, medicated bandages, orthotic compression devices and pneumatic compression pumps ▸▸ Appropriate moisturising of surrounding skin, control of exudate and eczema, and treat infection	▸▸ Pure superficial venous incompetence either of the long or short saphenous system	▸▸ Ligation and stripping of superficial veins or subfascial interruption of perforating veins ▸▸ Sclerotherapy ▸▸ Endovenous ligation ▸▸ Skin grafting for large ulcers after treating the underlying cause
Arterial	▸▸ Control of any underlying diabetes, hypertension and hypercholesterolaemia ▸▸ Smoking cessation and regular exercise	▸▸ Non-healing ulcer(s), disabling claudication, rest pain and gangrene	▸▸ Revascularisation surgery such as bypass grafting or stenting to restore blood supply to the affected limb ▸▸ Amputation of the affected digit or part of the limb (e.g. below knee) may be indicated in recalcitrant wounds +/- severe rest pain +/- ongoing local infection +/- sepsis
Diabetic	▸▸ Good glycaemic (diabetic) control ▸▸ Appropriate foot wear ▸▸ Assess vascular status regularly ▸▸ Treat infections promptly	▸▸ Non-healing ulcers and gangrene ▸▸ Local or systemic infection	▸▸ Wound debridement ▸▸ Amputation of the affected digit or part of the limb (e.g. below knee) may be indicated in recalcitrant wounds +/- ongoing local infection +/- sepsis
Pressure	▸▸ Pressure relief ▸▸ Regular repositioning of patient ▸▸ Support surfaces such as air-fluidised mattresses ▸▸ Regular skin inspection ▸▸ Optimise nutritional status	▸▸ Non-healing ulcers and gangrene ▸▸ Local or systemic infection	▸▸ Wound debridement ▸▸ Osteotomy/removal of affected bone ▸▸ Reconstructive surgery (e.g. flap coverage) to provide tissue over affected bony prominence

of specific genes to the target cell(s) to enhance, amend or negate the biological function of the cell(s) and its inherent genetic coding (Branski et al, 2009). Genes, once incorporated in the cell, affect the cell and its environment by changing the way their products (e.g. proteins) are expressed. In the context of wound healing, these are growth factors, receptors, adhesion molecules and inhibitors of proteases (Branski et al, 2009).

Classical gene therapy involves incorporating the gene into cells to directly influence the wound by its product of expression. Genes can be delivered by different methods — the important ones being biological (viral vectors), physical (e.g. microinjection), and chemical (e.g. cationic liposomes).

Another method for sustained delivery of genes to the wound environment called gene activated matrix (GAM) therapy is also being considered (Chandler et al, 2000). This involves embedding genes onto a matrix, which remains in the wound increasing the length of exposure of target cells to the genes. Transfer could be established *in vivo* (the gene being delivered to the cells in the wound directly), or *in vitro* (gene transfer is achieved outside the wound environment in a selected population of cells that are then transplanted into the wound). Once in the wound environment, externally applied substances may also control the genes through specific mechanisms called genetic switches.

Genes may be employed to augment an effect (e.g. promote healing). These include genes for growth factors and their receptors. Alternatively, they may be used to inhibit an effect (e.g. suppress excessive scarring). These include genes for antibodies against specific growth factors. Gene therapy as applied to wound healing is currently

Table 7
Tissue engineered substitutes in wound healing

Product	Content and description	Uses/advantages	Disadvantages
Epicel® (Genzyme Biosurgery), (Laserskin *	Cultured epidermal autograft (sheet)	Permanent coverage for superficial and partial-thickness burns	Two–three-week lag period between biopsy and obtaining epidermis; lacks dermal component
Integra †	Two-layered skin substitute comprising biodegradable matrix and bovine collagen, and outer silicone layer	Immediate permanent coverage for surgically excised full-thickness burns; reconstructive surgery	Requires healthy and non-infected wound base; in burns, autograft is needed after 3–4 weeks for epithelial cover
AlloDerm® † (LifeCell)	Processed human cadaver skin with a cellular dermal matrix and intact basement membrane	Intended to permanently cover full-thickness burns and deep ulcers; reconstructive surgery	In burns, may necessitate removal after 2–3 weeks; autograft is needed for epithelial cover; not suitable for infected wounds
Biobrane® † (LifeCell)	Porcine dermal collagen bonded to semipermeable silicone membrane	To cover extensive partial-thickness burns and donor sites	Temporary; not suitable for infected burn wounds
TransCyte® ‡ (Smith and Nephew and Advanced Tissue Services)	Allogenic human fibroblasts cultured on nylon mesh coated with porcine collagen	To cover surgically excised full-thickness burns and non-excised partial-thickness burns	Temporary (may need skin grafting after 2–3 weeks); not suitable for infected wounds and patients allergic to porcine collagen
Dermagraft® ‡ (Advanced BioHealing)	Allogenic human fibroblasts cultured on bioabsorbable scaffold	Non-healing diabetic foot ulcers and venous leg ulcers	Not for infected wounds or ulcers with sinus tracts
Apligraf® § (Organogenesis)	Allogenic cultured skin containing keratinocytes, fibroblasts, and bovine collagen	Non-healing diabetic foot ulcers and venous leg ulcers	Not for infected wounds or patients allergic to bovine collagen
OrCel® § (Forticell Bioscience)	Allogenic cultured skin containing keratinocytes, fibroblasts, and bovine collagen	Acute and chronic deep dermal ulcers, partial-thickness burns and donor site wounds	Not for infected wounds or patients allergic to bovine collagen

* Epidermal; † Dermal, accellular; ‡ Dermal, cellular; § Composite. Adapted from Enoch et al, 2006

in its primitive stages (Charruyer and Ghadially, 2009).

A study using porcine has shown accelerated dermal and epidermal regeneration, as well as graft adhesion rates by using liposomal PDGF-complementary DNA (cDNA) gene transfer (Branski et al, 2010).

Currently, trials are also underway (Enoch et al, 2006b) exploring the use of PDGF, VEGF and fibroblast growth factor (FGF) genes in diabetic foot and venous ulcers. Future developments may include using multiple genes concurrently (e.g. genes for growth factors and their receptors), along with genetic switches to fine-tune the gene expression.

Despite novel treatment modalities and the optimism anticipated from advances in gene and stem cell research, good basic wound care... should remain an integral component in treating chronic wounds.

Conclusion

Cutaneous wound healing is a multi-step process requiring the collaboration and coordination of many different cell types and molecules such as growth factors, cytokines and proteases. Thus, given the multiple molecular mechanisms involved, it is unlikely that any one single mediator, molecule or gene will be successful in accelerating healing. However, identifying cellular and molecular dysfunction in individual wounds and targeting or supplementing them is certainly a realistic option in selected wounds.

Table 8
Growth factors involved in wound healing

Growth factor	Major source	Wound-healing related function
VEGF	Plateles, Neutrophils	›› Stimulates angiogenesis in granulation tissue ›› Stimulates collateral blood vessel formation in peripheral vascular disease
FGFs	Fibroblasts, endothelial cells, smooth muscle cells and macrophages; also brain and pituitary	›› Fibroblast and epithelial cell proliferation; matrix deposition; wound contraction; angiogenesis ›› Accelerates granulation tissue formation
KGFs	Fibroblasts	›› Proliferation and migration of keratinocytes
EGF	Platelets, macrophages, keratinocytes; also saliva, urine, milk and plasma	›› Keratinocyte differentiation, proliferation, migration and adhesion ›› Granulation tissue formation
PDGF	Platelets, fibroblasts, macrophages, endothelial cells	›› Mitogenic for smooth muscle cells, endothelial cells and fibroblasts ›› Chemoattractant for neutrophils and fibroblasts ›› Fibroblast proliferation and collagen metabolism
G-CSF	Monocytes, fibroblasts, lymphocytes	›› Stimulates production of neutrophils ›› Enhances neutrophil and monocyte function ›› Promotes keratinocyte proliferation
GM-CSF	Keratinocytes, macrophages, lymphocytes, and fibroblasts	›› Mediates epidermal cell proliferation
TGF-a	Activated macrophages, platelets, epithelial cells	›› Stimulates epithelial cell and fibroblast proliferation ›› Granulation tissue formation
TGF-ß	Platelets, macrophages, fibroblasts, neutrophils, keratinocytes	›› Mitogenic for fibroblasts and smooth muscle cells ›› Chemotactic for macrophages ›› Stimulates angiogenesis (indirect) and collagen metabolism
IL-1	Macrophages, lymphocytes, many other tissues and cells	›› Neutrophil chemotaxis ›› Fibroblast proliferation
TNF	Macrophages, mast cells, T-lymphocytes	›› Fibroblast proliferation
IGF-1	Fibroblasts, plasma, liver	›› Fibroblast proliferation ›› Stimulates synthesis of sulphated proteoglycans and collagen
HGF	Fibroblasts, keratinocytes, endothelial cells, tumour cells	›› Re-epithelialisation ›› Neovascularisation ›› Granulation tissue formation

Abbreviations: VEGF, vascular endothelial growth factor; FGFs, fibroblast growth factors; EGF, epidermal growth factor; KGFs, keratinocyte growth factors; TGF-a, transforming growth factor a; TGF-ß, transforming growth factor-ß; IL-1, interleukin-1; TNF, tumour necrosis factor; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte macrophage colony stimulating factor; PDGF, platelet-derived growth factor

Despite novel treatment modalities and the optimism anticipated from advances in gene and stem cell research, good basic wound care consisting of adequate wound debridement, exudate management, rest, skin care and control of infection (along with specific modalities such as compression therapy for venous ulcers, pressure relief in pressure ulcers and increasing vascularity to the limb in arterial ulcers) should remain an integral component in treating chronic wounds. WUK

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