Wound inflammation and the role of a multifunctional polymeric dressing

Temporary inflammation is a normal response in acute wound healing. However, in chronic wounds, the inflammatory phase is dysfunctional in nature. This results in delayed healing, and causes further problems such as increased pain, odour and high levels of exudate production. It is important to choose a dressing that addresses all of these factors while meeting the patient’s needs. Multifunctional polymeric membrane dressings (e.g. PolyMem®, Ferris) can help to simplify this choice and assist healthcare professionals in chronic wound care. The unique actions of PolyMem® have been proven to reduce and prevent inflammation, swelling, bruising and pain to promote rapid healing, working in the deep tissues beneath the skin[1,2].

The mechanism of acute wound healing is a well-described complex cellular interaction[3] that can be divided into several integrated processes: haemostasis, inflammation, proliferation, epithelialisation and tissue remodeling. Inflammation is a key component of acute wound healing, clearing damaged extracellular matrix, cells and debris from zones of tissue damage. This is normally a time-limited orchestrated process. Successful progression of the inflammatory phase allows healing to enter the proliferative phase, where cellular ingrowth and the formation of a new extracellular matrix progresses the wound towards healing.

Inflammation describes a localised physical condition where the affected part of the body becomes reddened, swollen, hot and often painful. This reaction is a biological response to impending damage, in which the objective is to counter harmful stimuli and initiate the healing process.

One of the underlying mechanisms responsible for the failure of wounds to heal is an out-of-control inflammatory response that is self-sustaining[4]. Persistent wound inflammation is a recognised and damaging feature of the chronic wound environment and is frequently associated with wound ischaemia and infection. Together these factors are the major cause of non- or delayed wound healing.

Inflammation and tissue repair

To understand the role of inflammation in tissue repair, it is important to differentiate between acute and chronic inflammatory responses.

Acute wound inflammation
Two components constitute acute inflammation — the vascular and cellular stages. During vascular response, immediately on injury there is an initial transient vasoconstriction that can be measured in seconds. This is promptly followed by vasodilation under the influence of histamine and nitric oxide (NO) that cause an inflow of blood. An increase in vascular permeability promotes leakage of serous fluid (protein-rich exudate) into the extravascular compartment, which in turn increases the concentration of cells and clotting factors. The resulting stagnation of flow and blood clotting assists in limiting the spread of microbes that may have entered the site of injury[5].

In cellular response, when platelets (thrombocytes) come into contact with exposed collagen in the vessel wall, a platelet plug is formed (haemostasis). This process heralds the inflammatory response that typifies the body’s reaction to injury. Platelet adhesion and aggregation then follow, and the platelets and neutrophils trapped within the clot initiate a coagulation cascade and send signalling molecules to attract a variety of cells to the site of injury[6,7].

Through a process of chemotaxis, the recruitment of leucocytes signals activation of host defence systems. With the appearance of monocytes and tissue macrophages approximately 48 hours post-injury, the neutrophils phagocytose bacteria and cell debris using three stages: recognition and adherence, engulfment and intracellular killing[8,9]. Intracellular killing is accomplished through production of a number of endogenous oxidising agents, including hydrogen peroxide, hypochlorous...
acid and NO. Other inflammatory mediators (e.g., histamine) give rise to the four cardinal signs of inflammation: erythema, swelling (tissue oedema), heat and pain.

The pain experienced is also a consequence of increased pressure in the tissues and expression of bradykinin (vasodilation, vascular permeability, release of NO and increase in prostaglandins) and leukotrienes. The production of leukotrienes, synthesised by leucocytes, is associated with expression of histamine and prostaglandins. Prostaglandins enhance the action of histamine and sensitise neurones to noxious stimuli.

Two important pro-inflammatory cytokines (proteins that have a specific effect on interactions and communications between cells) are tumour necrosis factor-α (TNF-α) and interleukin 1 (IL-1). Both TNF-α and IL-1 cause endothelial cells to express adhesion molecules and release other cytokines and reactive oxygen species (ROS), otherwise known as free radicals, which are antimicrobial in action but can also be harmful to mammalian cells.

NO and ROS have multiple roles in inflammation and regulation of immune responses. NO relaxes smooth muscle and antagonises leukocyte and platelet adhesion to the vascular wall and regulates leucocyte recruitment. ROS are oxygen-containing molecules, which are released from neutrophils during normal metabolic activity or in phagocytic metabolic burst.

Proteases (proteins that lyse other proteins) are present in the acute wound where the matrix metalloproteases (MMPs) and the serine proteases, e.g. elastase, predominate. Some level of MMP expression is found in any repair or remodelling process, or where there is diseased or inflamed tissue. During early inflammation, monocytes, activated by platelet-derived growth factor and transforming growth factor-β, express proteases. These proteases assist in the removal of damaged extracellular matrix, wound cleansing and cleaving a path for angiogenic incursion. A major function is to regulate the balance between tissue synthesis and tissue degradation. MMP activity is balanced by the expression of tissue inhibitors of metalloproteases (TIMPs), ensuring that level and duration of MMP activity is kept in check.

Until recently, inflammation has been considered a passive process that resolves as the pro-inflammatory mediator signals subside. Catabasis (Greek κατα βαίνω) describes a guided process of returning to a non-inflammatory state through mediators such as resolvins, protectins and lipoxins. The fulcrum of the inflammatory process and its resolution pivots on neutrophils, which have a life of just 8–20 hours, as they are removed by scavenging macrophages (apoptosis). Controlled inflammation as seen in the acute wound is a regulated phase of the healing process where cells, in response to infection or trauma, attempt to neutralise the cause of the event and then repair the tissue damage. These effector cells are then removed as part of the resolution process. For successful wound healing, the inflammatory response must be ‘switched off’ and moved into the resolution phase – a prolonged or excessive inflammatory phase causes tissue damage and delays healing.

Chronic wound inflammation
In chronic wounds, the inflammatory phase is dysfunctional in nature. Unregulated proteolytic activity is driven by expression of pro-inflammatory cytokines that, in turn, down-regulates expression of TIMPS and the denaturing of growth factors.

Chronic wounds are those that do not heal within an expected timeframe and have not responded to ‘standard’ care practices. The factors that are responsible for delayed healing are listed in Table 1. According to Moore, a chronic wound is characterised by an out-of-control inflammatory response that is self-sustaining and results in the formation of an aberrant extracellular matrix.

This describes what is happening ‘under the surface’, where a persistent state of inflammation with high levels of pro-inflammatory cytokines, proteases and neutrophils are the result of a dependent host-centred pathological process. More recent work suggests that biofilm may be responsible for this persistent inflammatory state. Although skin has evolved several defence mechanisms such as acidic pH, a high salt content, or the synthesis of antimicrobial peptides, these are impaired as soon as skin integrity is disrupted. The longer wound healing is delayed, the more likely it becomes that contamination will proceed to colonisation and subsequently result in wound infection. All chronic wounds are polymicrobial. The main bacterial species found are the aerobes Staphylococcus aureus, Pseudomonas aeruginosa, and Proteus mirabilis, as well as the anaerobes Bacteroides, Propionibacterium, and Clostridium species.

It is easy to acknowledge that bacteria play an important role in driving chronic inflammation and chronic wounds, but how do bacteria and host interact? During wounding, microbes enter the body, forming the ‘wound microbiota’. In the case of normal wound healing, bacterial contamination is resolved rapidly, skin integrity is re-established and cells return to a physiological state. In chronic wounds, the combination of necrotic tissue and low oxygen content promotes
the proliferation of bacteria\textsuperscript{[18]}. Moreover, the effects of wound microbiota seem to be more aggressive, and decreased pathogen exclusion is observed, as well as a reduced epithelial ROS production\textsuperscript{[18]}. The bacteria present interfere with cell-matrix interactions. Leukocyte numbers are increased in chronic wounds but they show a diminished phagocytosis, chemotaxis and bactericidal activity – for example, in diabetic foot ulcers\textsuperscript{[19]}. Toll-like receptors, which act as ‘damage signals’ to alert the body to injury, are activated; this further induces inflammation by stimulation of myofibroblasts to produce chemokines and cytokines such as interleukin 8, which is chemotactic for neutrophils\textsuperscript{[18]}. As such, the maintenance of leukocytes and myofibroblasts in a heightened state of activity by microorganisms has detrimental effects on wound healing. In addition, there is the issue of biofilm formation: in 60% of biopsies from chronic wounds, biofilms could be identified by electron microscopy, while only 6% of acute wounds exhibited biofilm features\textsuperscript{[20]}. Moreover, the microbe’s ability for biofilm formation could be correlated to illness duration and chronicity\textsuperscript{[21]}. The consequences of a mature biofilm are severe, as bacteria are closely located to each other and surrounded by a self-produced matrix, which protects the microbes from the immune system and antibiotics, as well as topical antiseptic treatments\textsuperscript{[22]}. Quorum-sensing molecules that govern bacteria interactions may further affect host cells\textsuperscript{[16]}, and bacterial toxins play a key role in delayed healing by stimulation of inflammatory mediators and induction of MMPs\textsuperscript{[23]}. **Significance of chronic wound inflammation** As well as being associated with delayed wound healing, a persistent inflammatory response is a

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**Table 1. Factors delaying wound healing (adapted from Percival and Dowd, 2010).**

<table>
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<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>Microbial numbers/pathogenicity/virulence/synergy</td>
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<tr>
<td>Granulation tissue haemorrhagic/friable</td>
</tr>
<tr>
<td>Inflammatory mediators</td>
</tr>
<tr>
<td>Inactivated state of neutrophils</td>
</tr>
<tr>
<td>Bacterial and human proteases</td>
</tr>
<tr>
<td>Tissue hypoxia</td>
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<tr>
<td>Metabolic wastes</td>
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<td>Reduced fibroblasts number/collagen production</td>
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**Figure 1. Summary of the effects of different wound microbiota on the cellular inflammatory processes leading to wound healing or the formation of a chronic wound (adapted from Scales & Huffnagle, 2013).**
major cause of wound pain, odour and high levels of exudate production. These external signs of persistent wound inflammation impact not only on patient health-related quality of life but also result in increased healthcare costs; wounds with high levels of inflammatory markers often require more frequent dressing changes with higher-cost dressing products for prolonged periods of time.

Effective wound management requires regular reassessment, as wound status may vary over time with fluctuating levels of inflammation, bacterial load and ischaemia. These changes may reflect a reaction to persistent or re-accumulating debris and slough in or on the wound bed, and indicate the need for an ongoing programme of maintenance debridement. Regular careful wound observation is necessary to detect these changes if appropriate, and timely modifications to treatment should be applied. Failure to effectively evaluate wound progress may allow undetected wound deterioration and inappropriate treatment, with periwound skin damage (e.g. maceration) due to the destructive nature of chronic wound exudate generated during the persistent inflammatory process.

Do dressings have a role in reducing inflammation?
The role of dressings in managing inflammation and its associated symptoms is recognised. The use of PolyMem® dressings in clinical practice resulted in unexpected findings; anecdotal evidence showed that inflammation, swelling, bruising and pain were reduced with use of the dressings, which instigated a controlled animal study to investigate these effects. The study found that the polymeric membrane dressing was effective in preventing the development of pain, bruising, swelling and inflammation in the deep tissues beneath the skin. This effect was found even when the dressing was applied to intact skin.

Reductions in pain were also noted. A further independent study, investigating the antinociceptive effects of polymeric membrane dressing, found that pain levels were significantly reduced with use of the dressing. In addition to the anticipated antinociceptive properties, the PolyMem® dressing also showed an unexpected analgesic effect.

A clinical study evaluated the use of PolyMem® versus standard dressing on pain levels in human patients after routine knee arthroscopy. This study found that the PolyMem® group had lower pain ratings and less post-operative swelling than patients who received standard gauze dressing. The evidence shows that polymeric membrane dressings reduce the nociceptor response that normally leads to inflammation and pain. Importantly, it has also been proven that this occurs without interfering with the normal inflammatory response required for wound healing.

Polymeric membrane dressings may therefore help to reduce inflammation, wound-related pain and swelling to stimulate wound healing.

Do polymeric membrane dressings have a wider role?
Treating wounds where persistent and potentially damaging inflammation is suspected requires extra consideration. Practitioners should select a dressing that provides a moist wound environment for wound healing, but also facilitates ongoing debridement, absorbs and removes destructive exudate from the immediate wound area, protects the periwound skin and reduces bacterial load by either binding bacteria or releasing antimicrobials into the wound itself. To achieve this combination of actions requires the use of either a combination of dressings and skin barrier products, or the use of a multifunctional dressing.

A single dressing that performs a variety of basic wound management functions has a number of potential advantages and simplifies dressing selection choice. A key feature of PolyMem® dressings is their ability to combine wound

Box 1. The components of PolyMem® dressing, which work individually and synergistically to facilitate healing.

- **Wound cleanser:** Following application of the dressing, the wound cleanser is continually released into the wound bed. It helps loosen the bonds between slough/fibrotic tissue and healthy granulation tissue for effective autolytic debridement. This minimises (and often excludes) the need for wound cleansing at dressing change, which simplifies dressing change procedure, saves time for clinical staff, causes less pain and ensures that the healing process is not disturbed.

- **Moisturiser:** The moisturiser (glycerin) is simultaneously released to prevent the dressing sticking to the wound bed. It draws fluid (including nutrition and growth factors) from deeper tissue into the wound bed to stimulate healing.

- **Superabsorbents:** The superabsorbents draw wound exudate into the dressing. The excess fluid binds to the superabsorbents, which prevent it from being released back into the wound. This helps balance moisture levels and reduce the risk of maceration.

- **Semi-permeable membrane:** The membrane protects the wound and also controls moisture levels, allowing excess exudate to evaporate.
cleansing, debridement and fluid handling (absorption and retention of fluid). They are able to provide these different functions through the ability of the dressing components to work individually and synergistically to support healing [Box 1], while reducing inflammation, pain and swelling [20].

Conclusion

Tissue injury causes the immediate onset of acute inflammation. In chronic wounds, the inflammatory phase is dysfunctional in nature. This differentiation is important for understanding the process of wound healing, since delayed healing of chronic wounds often results from an imbalance in the wound that prevents progression from one phase to another in the predictable manner.

As well as being associated with delayed wound healing, a persistent inflammatory response is a major factor in wound pain, odour and high levels of exudate production. It is important to use an appropriate dressing, which addresses these factors while meeting patient needs.

The use of a multifunctional dressing (e.g. PolyMem®) can help to simplify dressing selection choice, being suitable for a wide range of wound types and highly suitable for a wide variety of wounds. This can help to make dressing selection less confusing and reduce the risks of placing the wrong dressing on a wound. PolyMem® has been proven to reduce inflammation, swelling and pain as well as create an optimal wound environment for healing. The combination of actions makes PolyMem® a uniquely effective choice for managing multiple factors, providing advantages to both healthcare professionals and patients.

References

29. Sessions RC. Can a drug-free dressing decrease inflammation and wound pain? Poster IR-09. SAWC, September 2009