Wound inflammation and healing- The potential for hyaluronan-derived wound management products

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Inflammation is critical to mammalian survival. When the integrity of the body is challenged by injury or infection it is critical that closure of the wound and cure of the infection is completed as quickly as possible to minimise exposure to risk. Inflammation, which generates pain, is an important first sign signaling damage and triggers a visit to the doctor. Lack of pain, for example in neuropathic foot ulcers (NFU), often leads to delayed referral to a medical practitioner because the sufferer is unaware of damage. The outcome can be amputation.

Inflammation can also be highly destructive to tissue. In chronic wounds such as pressure ulcers, venous ulcers, arterial ulcers or NFU, excessive uncontrolled inflammation leads to over-expression of enzymes which destroy tissue. Even though inflammation can be a protective or destructive force, there are many common features in the biological pathways which lead to it. Whether inflammation is protective or destructive depends on the intensity of the reaction along a spectrum from mild to fiery.

All inflammation is triggered by an event such as burn, cut, graze, or scalpel in acute wounds, bacterial invasion in infection, or pathology in chronic wounds. Initially, the endothelium is activated by damage. Blood leakage and platelet activation, in acute wounds, triggers

vasoactivity, first to impede blood loss while clotting occurs, and later to increase blood flow to the site to ensure efficient delivery of essential factors for healing. In infection, vasoactivity is brought about by inflammatory signals. Increased blood flow to the site gives rise to the first diagnostic signs - erythema and local warming. Erythema and warming are normal in inflammation, but are often pronounced in invasive infection. Vasoactivity increases blood vessel permeability. Blood-borne white cells such as PMN's and macrophages adhere to activated endothelium via P-selectin receptors which slow down their movement. White cells, movement of which is finally arrested by (2 integrins, then migrate by diapedesis between the endothelial cells of the blood vessel wall to the extravascular space. Increased permeability further leads to fluid and protein leakage into the extravascular space causing other diagnostic features of inflammation - oedema and exudation. Oedema is thought to lead to pain by compression of sensory nerve endings. Extravasation of white cells proceeds actively under the influence of chemotactic signals which specifically draw the important cells into the tissue.

Inflammation proceeds to a phase of fibrosis, directed by signals from platelets, macrophages and PMN's, during which tissue matrix is laid down and neoangiogenesis takes place. In infection, PMN's and macrophages deal with invaders, and fibrosis leads to tissue hardening, whereas in a wound, granulation tissue is generated. Many growth factors are involved in this process. At the same time as granulation tissue develops in a wound, epithelial cells from the wound edges or skin adnexae, proliferate and migrate across the wound surface to close the wound. In partial thickness acute wounds or resolving infection, inflammation dies down and fibrosis resolves, oedema declines, redness recedes and skin returns to relatively normal appearance and function.

Many things can go awry during inflammation. For example, full thickness wounds close predominantly by contraction and scarring to varying degrees. In most cases, the inflammation leads to a "cosmetic" scar, but in some cases the inflammation proceeds to cause hypertrophic or keloid scarring, which is characterised by disorganised tissue and continued cellular activity. In chronic wounds, inflammation continues unabated due to repeated or continuous stimulation of endothelium, leading to hyperinflammation.

ConvaTec WHRI has studied chronic wound tissue pathology for some years. It has become clear from these studies that many differences exist between the inflammation in chronic and acute wounds. The inflammatory trigger is different; the number and spatial and temporal distribution of PMN's and macrophages is different; the extent of fibrosis is greater in chronic wounds; expression of inflammation-related and tissue-destructive enzymes is greater in chronic wounds and non-healing burns; and oxidative potential is higher in chronic wounds. These studies suggest that inflammatory modulation, not stimulation, is required for chronic wound healing. It helps us understand why compression is essential in venous leg ulcers, and why exogenous growth factors have not been successful clinically.

It has been known for many years that hyaluronan (HA) plays an important role in inflammation. HA's persistence is associated with regeneration rather than repair in embryonic wounds, and when added to adult wounds, it improves speed and quality of healing. HA is critical to mammalian survival, and acts as "nature's moisturiser", as well as having a vital role in cell proliferation and migration, matrix organisation, and many other functions. An important characteristic is its ability to inactivate highly damaging reactive oxygen metabolites, and the fact that it can potentially interfere in white cell migration by binding to receptors. HA is able to modulate inflammation. A drawback is its physical nature.

It is a gel making it difficult to process. In vivo it is degraded very rapidly, so its presence is not sustained.

A new technology - HYAFF - enables us to deliver sustained HA to a wound. HYAFF is the benzyl ester derivative of HA, which in the wound environment slowly biodegrades to release HA. HYAFF is available in Hyalofill and Hyalogran, and is the subject of clinical trials and biological investigation to establish the changes that take place in wounds under its influence. Case studies in acute trauma, venous leg ulcers and diabetic foot ulcers strongly suggest a beneficial effect in inflammatory, difficult to heal wounds.

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