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Wound care

A. WOUNDS AND WOUND HEALING

I. WOUND HEALING AND TISSUE TRANSPLANTATION

WOUND HEALING

Wound repair proceeds through several stages that overlap somewhat:

- Inflammation (haemostasis, then increased vascular permeability and cell infiltration)
- Proliferation (re-epithelialization, fibroplasia)
- Remodelling (maturation)

INFLAMMATORY PHASE (DAYS 0–6)

Haemostasis – this phase is immediate, short-lived (lasting minutes) and characterised by **vasoconstriction** and **coagulation**. Haemostatic cascades lead to the formation of a thrombin–platelet plug (clot) that is adherent to type II collagen exposed by endothelial disruption. This clot has several functions:

- The **fibrin** acts as a scaffold for incoming cells and concentrates cytokines and growth factors such as platelet-derived growth factor (PDGF), transforming growth factors (TGF), α and β at the site.
    - It traps more platelets to perpetuate the cycle.

    - Fibrin is an essential component of wound healing.
- It releases chemotactic factors such as interleukin 2 (IL-2), tumour necrosis factor (TNF)-α, TGF-β.

Inflammation – this phase (lasting 3–5 days) is defined by the **vasodilation** (due to inflammatory mediators such as **histamine,** kinins, complement), **increased vascular permeability** and **cell infiltration. Cells** clear debris and initiate the proliferative phase; close regulation is needed to avoid overactivity (SIRS) or underactivity (chronic wounds – wounds that do not heal in an orderly set of stages in a timely manner, usually within 3 months; these are characterised by persistently elevated levels of matrix metalloproteinases, MMPs).

- **Neutrophils**
    - Within 12 hours of wounding, cells appear in the wound, attracted by chemotaxins including fibrin degradation products (FDPs), complement proteins, IL-1s, TGF-β, TNF-α, platelet factor 4 (PF4) and PDGF. Translocation of marginating neutrophils (at 24–48 hours) through capillary endothelium and basement membrane is facilitated by collagenase.
    - Neutrophils produce inflammatory mediators and cytokines, and remove debris; the response and population decline after a few days, whereupon the function of debris removal is taken over by macrophages. Neutrophils are not essential for wound healing.

- **Macrophage**s arrive after 48–96 hours and begin to phagocytose debris and release cytokines and growth factors, thus coordinating and promoting healing. They are **vital to wound healing**.
- **Fibroblasts** become the dominant cell type 1 week after injury, with a key role in the production of collagen. TGF-β promotes migration and proliferation of dermal fibroblasts.
- **T-lymphocytes** migrate into wounds after the macrophages (at 5–7 days) and persist for up to 1 week – a reduced response may lead to inferior wound healing. Their primary role seems to be to mediate in fibroblast recruitment and activation.
- **Keratinocytes** – differentiated cells are converted to immature cells that migrate over the wound surface.

PROLIFERATIVE PHASE (4 DAYS TO 3 WEEKS)

Re-epithelialisation begins within hours of wounding with migration of marginal keratinocytes over the matrix due to **loss of contact inhibition**, staying beneath the eschar. There is a phenotypic conversion of differentiated keratinocytes into non-polarised cells expressing basal cytokeratins similar to cultured cells; increased mobility comes from dissolution of anchoring junctions and reorganisation of the cortical actin cytoskeleton to form lamellipodia. Cells stop migrating when they form a contiguous layer (contact inhibition). As the basement membrane is reconstituted, the cells are induced to adopt their previous morphology and form anchoring junctions with fibronectin. A **moist environment** increases the rate of (re)-epithelialisation.

- **Epidermal growth factor** (EGF) – mRNA levels increase rapidly after wounding to promote re-epithelialisation. Abnormalities of EGF expression are thought to impair wound healing; glucocorticoids suppress EGF expression in cutaneous wounds but have less effect on EGF receptor levels.
- **Growth-related oncogene α** (GRO α), originally called 'melanocyte growth-stimulating activity' due to its mitogenic activity on melanocytes, is also a chemoattractant for neutrophils that is more potent than IL-8. Both GRO α and IL-8 stimulate keratinocyte proliferation in vitro; both are maximally expressed on day 1 after injury and subside after wound closure.
- **Insulin-like growth factor-1 (IGF-1)** and IGF-binding protein-1 have been demonstrated to act synergistically to accelerate the healing of adult skin wounds; exogenous IGF-1 increases myofibroblast expression in rat wound models (Achar RA, *Acta Cir Bras*, 2014). IGF-1 levels seem to be predictive of the response of diabetic foot ulcers in patients treated with HBO (Aydin F, *J Diabetes Res*, 2013).

Fibroplasia – there is an influx of fibroblasts over the fibronectin scaffold; they are activated by PDGF and TGF-β. These cells synthesise type **III collagen**, which with ongoing neovascularisation forms **granulation tissue**. Wound tensile strength increases during the fibroblastic phase.

- **Activin** is strongly expressed in wound skin. Overexpression in transgenic mice improves wound healing and enhances scar formation; activin A has been implicated in stimulating formation of granulation tissue whilst activin B mRNA has been localised to hyperproliferative epithelium at the wound edge.
- Secretion of glycosaminoglycans (GAGs) such as hyaluronic acid (HA), chondroitin sulphate and dermatan sulphate, which become hydrated to form