Wound healing involves a highly orchestrated sequence of events which is triggered by tissue injury and ends in either partial or complete regeneration or more commonly by repair. The purpose of this process is to restore tissue integrity and haemostasis. It is a dynamic and interactive process involving soluble mediators, blood cells, extracellular matrix and parenchymal cells. During this process it passes through three phases of inflammation, proliferation and remodelling which are clinically indistinct and overlap in time.

**Haemostasis and the inflammatory phase**

Haemostasis starts immediately after injury and is usually completed within a few hours. Injury to the tissue causes disruption of blood and lymph vessels exposing the platelets to fibrin and collagen. This activates the platelets and the complement cascade. The activated platelets release cytokines and growth factors including thromboxane A-2 and serotonin which are important inflammatory mediators and also cause vasoconstriction. Platelets also interact with the injured tissue, causing the release of thrombin, which converts soluble, circulating fibrinogen to fibrin, which in turn traps and activates platelets and forms the physical entity of the haemostatic “plug” [1].

Coagulation performs its function of haemostasis, initiating healing and leaving behind messengers that bring on an inflammatory process. The clot also serves to concentrate the elaborated cytokines and growth factors including platelet-derived growth factor (PDGF) and transforming growth factor (TGF)β1 [2]. Deficiency of clotting factors (XII) is associated with impaired wound healing [3].

The stage of inflammation starts soon after haemostasis and is usually complete within the first 48 to 72 hours but may last as long as five to seven days [4]. The initial vasoconstriction is followed by vasodilatation and increased vascular permeability in response to histamine. This is in response to secretion of growth factors and other vasoactive amines from mast cell and platelets. The net result is an influx of polymorphonuclear cells (PMNs) and monocytes in the injured area with vasodilatation and increased capillary permeability.

PMNs protect the wound from infection by killing bacteria and assisting in the removal of devitalized tissue fragments and debris through the release of oxygen free radicals and lysosomal enzymes [5]. PMNs are short-lived and are soon replaced by tissue macrophages which are in fact mature monocytes.

Macrophages play a central regulatory function in fibroblast chemotaxis, proliferation and the subsequent collagen synthesis and degradation. They also help in wound decontamination by phagocytosis. Macrophages secrete PDGF, TGF-β, interleukins (IL), nitric oxide and tumour necrosis factor (TNF) which help in the angiogenesis, migration and activation of fibroblasts thus setting the stage for proliferation [6].

**Proliferation**

This phase starts around 3rd or 4th day after injury and continues for up to four weeks. It is characterized by three important changes in the injured tissue, namely...
Epithelisation, Angiogenesis, and Provisional Matrix Formation which lead to the formation of granulation tissue.

The initial event in epithelialization is migration of undamaged epithelial cells from the wound margins. They also start to proliferate and send out projections to establish a protective barrier against fluid losses and further bacterial invasion. The stimulus for epithelial proliferation and chemotaxis is EGF and TGF-α produced by activated platelets and macrophages [7]. Wounds in a moist environment demonstrate a faster and more direct course of epithelialisation.

Fibroblasts migrate into the wound site from the surrounding tissue under the influence of cytokines and growth factors. Here, they are activated by PDGF, EGF, lactate, and oxidants to synthesize and deposit collagen and proteoglycans, which ultimately bridge the edges of the wound and give it tensile strength [8]. By the end of the first week, fibroblasts are the main cells in the wound. Initially they deposit ground substance into the wound bed, and later on collagen.

Angiogenesis accompanies this fibroblastic phase and is essential to scar formation. Endothelial cells located at intact venules are stimulated by VEGF which is secreted mainly by keratinocytes at the wound edge and also by macrophages, fibroblasts and platelets in response to hypoxia and the presence of lactic acid [9]. They begin to form new capillary tubes which produce the enzymatic degradation of fibrin clot and new scar tissue.

All these changes in the wound lead to the formation of granulation tissue which consists of inflammatory cells, fibroblasts and new vasculature in a hydrated matrix of glycoproteins, collagen and glycosaminoglycans, the components of a new, provisional ECM. The provisional ECM is different in composition from the ECM in normal tissue and includes fibronectin, collagen, glycosaminoglycans, and proteoglycans [10].

**Collagen Deposition**

One of the main functions of fibroblasts is the deposition of collagen. This starts on day two or three and continues rapidly for up to one week. Collagen deposition increases the tensile strength of the wound. Also, cells involved in inflammation, angiogenesis, and connective tissue construction attach to, grow and differentiate on the collagen matrix laid down by fibroblasts [10]. Initially collagen levels in the wound increase but later on a stage of homeostasis is reached as the collagen is also being degraded by collagenases. This homeostasis signals the onset of the maturation phase.

**Maturation and Remodelling: From week two to up to one year**

At the end of the granulation phase, fibroblasts begin to commit apoptosis, converting granulation tissue from an environment rich in cells to one that consists mainly of collagen [11]. Myofibroblasts (differentiated fibroblasts) are activated and the wound begins to contract. Contraction can last for several weeks and continues even after the wound is completely re-epithelialized [10]. Length of the maturation phase varies considerably according to the size of the wound and whether it is closed, bringing the wound edges together and then holding them in place by mechanical means (primary intention) or left open to heal from the base upwards, by laying down new tissue (secondary intention) [12].

This phase is characterised by the removal of type III collagen and its replacement by mature type I collagen. Originally disorganized collagen fibres are rearranged, cross-linked, and aligned along tension lines but will never become as organised as the collagen found in uninjured skin.

The second characteristic feature of this stage is programmed cell death or apoptosis and thus the number of cells such as macrophages, keratinocytes, fibroblasts and myofibroblasts is reduced. The scar loses its erythematous appearance as blood vessels that are no longer needed are removed by apoptosis [13].

The end result of uncomplicated healing is a fine scar with minimal wound contraction, little fibrosis and a return to near normal tissue architecture and organ function. If the healing does not progress appropriately it may lead to a chronic wound or keloid scar.

**Glossary**

- PDGF: platelet-derived growth factor
- TGF: transforming growth factor
- PMNs: polymorphonuclear cells
- TNF: tumour necrosis factor
- EGF: epithelial growth factor
- VEGF: vascular endothelial growth factor
- ECM: extra-cellular matrix

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**References**