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Review article

Current understanding of molecular and cellular mechanisms in fibroplasia and angiogenesis during acute wound healing

Nicholas S. Greaves [a,b,1], Kevin J. Ashcroft [a,c,1], Mohamed Baguneid [b], Ardeshir Bayat [a,b,c,d,*]

[a] Plastic and Reconstructive Surgery Research, Manchester Institute of Biotechnology, University of Manchester, UK
[b] The University of Manchester, Manchester Academic Health Science Centre, University Hospital South Manchester Foundation Trust, Wythenshawe Hospital, Manchester, UK
[c] Inflammation Sciences Group, School of Translational Medicine, University of Manchester, Manchester, UK
[d] Department of Plastic and Reconstructive Surgery, University Hospital South Manchester Foundation Trust, Wythenshawe Hospital, Manchester, UK

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ABSTRACT

Cutaneous wound healing ultimately functions to facilitate barrier restoration following injury-induced loss of skin integrity. It is an evolutionarily conserved, multi-cellular, multi-molecular process involving co-ordinated inter-play between complex signalling networks. Cellular proliferation is recognised as the third stage of this sequence. Within this phase, fibroplasia and angiogenesis are co-dependent processes which must be successfully completed in order to form an evolving extracellular matrix and granulation tissue. The resultant structures guide cellular infiltration, differentiation and secretory profile within the wound environment and consequently have major influence on the success or failure of wound healing. This review integrates *in vitro*, animal and human *in vivo* studies, to provide up to date descriptions of molecular and cellular interactions involved in fibroplasia and angiogenesis. Significant molecular networks include adhesion molecules, proteinases, cytokines and chemokines as well as a plethora of growth factors. These signals are produced by, and affect behaviour of, cells including fibroblasts, fibrocytes, keratinocytes, endothelial cells and inflammatory cells resulting in significant cellular phenotypic and functional plasticity, as well as controlling composition and remodelling of structural proteins including collagen and fibronectin. The interdependent relationship between angiogenesis and fibroplasia relies on dynamic reciprocity between cellular components, matrix proteins and bioactive molecules. Unbalanced regulation of any one component can have significant consequences resulting in delayed healing, chronic wounds or abnormal scar formation. Greater understanding of angiogenic and fibroplastic mechanisms underlying chronic wound pathogenesis has identified novel therapeutic targets and enabled development of improved treatment strategies including topical growth factors and skin substitutes.

Contents

* Corresponding author at: Plastic and Reconstructive Surgery Research, Manchester Institute of Biotechnology (MIB), 131 Princess Street, Manchester M1 7DN, UK. Tel.: +44 161 306 5177; fax: +44 161 306 5177.
E-mail address: ardeshir.bayat@manchester.ac.uk (A. Bayat).
[1] Co-first authors.

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1. Introduction

A wound comprises a break in skin epithelial continuity and is characterised by disruption of structure and function of underlying tissues [1]. After injury, skin integrity must be restored promptly in order to re-establish homeostatic mechanisms, prevent infection and minimise fluid loss [2,3]. This is achieved through wound healing which describes a complex biological process where multiple parallel and interrelated pathways are activated and synchronised to induce wound repair [2,4]. Once complete, they must be shut down in a precise order to prevent exaggerated or delayed responses [5,6]. Traditionally acute wound healing is divided into 4 overlapping phases known as haemostasis, inflammation, cellular proliferation and remodelling (Fig. 1). The proliferative phase involves numerous important cellular and molecular components that contribute to extracellular matrix (ECM) and granulation tissue formation (Table 1). ECM, produced as a result of fibroplasia, provides a scaffold and signals for cellular adhesion and migration during tissue restoration and ultimately the architecture of the healed wound [7]. Angiogenesis is essential to replace damaged capillaries and restore the supply of oxygen, blood constituents and nutrients to wounded tissue, helping to return normoxia and promote fibroplasia [8]. This review provides an update on cellular and molecular mechanisms crucial to fibroplasia and angiogenesis. Furthermore, it describes mechanisms within these processes that may become deranged resulting in delayed healing or chronic wounds.

2. Overview of the proliferative phase of wound healing

Cellular proliferation represents the third phase of the 4-stage acute wound healing model [9,10]. Proliferation of cellular and structural components is triggered by factors secreted during the preceding inflammatory phase. It begins 3–4 days after injury and continues for 2–4 weeks. During this time there is fibroblast and endothelial cell proliferation, phenotypic alteration and migration as well as ECM deposition and granulation tissue formation [3,8]. Fibroblast derived ECM provides support for further cellular influx, adhesion and differentiation [4,11]. After its formation, ECM undergoes continuous synthesis and remodelling, reaching a steady state 21 days after wounding [5]. Initially disorganised fibrin is later remodelled with hyaluronan, proteoglycans and fibronectin (FN) before a predominantly collagenous final structure (mostly types I and III) is formed [11–13]. Remodelling is achieved by specific matrix metalloproteins (MMPs) influenced by transforming growth factor-β (TGF-β), platelet derived growth factor (PDGF), interleukin-1 (IL-1) and epidermal growth factor (EGF), which are tightly regulated. Blood vessel sprouts invade the wound concurrent with fibroblast in-growth. Neovascularisation occurs in response to pro-angiogenic factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), angiogenin, angiotropin, and angiopoietin-1 (Ang-1) released by infiltrating macrophages and keratinocytes [14–16]. The dense population of fibroblasts, macrophages and neovasculature, embedded within a loose matrix of collagen, FN and hyaluronic

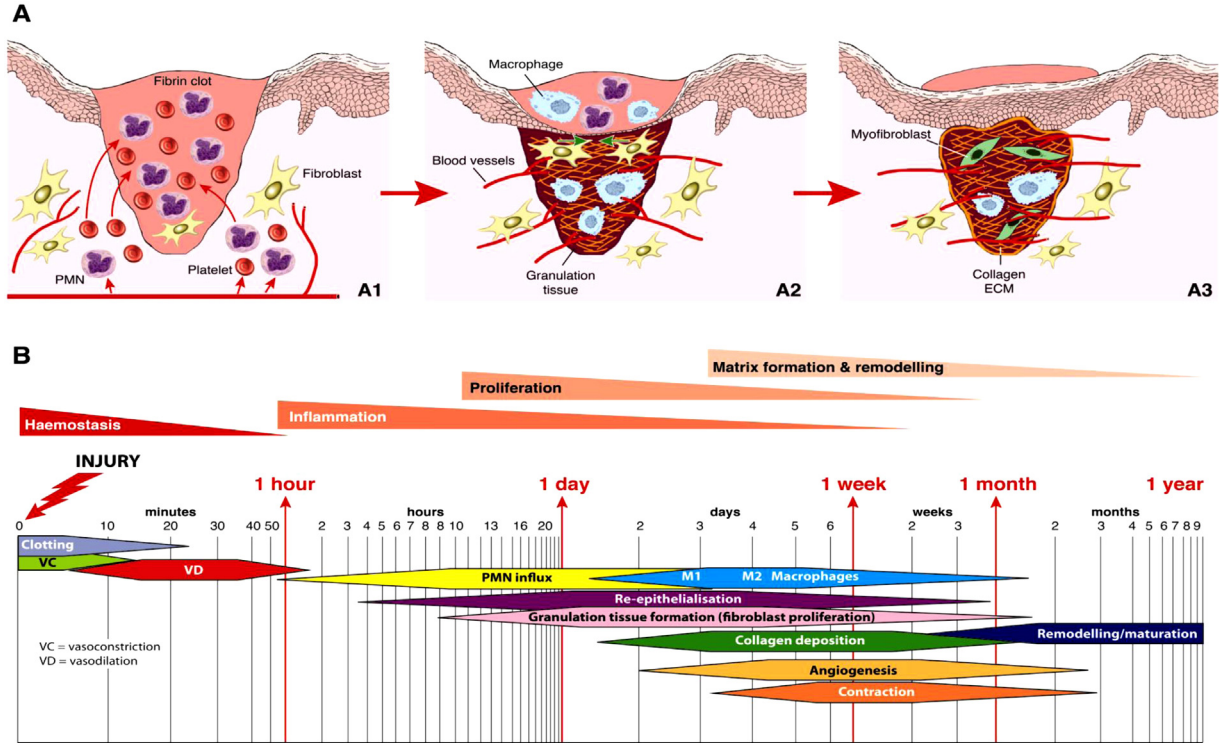

Fig. 1. Overview of acute wound healing. (A) Cellular influences in acute wound healing; (B) overlapping 4-phase model of acute wound healing and its timeframe. Phase 1 – haemostasis. After cutaneous injury vasoconstriction, clotting cascades and platelets act together to prevent prolonged haemorrhage. Once fibrin clot forms there is vasodilation enabling PMN extravasation and migration to the wound site; phase 2 – inflammation (Fig. A1). An initial influx of neutrophils is later replaced by macrophages which have an early inflammatory (M1) and later reparative (M2) phenotype. There is phagocytosis of bacteria and wound debris with concurrent secretion of multiple growth factors, chemokines and cytokines which drive fibroblast and endothelial cell recruitment to the wound bed; phase 3 – cellular proliferation (Fig. A2). Migratory endothelial cells and fibroblasts proliferate resulting in ECM deposition, angiogenesis and granulation tissue formation. ECM forms a scaffold for further cellular influx and is remodelled by a variety of enzymes so that its composition changes throughout wound healing; phase 4 – remodelling (Fig. A3). Wound maturation occurs with continued ECM remodelling into a predominantly collagenous structure, fibroblast differentiation into myofibroblasts, wound contraction and gradually reducing cellularity with eventual scar formation. Re-epithelialisation occurs concurrently beginning within hours of injury until there is restoration of epithelial continuity. PMN, polymorphonuclear cells; ECM, extracellular matrix.