

of damage signals, which can be both mechanical and chemical. Cells at the edge of a wound are ruptured, as are vessels in the wound vicinity. Damaged and stressed cells respond by activating several 'stress signal' pathways within minutes. For example, signaling via the SAPK/JNK and p38 pathways (Kobayashi et al., 2003; Yano et al., 2004) results in phosphorylation of a cascade of signaling molecules, which ultimately culminates in cellular changes including alterations in gene expression, cell survival and metabolism. The same cells leak endogenous molecules, including damage-associated molecular pattern molecules (DAMPs), which might act as activation cues and/or chemotactic factors for other cells in the area (Bianchi, 2007).

One of the earliest responses to injury stems from the damage that is caused to local blood vessels. It is necessary to stop local hemorrhage immediately, and this is achieved by platelet activation and aggregation, which results in formation of a fibrin clot consisting of a network of insoluble fibrin fibers. As well as plugging vessels, the clot acts as a provisional matrix to which growth factors bind and through which cells can crawl (Nurden et al., 2008). Activated platelets are themselves an important source of growth factors [such as platelet-derived growth factor, CXCL4, basic fibroblast growth factor, transforming growth factor- β (TGF β), vascular endothelial growth factor and RANTES (Bahou and Gnatenko, 2004)] and are known to promote various aspects of the repair process through this growth factor release, including angiogenesis, inflammation, and migration of both keratinocytes and fibroblasts.

In addition to the platelet-derived growth factors, cells are bathed in other serum factors. Serum, the fluid component of clotted blood, contains many interleukins, colony-stimulating factors, tumour necrosis factor- α , interferon- γ and other components that together lead to induction of serum response factor (SRF). SRF binds to and induces transcription of immediate early and other genes [such as *fos*, *jun* and early growth response genes (*egr-1* and *egr-2*)] (Chai and Tarnawski, 2002; Grose et al., 2002). Transcriptional profiling of in vivo wounds (Cole et al., 2001; Cooper et al., 2005; Deonaraine et al., 2007; Roy et al., 2008), and of fibroblasts exposed to serum in vitro (Iyer et al., 1999), reveals an immediate response to wounding in which upwards of several hundred genes are up- or downregulated within an hour of damage.

Several other cues that might influence wound cells in vivo include mechanical signals such as 'stretch', which occurs in response to changing tissue tensions (Kippenberger et al., 2000); electrical currents that result from

membrane damage and breaks in the epithelial barrier (Nuccitelli et al., 2008); and exposure to various microorganisms whose epitopes are largely recognized by Toll-like receptors (TLRs) (Shaykhiiev et al., 2008). Activation of epithelial cell TLRs triggers the expression and release of pro-inflammatory mediators and anti-microbial peptides.

The inflammatory response

The inflammatory response to wounding (see poster, panel 2) begins immediately with the passive leakage of circulating leukocytes (largely neutrophils) from damaged blood vessels into the wound. There is also rapid activation of immune cells that are already resident within the tissue [such as mast cells (Noli and Miolo, 2001), $\gamma\delta$ T cells (Jameson et al., 2004) and Langerhans cells (Cumberbatch et al., 2000)], which in turn release a rapid pulse of chemokines and cytokines. The inflammatory response continues with active recruitment of neutrophils and then macrophages from nearby vessels, which is orchestrated by growth factor signals from the resident cells and serum, and by foreign epitopes such as the lipopolysaccharides (LPS) of invading microorganisms (Eming et al., 2007). Together, these signals trigger local endothelial cell 'activation' and thus expression of selectins. Selectins control the rolling and then tethering of leukocytes to the vessel wall and subsequent crossing of the endothelial barrier (Yukami et al., 2007). This is enhanced by vessel dilation and an increase in vascular permeability that is triggered by inflammation-associated nitric oxide (NO), mast cell-derived histamine, tissue plasminogen activator and other factors (Eming et al., 2007).

The role of inflammatory cells

Neutrophils are activated and recruited to a wound within minutes (Kim et al., 2008). They have an important cleansing role and kill invading microorganisms through several strategies, including bursts of reactive oxygen species (ROS) (Dovi et al., 2004). Profiling of the genes whose expression is induced in neutrophils upon recruitment to a wound hints that these cells also influence many other aspects of repair, such as resolution of the fibrin clot and provisional ECM, promotion of angiogenesis, and re-epithelialization (Theilgaard-Monch et al., 2004).

Monocytes are drawn from the circulation somewhat later than neutrophils, and their numbers peak a day or so after injury (Mori et al., 2008). Monocytes mature into macrophages once they leave the circulation and 'turn on' distinct gene expression and behavioural programs according to their surroundings and stimuli (Martinez et al., 2006).

At the wound site, they are professional phagocytes and clear up matrix and cell debris, including spent neutrophils (Eming et al., 2007). Close analysis of the temporal profiles of macrophage-specific genes suggests that both classically activated (M1, pro-inflammatory) and alternatively activated (M2, anti-inflammatory and pro-angiogenic) macrophages are present early in repair, whereas M2 macrophages predominate later in repair (Deonaraine et al., 2007).

In addition to the release of cytokines and growth factors, inflammatory cells exert their influence on the surrounding tissue by generating NO and large amounts of ROS (Schafer and Werner, 2008). NO and ROS are known to drive certain aspects of repair (Sen and Roy, 2008) but, in response to these stressors, affected wound cells must induce cytoprotective and detoxifying programs (Schafer and Werner, 2008). A number of microarray studies have compared gene signatures in wounds with and without inflammation (Cooper et al., 2005; Deonaraine et al., 2007; Roy et al., 2008). These studies have been valuable for identifying genes expressed by the inflammatory cells themselves, as well as the downstream consequences of inflammation within a wound setting. Although the issue of whether inflammatory cells are an essential requirement for repair remains controversial (Martin and Leibovich, 2005), it is clear that these cell populations exert a profound influence on all other cells within the wound and in the surrounding tissue. For example, one of the important roles of inflammatory cytokines is to regulate angiogenesis, which they accomplish in concert with signals from other wound cells and from serum (Tonnesen et al., 2000).

Angiogenesis and lymphangiogenesis

Angiogenesis, which is integral to successful wound repair, involves sprouting of wound-edge capillaries followed by their invasion into the site of damage. After a few days, a microvascular network is apparent throughout the wound (Tonnesen et al., 2000), which provides nutrients and oxygen to the growing tissues and aids in the formation of the provisional wound matrix, also known as granulation tissue (described below). The complex response of blood vessels to damage has been studied using microarray analysis, with a comparison of gene expression profiles of blood vessels in intact and wounded skin (Roy et al., 2007).

Fluid accumulation is a common aspect of tissue damage and results from local vasodilation, increased vascular permeability and/or damage to lymphatic vessels (Adams and Alitalo, 2007). Lymphangiogenesis (repair of lymph vessels) has been studied much less than

angiogenesis, but is likewise under tight regulation by a plethora of similar, as well as some unique, growth factors (Adams and Alitalo, 2007; Karkkainen et al., 2004).

Proliferation, migration and contraction

The clot, or scab, that forms during the immediate response to an insult is a temporary mechanism for restoring the function of the skin as a protective barrier. The next phase depicted in this poster (panel 3), which we have called 'Proliferation, migration and contraction', involves the actions taken by cells within a wound to achieve permanent closure of the wound gap and replenishment of lost tissue. These processes initiate within hours, but the time required to heal is highly variable and depends on the size and location of the wound as well as on the age and health of the tissue. A small incisional skin wound on a neonatal mouse can heal completely in less than a day, whereas in aged or diabetic humans, the repair process can take weeks or months.

Epidermis

Re-epithelialization of a wound by keratinocytes is achieved by a combination of migration and proliferation of cells in the vicinity of the damage (Martin, 1997; Matoltsy and Viziam, 1970). Generally, the advancing cells of the wound epidermis migrate collectively (Ilna and Friedl, 2009) after undergoing a number of changes to facilitate their movement. Firstly, they alter cell-cell and cell-matrix adhesions to enable their progression from a laminin-V- and collagen-IV-rich BM onto and through provisional matrix substrates that constitute the clot, such as dermal collagen and fibronectin (Nguyen et al., 2000). Migrating cells also assemble actin-rich lamellar protrusions for crawling (Mithison and Cramer, 1996), and upregulate the expression of proteolytic enzymes such as matrix metalloproteinases (Pilcher et al., 1999). This enables them to bore a pathway at the interface between the scab and viable tissue. In vitro scratch wound assays of human keratinocytes, although not a perfect model of in vivo re-epithelialization, reveal a gene profile from microarray analysis that progresses our understanding of this aspect of skin wound healing (Cheng et al., 2008; Dayem et al., 2003; Fitsialos et al., 2007).

The regenerating epidermis also draws upon stem cells that are resident in the epidermis and the bulge region of hair follicles (Fuchs, 2008). In response to injury, bulge stem cells commit to an epidermal phenotype, and then migrate into the epidermis to participate in the repair process (see poster, panel 3) (Ito et al., 2005).

Dermis

In addition to the healing epidermis, the underlying dermis must also be reconstituted. The new stroma that replaces the fibrin clot is called granulation tissue and is contributed to by fibroblasts that are drawn from several sources: primarily the healthy dermis at the wound margins, from which fibroblasts can divide and migrate (Hinz, 2007); circulating fibrocytes; and bone marrow progenitor cells (Abe et al., 2001). Fibroblasts can also be recruited from multipotent cells that are resident in the dermis and have the potential to differentiate into dermal fibroblasts (Fernandes et al., 2004; Toma et al., 2001) and/or from pericytes that are associated with nearby blood vessels (Rajkumar et al., 2006). Fibroblasts in close proximity to the wound respond by forming stress fibres (weakly contractile actin bundles), which enable some connective tissue contraction. The contractility of the bundles is greatly enhanced, however, when the cells are driven to differentiate into α -smooth muscle actin-expressing myofibroblasts by the action of growth factors (such as TGF β 1), the ECM and/or mechanical stress (Hinz, 2007). Together, wound fibroblasts and myofibroblasts help to draw the wound closed, and contribute to the synthesis, bundling and alignment of collagen fibres (Hinz, 2007), the primary constituent of scar tissue. In the future, information about the gene signatures of these cells might be obtained by mining gene expression analyses of other fibrotic conditions in which wound fibroblasts and myofibroblasts are significant players, such as pulmonary fibrosis (Brass et al., 2008).

Resolution

The resolution phase of wound repair (see poster, panel 4) is essential for restoration of full functionality and a 'normal' appearance to the injured tissue. Migrating and proliferating keratinocytes at the wound edge confront one another as the wound seals, and must then stop and subsequently re-stratify. Our group (Cooper et al., 2005) temporally dissected the wound transcriptome in order to gain insight into how this 'stop phase' is regulated; however, more work is needed to understand the molecules and signalling pathways involved in the contact inhibition and epithelial fusion that occurs as cells from the two epidermal wound fronts confront one another.

Simply reforming a continuous epidermal sheet does not, however, return the tissue to its pre-wound state, because epidermal appendages such as hair follicles and sebaceous glands also need to regenerate. Appendages do not readily develop within a scar, but it has been reported that inflammation can promote appendage

re-growth (Osaka et al., 2007), and this is thought to require re-enactment of the epidermal developmental program, in which Wnt signalling has a pivotal role (Ito et al., 2007).

During wound resolution, many changes also occur in the dermis. The blood vessels within the scar are refined, and mature to form a functional network (Adams and Alitalo, 2007). The dense ECM that was haphazardly deposited early in repair is remodelled. This remodeling, which aims to restore normal architecture to the dermis, is accomplished by a delicate balance of collagen synthesis, bundling and degradation (for example, by matrix metalloproteinases). Moreover, most myofibroblasts undergo apoptosis at this stage (Hinz, 2007; Ulrich et al., 2007).

The inflammatory response to wounding also resolves once healing is complete. Neutrophils are cleared from the wound site, at least in part by apoptosis and subsequent phagocytosis by macrophages (Haslett, 1992). Some neutrophils and macrophages return to the vasculature, as observed in zebrafish larval wounds (Mathias et al., 2006), and/or emigrate via lymphatic vessels (Cao et al., 2005; Schwab et al., 2007). Macrophages are thought to be deactivated by anti-inflammatory cytokines, glucocorticosteroids, cell-cell contact or phagocytosis (Ma et al., 2003). Other strategies in place to dampen inflammation include sequestration of pro-inflammatory chemokines by non-functional 'decoy' receptors on the inflammatory cells themselves (D'Amico et al., 2000) and production of endogenous anti-inflammatory molecules such as resolvin E (Schwab et al., 2007) and annexin I (Perretti and Gavins, 2003).

Imperfect regulation of wound resolution can result in hyperproliferation, persistence of an inflammatory reaction and, consequently, fibrosis and excessive scar formation, all of which can contribute to numerous pathologies (Coussens and Werb, 2002; Wynn, 2008). We and others suggest that epigenetic mechanisms (such as histone modifications and microRNA-based regulation) contribute both to the concerted induction of the 'repair transcriptome' by wound-edge cells and to the subsequent repression that is so clinically important (Shaw and Martin, 2009; Shilo et al., 2007).

Conclusion

This poster article briefly illustrates and describes the complex process of wound repair. We refer you to a number of recent microarray studies that provide transcriptional information about specific aspects of the process. On the basis of these publications, as well as the first reported proteomic analyses of wound exudates (Fernandez et al., 2008; Huang et al., 2006), it is

evident that the wound milieu contains many potentially novel proteins that influence wound repair. Studies using transgenic and knockout mice, as well as other strategies such as topical treatment of wounds with ligands and/or inhibitors, have already confirmed that a plethora of factors influence the migration and proliferation of epidermal and dermal cells, and wound contraction. Validation and substantiation of the array findings should bring us one step closer to fully understanding the molecular intricacies of each phase of the repair process. Such an understanding will be clinically valuable, and could lead to treatments that increase the rate and quality of normal tissue repair, and that prevent or reverse the adverse consequences of improper wound resolution.

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Commentaries

ABL-family kinases *Tony Koleske*
 Tail-anchored protein biogenesis – the beginning for the end? *Stephen High*
 Cytoskeletal dynamics in axon guidance *Phillip Gordon-Weeks*
 PIP5K-regulated PtdIns(4,5)P₂ synthesis *Nullin Divecha*
 Apical trafficking in epithelial cells *Enrique Rodriguez-Boulan*
 Matrix elasticity, cytoskeletal forces and physics of the nucleus *Dennis Discher*

Although we discourage the submission of unsolicited Commentaries and Cell Science at a Glance poster articles to the journal, ideas for future articles – in the form of a short proposal and some key references – are welcome and should be sent by email to the Editorial Office (jcs@biologists.com).

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