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Medicine in focus

The regenerative potential of epithelial stem cells in tissue repair☆

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ABSTRACT

Acute and chronic wounds encompass devastating injuries with significant physical, emotional and economic costs at both the individual and societal level. The pathogenesis of chronic wounds is as varied as the potential causes; however, contributing factors include repetitive ischaemia/reperfusion injury coupled with bacterial infection, inflammation and matrix degradation at the wound site. Similarly, the acute physical damage of burns may leave patients vulnerable to dehydration and infection, and in certain cases this may be followed by a body-wide systemic response with debilitating consequences. Epithelial stem cells provide a promising avenue for the treatment of burns and chronic wounds. This is exemplified by recent achievements such as the restoration of corneal epithelium using limbal stem cells, and the treatment of epidermolysis bullosa via a gene therapy approach. Nevertheless, many technical and regulatory challenges remain to be addressed.

This article is part of a Directed Issue entitled: Regenerative Medicine: the challenge of translation.

1. Introduction

Despite its remarkable mechanical and physiological properties, environmental and genetic factors pose a variety of threats to the integrity of human skin. In the United States, chronic wounds are estimated to affect at least 6.5 million people, with an associated cost of US$25 billion (Singer and Clark, 1999; Brem et al., 2007). These grave economic consequences are not restricted to North America: 2% of the yearly health budget of the European Union is allocated to wound care, while in the UK approximately £400 million per annum are directed to chronic ulcer treatment (Crovetti et al., 2004; Ruckley, 1997). Despite only affecting 1% of the population at any given time, the cost of chronic wounds is disproportionately amplified due to slow rates of healing and the need for repetitive treatment (Chen et al., 2009). Alarmingly, the burden seems set to be compounded by the increasing incidence of exacerbating factors such as obesity and diabetes, as well as an ageing population and increasing healthcare costs (Sen et al., 2009).

Of course, ulcerated wounds are only half the picture of socio-economically debilitating skin trauma. Severe burns are among the most crippling and devastating injuries and they represent a critical burden on public health all over the world. Indeed, it is difficult to articulate the full impact of this injury given its propensity to often result in lifelong complications at a physical, emotional and aesthetic level. At any rate, in the United States there are an estimated 500,000 burn injuries each year which receive medical treatment, with 40,000 of these requiring hospitalisation (Esselman, 2007). According to the World Health Organisation, 2004 saw nearly 11 million people worldwide require medical care for burn injuries, generating the fourth-highest incidence of any injury type and establishing fire-related burns as a leading cause for loss of disability-adjusted life years in low and middle-income countries (Peck, 2011). Indeed, up to 90% of burn-related skin injuries occur in developing nations, where more traditional methods of lighting and cooking are still commonplace and where prevention programmes, together with the quality of acute care, are lacklustre (Ahuja et al., 2009; Peck, 2011). Together, burns and chronic wounds encompass a significant health care burden to developed and developing nations alike, and if treated unsuccessfully these injuries may leave patients vulnerable to systemic injury, dehydration and infection, causing increased morbidity and mortality while also wasting healthcare resources.

2. Pathogenesis of burns and chronic wounds

The intrinsic ability to repair wounds represents a complex cascade of biochemical and cellular events which is only beginning

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to be unravelled and understood at the physiological level. Repair may be divided into four main phases: hemostasis, inflammation, proliferation and remodelling, and the disruption or complete failure of these processes, either together or individually, may result in the formation of undesirable scar tissue or a nonhealing wound, along with subsequent emotional, physical and socio-economic damage (Chen et al., 2009).

2.1. Chronic wounds

Given the variety of factors which may compromise tissue integrity, from acute burns and pressure sores to diabetic ulceration and congenital defects, it is unsurprising that the pathogenesis of chronic wounds is difficult to encompass in a single molecular pathway. Nonetheless, there are common threads which tie together the tapestry of chronic injury formation, although it should be noted that a complete analysis of the pathogenetic factors and cellular impairments is beyond the scope of this review.

2.1.1. Ischaemia and reperfusion

It is generally accepted that ischaemia – that is, inadequate blood supply to local tissue – is a key player in chronic wound development, with the consequent hypoxia resulting in compromised wound repair and cellular proliferation (Mustoe et al., 2006). However, ischaemia often occurs in conjunction with a reperfusion event during which circulation is restored and the subsequent inflammatory response serves to worsen the injury. During this process leukocytes are recruited to the site of injury by cytokines such as tumour necrosis factor-alpha and interleukin-1 (Toledo-Pereyra et al., 2004), where they migrate into the interstitial space after adhering to integrins found on the endothelial cell surface. Upon infiltration leukocytes may induce further tissue damage by expressing pro-inflammatory cytokines, secreting proteolytic enzymes, and releasing destructive oxygen free-radicals such as superoxide (O_2^-) and the hydroxyl radical (OH) (Anaya-Prado et al., 2002; Mustoe, 2004). Furthermore, a significant decrease in nitrous oxide levels has been observed in ischaemia-reperfusion injury, serving to further exacerbate the inflammatory and free radical conditions while also disrupting vasodilation and tissue perfusion (Anaya-Prado et al., 2002). Cumulatively, the effects of ischaemia-reperfusion injury play an important role in cellular stress and necrosis, and in the context of chronic wounds this event is typically repeated by a cycle of pressure-induced ischaemia followed by reperfusion when a change in position re-establishes circulation (Mustoe et al., 2006; Mustoe, 2004; Peirce et al., 2000).

2.1.2. Bacteria, cytokines and ECM dysregulation

When the skin barrier is broken a succession of cellular and biomolecular events characterises the site of injury. Bacterial colonisation of the wound bed coupled with the disruption of extracellular matrix (ECM) components, including collagen, elastin, laminin and hyaluronan, results in the activation and extravasation of macrophages and neutrophils (Schultz and Wysocki, 2009). When active, these cells secrete additional pro-inflammatory cytokines such as TNF-α and IL-1β which in turn stimulate the production and release of matrix metalloprotease (MMP) enzymes (Mast and Schultz, 1996; Wysocki et al., 1993). In difficult to heal and chronic wounds, the homeostatic imbalance between matrix proteases and their inhibitors results in a dysfunctional ECM environment, diminishing the integrity of the connective tissue while also interfering with factors such as epithelial cell migration and proliferation. Wound closure is further impaired by the protease degradation of growth factors (transforming growth factor-beta [TGF-β], platelet-derived growth factor [PDGF]) and their target receptors, as well as the exacerbating effect of exogenous bacterial proteases and antigens on the inflammatory response (Mustoe, 2004; Sorsa et al., 1992). At this point, it is important to note that both acute and chronic wounds begin with the same pro-inflammatory cytokine response aimed at clearing the bacterial load, and both culminate in the production of growth factors aimed at stimulating ECM organisation, re-epithelialisation and subsequent scar formation. In most chronic or nonhealing wounds, however, the regenerative process may be interrupted during any (or all) of the four key stages of hemostasis, inflammation, proliferation and remodelling (Hassan et al., 2014). The result is a pathological state characterised by a deregulated inflammatory cascade, failed epithelialisation and ECM organisation, and a dysfunctional network of growth factors and their respective target cells (Guo and DiPietro, 2010; Bjarnsholt et al., 2008; Cook et al., 2000). In conjunction with factors such as age and disease state (diabetes and obesity represent significant challenges to wound repair), the result is an endogenous repair response unable to progress to the advanced stages of healing.

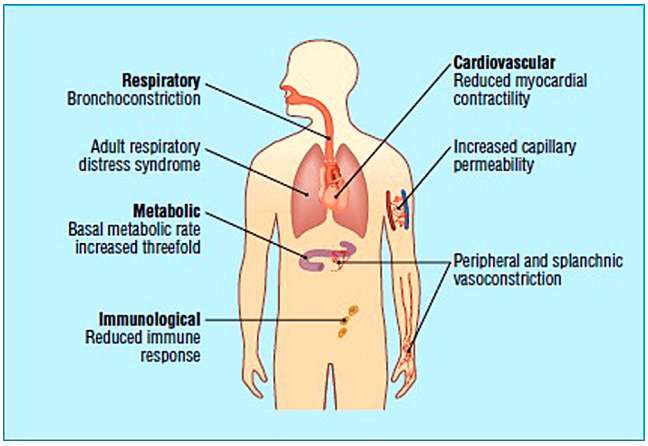

Fig. 1. Systemic response following burn injury. The consequences of severe burn trauma often manifest in a cascade of immunological, metabolic, cardiovascular and respiratory burdens. Together, these pathologies contribute to a systemic injury which prolongs and accentuates the physical, economic and psychological pressures of burn management and treatment.

From Hettiaratchy and Dziewulski (2004) with permission.

2.2. Burns

On top of the acute physical damage caused by burns, the release of inflammatory mediators at the site of injury may signal the onset of a systemic response affecting multiple organs and body systems (Fig. 1) (Evers et al., 2010; Hettiaratchy and Dziewulski, 2004). For example, vascular permeability is increased as a result of vasoactive mediators, such as histamine and bradykinin, originating from the injured site. In turn, this causes intravascular proteins and fluids to be lost to the interstitial space which, in conjunction with decreased cardiac output and the loss of fluid directly from the burn site, may result in systemic hypotension and a lack of perfusion to end organs (White et al., 2002; Grunwald and Garner, 2008). Additionally, the basal metabolic rate of burns patients is known to increase by up to three times the normal physiologic output, a hypermetabolic state which is influenced by significantly high levels of catecholamines, prostaglandins and glucocorticoids. Some of the consequences of this hypermetabolic episode include high levels of catabolism, immune dysfunction, muscle proteolysis and negative nitrogen balance (Murphy et al., 2003; Herndon et al., 2001; Yu et al., 1999). The acute and systemic injuries associated with burns may endure far longer than the initial days or