Seminars in Immunology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

Inflammation and wound repair

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ARTICLE INFO

Article history:
Received 19 March 2014
Accepted 22 April 2014

Keywords:
Inflammation
Chronic wounds
Wound repair
Regeneration

ABSTRACT

Wound repair requires the integration of complex cellular networks to restore tissue homeostasis. Defects in wound repair are associated with human disease including pyoderma gangrenosum, a heterogeneous disorder that is characterized by unhealed wounds and chronic inflammation of unclear etiology. Despite its clinical importance, there remain significant gaps in understanding how different types of cells communicate to integrate inflammation and wound repair. Recent progress in wound and regenerative biology has been gained by studying genetically tractable model organisms, like zebrafish, that retain the ability to regenerate. The optical transparency and ease of genetic manipulation make zebrafish an ideal model system to dissect multi-cellular and tissue level interactions during wound repair. The focus of this review is on recent advances in understanding how inflammation and wound repair are orchestrated and integrated to achieve wound resolution and tissue regeneration using zebrafish.

1. Introduction

An inability to repair wounded tissue is a major clinical problem. The response to tissue damage is different depending on the tissue type and the severity of damage [1]. Some human tissues retain the ability to regenerate, like the human liver [2]. Most tissues, however, have limited capacity for regeneration and the outcome of tissue damage is often scarring [1]. Scarring can have detrimental effects in tissues like the heart where it leads to congestive heart failure [3–5]. Tissues such as the central nervous system also have limited regeneration after injury and display poor recovery of function [6,7]. Therefore, there is considerable interest in understanding how to improve functional outcomes in human tissues that fail to regenerate or result in scar formation after tissue damage. To understand tissue repair, there has been an interest in studying vertebrate models in which wound healing occurs with minimal scarring in an attempt to understand how to optimize healing in humans. Herein we will focus on recent studies that have used zebrafish to study wound repair and regeneration. For general reviews on wound biology, we refer the readers to many outstanding general reviews [8–12].

2. Impaired wound healing and pyoderma gangrenosum

A useful model to understand tissue repair is wound healing of the skin. In response to tissue damage, the skin is repaired through a sequence of steps that involves the interactions between different types of cells including leukocytes, blood cells, fibroblasts and epithelial cells [13,14]. The complex process of cutaneous wound repair includes distinct and often overlapping steps including the formation of a blood clot to re-establish tissue homeostasis, inflammation, re-epithelialization, granulation tissue formation and finally remodeling with the potential for scar formation [15]. A disruption of these steps can lead to chronic inflammation and impaired wound healing.

There are many human diseases characterized by impaired wound healing and chronic skin ulcers including diabetes [16]. In addition, inherited human diseases including immunodeficiencies like leukocyte adhesion deficiency (LAD) are associated with impaired wound healing due to persistent infection and have been successfully recapitulated in the zebrafish [17,18]. There are also heterogeneous disorders characterized by non-resolving skin lesions in the absence of infection. Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that is characterized by ulcer formation and chronic non-resolving wounds even in the absence of infection [19]. PG is often associated with other underlying conditions including inflammatory bowel disease, but in many cases the etiology is unclear. There have been single gene autoinflammatory diseases associated with PG, including the autosomal dominant disorder pyogenic arthritis, pyoderma gangrenosum and acne (PAPA)

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http://dx.doi.org/10.1016/j.smim.2014.04.007
1044-5323/

syndrome [20]. Other autoinflammatory disorders are also associated with unhealed wounds and pustules including early onset inflammatory bowel disease and caspase recruitment domain-containing protein 14 (CARD14) mediated psoriasis [21].

Understanding these rare autoinflammatory diseases can contribute to progress in dissecting underlying mechanisms that contribute to wound repair. For example, in the case of PAPA syndrome the prevailing view is that wounds do not heal because of persistent inflammation within the skin, due to elevated interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) production [20,22–24]. This is likely an important factor that contributes to the pathogenesis of PAPA syndrome. However, treatment with anti-inflammatory drugs that target IL-1β or TNFα do not always improve disease symptoms [20]. This raises the intriguing idea that other factors may contribute to chronic tissue damage in patients with PAPA syndrome. In support of this idea, a recent report using human cells suggests that macrophages may play a driving role in some forms of PAPA syndrome. In particular, a novel mutation in the SH3 domain of the adaptor protein Proline-Serine-Threonine Phosphatase-Interacting Protein 1 (PSTPIP1) expressed in macrophages induces altered organization of the actin cytoskeleton and exaggerated release of matrix metalloproteinases (MMPs) *in vitro* [25]. These changes may contribute to the tissue destruction and the development of chronic ulcers characteristic of PAPA syndrome. This raises an interesting question about alternative drug targets like MMP inhibition or drugs that target cytoskeletal organization. Further studies will be needed to determine if MMP inhibition or alternative therapies will benefit patients with PAPA syndrome or other forms of PG. Single gene disorders such as mutations in PSTPIP1 represent a unique opportunity to dissect specific pathways involved in inflammation and wound repair. They also highlight the need for improved animal models, like zebrafish, to aid in understanding the pathogenesis and treatment of wound repair disorders.

3. Continuum from wound to resolution and repair

A fundamental question in wound biology involves an understanding of the relationship between inflammation and wound repair. It is generally believed that if inflammation does not resolve, wound healing and regeneration will not occur [26]. This is particularly interesting in the context of the central nervous system (CNS), a tissue that exhibits limited recovery and regeneration after damage. In a recent review, Shechter and Schwartz propose that CNS injury may be similar to a chronic and unhealed wound [27]. They go on to suggest that regeneration may be limited in the CNS because of impaired wound healing and view CNS damage as a type of chronic wound [27]. Therefore, an important component of regeneration research is to understand the steps that occur during wound healing, including the links between inflammation, repair and regeneration.

Wound resolution occurs when the damaged tissue seals and generally coincides with the resolution of inflammation [28]. Regeneration, on the other hand, is defined as the reconstitution of the damaged tissue in a scar-free manner that occurs after the wound resolves, representing a final stage in the repair process [15,29]. This distinction raises interesting questions: what are the signaling networks responsible for driving the healing process toward regeneration, and why are some organisms better at integrating these signals to regenerate tissues? Why do some organisms maintain the ability to regenerate tissues throughout their lifespan and how does inflammation and early signaling at damaged tissue influence the repair process? Moreover, does differential integration of inflammatory signaling drive the outcome toward chronic wound *versus* resolution and regeneration?

The wound repair process is highly conserved across single and multi-cellular organisms [30–32]. This conservation positions simple model systems as important tools to understand how diverse cell populations integrate wound responses and to determine the kinetics of these interactions. It is important to consider that many organisms, including vertebrate genetic model systems like zebrafish, retain the ability to regenerate tissues without permanent scar formation [15,33–36]. It is possible that by understanding why some organisms perform scar-free regeneration, we will develop new insight into human wound biology. The zebrafish represents a powerful model system to dissect the wound repair process in both the larval period, where imaging is optimized, and in adult zebrafish, where many steps of the wound repair process are conserved [36,37].

4. Zebrafish as a model to understand wound repair

The development of transgenic zebrafish lines with fluorescently labeled neutrophils, and macrophages, in addition to reporter lines that label specific tissues including epithelial tissues, has revolutionized our ability to dissect the molecular mechanisms that regulate inflammation and wound healing in zebrafish [38–48]. The innate immune response to infection and tissue damage seems to be highly conserved in zebrafish, making it an ideal system to study inflammation and wound repair [41,42,46,47,49–55]. Support for the conservation of innate immune functions can be found in the recapitulation of human immunodeficiency phenotypes in zebrafish models of Wiskott–Aldrich syndrome (WAS), warts-hypogammaglobulinemia-infections-myelokathexis (WHIM) syndrome, and leukocyte adhesion deficiency (LAD)-like syndrome [18,56,57]. Moreover, zebrafish have retained the ability to regenerate many tissues, including the fin, heart, skin, photoreceptors, neurons, and the brain [36,37,58–63]. Adult zebrafish also retain regenerative potential and have provided new insight into regeneration of cardiac tissue, kidney and the CNS [60,61,64–68].

Use of tools to analyze spatial and temporal changes in gene expression after injury in zebrafish has supported a central role for changes in inflammatory gene expression during zebrafish regeneration [69,70]. Moreover, transcriptome analysis during spinal cord regeneration has been used to uncover a potential role for signal transducer and activator of transcription 3 (Stat3) in orchestrating both inflammation and proliferation after injury [70]. Finally, the potential of chemical tools to uncover mechanisms of regeneration in zebrafish provides an additional strength of the zebrafish model in wound biology research [71]. The combination of the optical transparency, conservation of the innate immune system and genetic tractability make zebrafish an ideal model to dissect mechanisms that integrate inflammation and tissue repair.

5. Wound-induced inflammation

At the beginning of the 20th century Ilya Mechnikov reported the response of inflammatory cells to wounds in starfish larvae. In his Nobel Prize lecture, he described the appearance of small moving “elements” that rapidly respond to wounds [72]. In the years following his initial observation, significant progress has been made in characterizing the nature of these elements as innate immune cells which include neutrophils and macrophages. Neutrophils are the most abundant leukocyte, and are generally the first responders to infection and tissue damage [73]. This infiltration of leukocytes is necessary to limit infection at the site of tissue damage [74]. Moreover, the response of macrophages is necessary for efficient wound repair by clearing debris from sites of tissue damage [75].

Please cite this article in press as: LeBert DC, Huttenlocher A. Inflammation and wound repair. Semin Immunol (2014), http://dx.doi.org/10.1016/j.smim.2014.04.007