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Review

Inflammation and wound repair

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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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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].

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There is substantial evidence to support the importance of macrophages in the wound healing process in mouse and guinea pig models, and recent studies in zebrafish also showed that depletion of macrophages results in a build-up of debris and impairs regeneration [76–80]. However, inflammation can also have detrimental effects on wound repair. For example, in mouse models the presence of neutrophils can contribute to scar formation after tissue damage and slow the wound closure rate [81]. In zebrafish, Li and colleagues showed using *runx1* mutants with impaired neutrophil function that larvae have improved regeneration, suggesting that neutrophils in zebrafish larvae may also have detrimental effects on regeneration and wound repair [76]. However, in the CNS of adult zebrafish, a recent study suggests that acute CNS inflammation induced by injection of microparticles promotes neurogenesis and regeneration through leukotriene signaling, suggesting complex inflammatory signaling integration is necessary during wound repair [82]. Taken together, a first step in understanding the role of inflammation in wound healing is to understand the signals that mediate leukocyte recruitment to wounds.

6. Signals guiding leukocyte recruitment in zebrafish

Leukocytes, both neutrophils and macrophages, are rapidly recruited to wounds in zebrafish larvae (Fig. 1) [41,42,73,83,84]. This has provided a useful system to dissect mechanisms that mediate leukocyte wound attraction. The chemotaxis of leukocytes to sites of injury involves the sensing of a chemotactic gradient, polarization and migration [85]. An early signal in zebrafish larvae is a wound-induced gradient of the reactive oxygen species (ROS), hydrogen peroxide (H_2O_2). Niethammer and colleagues showed that wounding induces a rapid and transient burst of H_2O_2 in the wounded epithelium of larval zebrafish, which mediates early neutrophil recruitment [86]. Inhibition of epithelial ROS production impairs the initial recruitment of neutrophils to wounded tissue. To uncover mechanisms that function downstream of epithelial ROS production, it was found that the Src family kinase (SFK) Lyn becomes activated and is necessary for early neutrophil wound attraction, suggesting that wound-generated ROS can modify signaling within zebrafish neutrophils [87].

The larval zebrafish has also provided insights into other signaling pathways that mediate neutrophil recruitment to wounds, including a key role for chemokine signaling through interleukin-8 (IL-8) generated at the wound edge [88]. Environmental tissue signals also mediate neutrophil recruitment, including changes in osmotic signals induced by wounding. Cellular swelling occurs after wounding and induces activation of cytosolic phospholipase A2 (cPLA2), the production of non-canonical arachidonate metabolites and leukocyte recruitment [89]. Finally, wound-induced waves of calcium (Ca^{2+}) in the CNS are associated with recruitment of microglial cells, supporting the idea that there are diverse environmental cues that mediate inflammation in response to damage [90]. Taken together, these studies highlight the complex changes that occur within tissues that orchestrate leukocyte recruitment and inflammation in response to tissue damage and highlight the importance of the zebrafish model.

7. Resolution of inflammation at wounds

Wound resolution occurs when the wound is sealed and inflammation resolves. In part, the resolution of inflammation occurs when the inciting triggers, including damage signals or infection, are no longer present [85]. However, with some diseases like pyoderma gangrenosum, there is impaired wound healing and inflammation does not resolve. This raises the intriguing question: what resolves inflammation? Is this a passive process that occurs when the positive trigger ends? Or are there active processes that mediate resolution through the release of pro-resolving factors [91]? In mammalian models there has been substantial progress in identifying factors like resolvins and other lipid mediators, that mediate resolution of inflammation, and this has been an area of great interest in terms of its therapeutic potential [91–94]. Resolution of innate immune inflammation is generally considered to be orchestrated by macrophages and is characterized by the clearance of apoptotic neutrophils by macrophages [75,95]. There is also evidence that this form of innate immune resolution occurs in zebrafish [41,47,76]. However, studies of neutrophil behavior in the zebrafish revealed that neutrophil apoptosis at the wound site is a rare event, with less than 3% undergoing apoptosis [96].

Live imaging of transgenic zebrafish larvae has identified a novel mechanism of inflammation resolution by the reverse migration of neutrophils from wounded tissue back toward the vasculature [42]. In subsequent studies, using photoconvertible Dendra2, the fate of wound-associated neutrophils was observed and it was found that neutrophils traffic repeatedly between damaged tissue and the vasculature before finally resolving this response by reverse migration away from the wound, often back into the vasculature where they traffic to diverse tissues [97]. The role of these sensitized neutrophils in subsequent host immune responses has not yet been defined. Studies in mice also suggest that neutrophils can undergo reverse migration from tissues into the vasculature [98]. The cues that mediate this reverse migration are just beginning to be uncovered in zebrafish but include pathways through hypoxia inducible factor-1 alpha (HIF-1α) [96]. There is also evidence that this reverse migration may be targeted using small molecules to optimize inflammation resolution [99].

An important aspect of inflammation resolution is the loss of signals that induce inflammation. An intriguing study by Pase et al., demonstrated that neutrophil myeloperoxidase (MPO) is an important factor that resolves inflammatory signaling by depleting H_2O_2 at the wound [100]. The zebrafish larvae, deficient in MPO, have sustained H_2O_2 signaling at the wound and impaired inflammation resolution [100]. This finding is interesting because humans who are deficient in MPO can have chronic inflammation [101]. These studies highlight that the zebrafish model system has been instrumental in the identification of novel regulators of leukocyte resolution and will certainly be poised to help identify other factors which mediate resolution by attenuating pro-inflammatory signaling at the wound site or alternatively promoting neutrophil phagocytosis or reverse migration.

8. The role of early wound signaling in wound resolution and regeneration

Early signaling at wounds through ROS and calcium are necessary for leukocyte recruitment to tissue damage in epithelial tissues and the CNS [86,87,90]. But what impact do these early signals have on wound resolution and repair? Recent studies suggest these early wound signals may, in fact, influence the wound healing outcome. For example, tail transection in zebrafish induces early ROS signaling and activation of the SFK Fyn within the epithelium. Inhibition of early ROS or SFK signaling for just 2 h around the time of wounding impairs late regeneration and resolution of healing three days later, suggesting that early signals may orchestrate the subsequent regeneration program [59]. However, it is not clear if this defect in regeneration is due to impaired wound resolution or alternatively is due to a direct link between early signaling and regeneration, independent of the effects on inflammation resolution. Early Ca^{2+} signaling waves in the epithelium and CNS in zebrafish are also associated with wound resolution and regeneration [59,90]. Moreover, a requirement for early wound signaling

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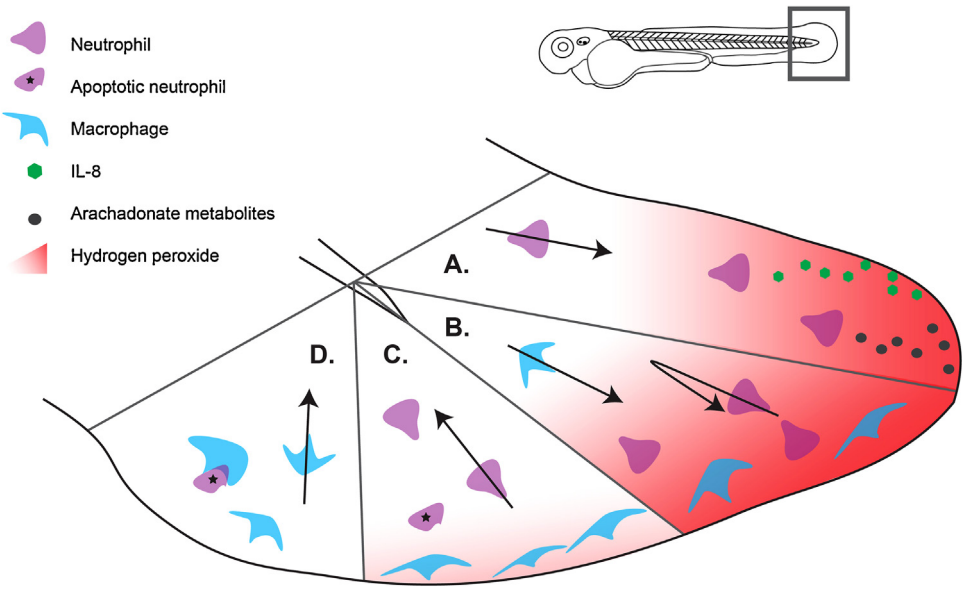

Fig. 1. Schematic of innate immune inflammation induced by wounding in zebrafish. (A) Wounding induces neutrophil recruitment through different cues including a tissue-scale gradient of hydrogen peroxide, cellular swelling-induced production of non-canonical arachadonate metabolites, and IL-8 production. (B) Recruitment of macrophages occurs after neutrophils, and the cues are not well defined. After recruitment, neutrophils can reverse migrate from the damaged tissue, the function of which is unknown. (C) Resolution is regulated by neutrophil reverse migration, and neutrophil apoptosis accompanied by a resolution of wound signals including hydrogen peroxide. (D) Wound debridement by macrophages further contributes to wound resolution and regeneration. Macrophages phagocytose apoptotic neutrophils to mediate resolution.

has been demonstrated during *Xenopus* tadpole tail limb regeneration, indicating a conserved regeneration pathway [102]. Future studies will need to continue to unravel both the pathways involved in early wound signals, and their roles in specific cell types in the damaged tissue.

Among the cells that regenerate during caudal-fin regeneration are sensory neurons, which re-establish axon branching. Interestingly, regeneration of these axons occurs more rapidly when the surrounding epithelium has been wounded, supporting a key role for the wound microenvironment [103]. This suggests that wounded epithelium release a factor(s) to promote axon regrowth. One such factor appears to be H_2O_2. Addition of exogenous H_2O_2 to axon ablations in which the surrounding epithelium is not damaged improves axon regeneration. Meanwhile, blocking of H_2O_2 production in axons regenerating in the presence of epithelial injury efficiently reduces the growth-promoting effect of the skin injury [103]. The study provides further evidence of inflammatory integration during damage repair, although the downstream effectors of the H_2O_2 were not identified.

There are many putative downstream targets of H_2O_2 that can mediate wound healing, including inactivation of phosphatases or activation of kinases through the oxidation of cysteine residues [104]. Our recent studies have implicated Lyn and Fyn as downstream targets that mediate H_2O_2 effects during wound healing [59,87]. To further characterize the effect of H_2O_2 signaling during tissue repair, Gauron et al., performed caudal-fin amputations on adult zebrafish and studied changes to blastema function [105]. The blastema is a mass of lineage-restricted progenitors that accumulate underneath the wounded epithelium. The blastema mediates the proliferation and patterning of the regenerating fin [106]. Adult zebrafish produce a prolonged burst of H_2O_2 (compared to larval zebrafish) at the site of amputation. In this context, the extended burst of H_2O_2 leads to the activation of c-Jun N-terminal kinase (JNK) and a wave of epidermal apoptosis. Inhibition of the apoptosis or JNK signaling results in a smaller blastema, suggesting that H_2O_2 can influence epidermal cell proliferation through the regulation of apoptotic/JNK signaling [105].

The CNS of the zebrafish shows improved regeneration of neurons compared to mammals. However, not all nerve cell types are easily repaired in zebrafish. For instance, Mauthner cells (M axon) are myelinated neurons that regenerate poorly after spinal lesion [61,107]. The inability to regenerate is thought to be the result of inhibitory molecules in the surrounding environment or alternatively from intrinsic factors. Attempts to identify the intrinsic factors have identified cyclic adenosine monophosphate (cAMP) as a regulator of axonal sprouting *in vitro* [108–110]. Acting as a second messenger, cAMP dampens inflammation and thus, inhibits the innate immune response [111]. To determine if cAMP could influence the regenerative outcome of the M axon in the larval zebrafish, Bhatt et al. induced spinal lesions and pressure injected membrane-permeable dibutyryl-cyclic adenosine monophosphate (db-cAMP) two days after injury. They found that addition of db-cAMP induced regeneration of the M axon, suggesting that cAMP promotes the regeneration of the injured M axon [112]. Interestingly, cAMP acts to dampen the innate immune response, suggesting the improved M axon regeneration may be mediated in part through changes in innate immune inflammation.

9. Future

Advances in imaging, genetic tools and chemical genetics have positioned zebrafish as a powerful tool to dissect the temporal and spatial relationship between inflammation and wound repair. Recent advances have unraveled key pathways that mediate early signaling at wounds and the onset of inflammation using zebrafish. The identification of reverse neutrophil migration as a mechanism that can resolve local inflammation is an example of how the zebrafish model can help to uncover new mechanisms during wound repair by exploiting live imaging to probe temporal and spatial interactions in live zebrafish. Moreover, the idea that acute inflammation can facilitate regeneration in the adult zebrafish brain raises exciting new avenues for investigations into CNS regeneration. Finally, zebrafish are poised to help unravel key pathways through which environmental cues like hypoxia regulate cell reprogramming and tissue repair [113,114]. In the long term, it is the type of information that may help to unravel mechanisms that

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identify new avenues for the treatment of patients with chronic tissue damage.

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