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Review

Innate immune system and tissue regeneration in planarians: An area ripe for exploration

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ABSTRACT

The immune system has been implicated as an important modulator of tissue regeneration. However, the mechanisms driving injury-induced immune response and tissue repair remain poorly understood. For over 200 years, planarians have been a classical model for studies on tissue regeneration, but the planarian immune system and its potential role in repair is largely unknown. We found through comparative genomic analysis and data mining that planarians contain many potential homologs of the innate immune system that are activated during injury and repair of adult tissues. These findings support the notion that the relationship between adult tissue repair and the immune system is an ancient feature of basal Bilateria. Further analysis of the planarian immune system during regeneration could potentially add to our understanding of how the innate immune system and inflammatory responses interplay with regenerative signals to induce scar-less tissue repair in the context of the adult organism.

1. Introduction

The process by which form and function is reestablished after tissue injury has puzzled the scientific community for hundreds of years [1–3]. Tissue injury triggers localized and systemic signals that orchestrate mechanical and cellular responses aimed at reducing the surface area of the wound, repair damage, and coordinating functional integration between new and pre-existing structures [4,5]. The immune system and the inflammatory responses associated with injury have been implicated as critical modulators of wound repair and regeneration [6–10]. For instance, effective repair of wounded skin in mammals, and regeneration of complex structures in amphibians (e.g. tail and limbs) rely on the correct synchronization of the immune response upon injury [6–11]. Recent studies suggest that the difference in regenerative capacity of some species is inversely correlated with the complexity of the immune system (Fig. 1) [7,9]. However, the mechanisms integrating immune responses to injury and the process of tissue repair remain poorly understood.

Upon injury the host-mediated immune response not only defends against infection, it facilitates the removal of cellular debris near the site of the wound. These functions may also modulate the cellular response that initiates repair and reestablishes tissue function. It is conceivable that both the injury-induced immune response and the process of tissue repair evolved together to promote and preserve multicellularity. The possibility of shared origin is supported by the fact that regeneration is an attribute widely distributed across multicellular organisms, and immunity is an ancient feature that emerged from the common ancestor of Cnidaria and Bilateria [12–18]. Coexistence of both regeneration and the immune system is observed in the simplest animals such as the diploblastic cnidarian Hydra, which regenerate entire body parts in presence of a primitive complement system and which have many genes associated with the mammalian immune response [16,17,19,20]. Evaluating the evolution and intermingling of the immune response and process of regeneration following injury may provide a new depth to our understanding of tissue repair mechanisms across the animal kingdom.

Planarians are non-parasitic flatworms that provide compelling evolutionary reasons to analyze injury-induced immune responses and the process of regeneration in metazoans [21,22]. Planarians display bilateral symmetry and derivatives of all three germ layers (ectoderm, mesoderm and endoderm). Adult planarians can regenerate any part of their body and constantly renew aging and damaged tissues (Fig. 2), which are features missing

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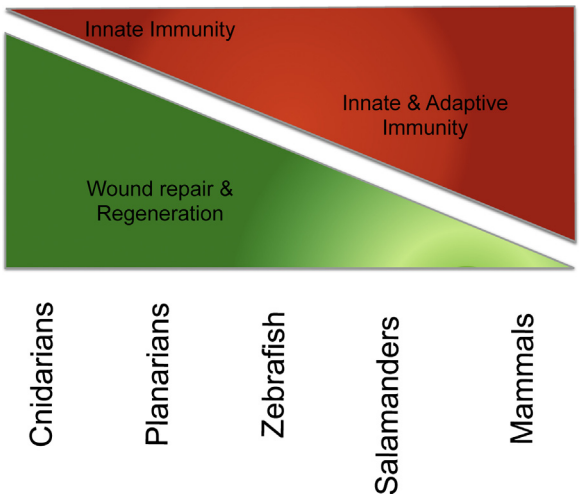

Fig. 1. Inverse correlation between immune system complexity and regenerative capacity. With increasing complexity of the immune system, the regenerative capacity of the organism is decreased. In some invertebrate species without an adaptive immune system, and salamanders with a more complex immune system scar-less repair occurs. In contrast, mammals tend to have scar-forming injury repair and reduced regenerative capacity.

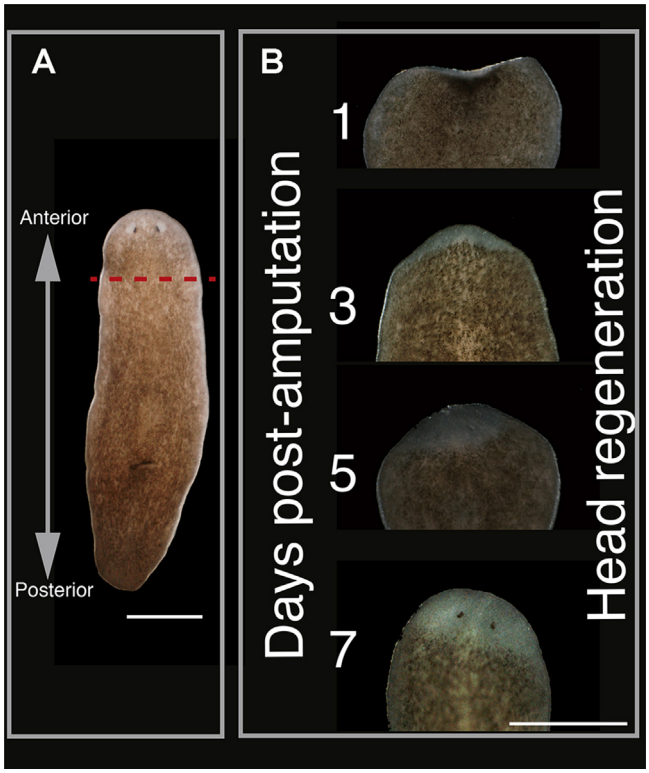

Fig. 2. The planarian *Schmidtea mediterranea* constantly renew aging and damaged tissues, and can regenerate any part of their body upon injury. (A) Adult specimen of *S. mediterranea*. Red dotted line describes plan of amputation. (B) Regeneration of the anterior part including the entire brain, part of the digestive system, muscles, and other derivatives of the three embryonic germ layers are re-established in only 7 days after decapitation. After amputation, tissue contraction around the injured area is followed by formation of the regenerative blastema, which is the unpigmented tissue where the progeny of the dividing neoblasts is instructed to recreate the missing parts. Scale bar is 200 μm.

in other commonly used invertebrate models (e.g. Drosophila and *Caenorhabditis elegans*). Regeneration and adult tissue turnover in planarians proceed through activation of somatic stem cells known as neoblasts [23–25]. Planarians have provided a classical model to study regeneration for over 200 years, but their immune system remains largely unexplored [1,26–28]. To our knowledge, no systematic analysis of the planarian immune system has been published to date. We present a brief survey of the most salient components of the innate immune system through genomic analysis between the freshwater planarian *Schmidtea mediterranea* and other animal species. We analyzed two sources: the *S. mediterranea* genome database, SmedGD [29] and transcriptomic work of Sandman et al. [30] to evaluate genes associated with the immune system and their expression during regeneration. Our findings suggest evolutionary conservation of the triclad immune system. We identified components of the *S. mediterranea* immune system that may protect against infections, distinguish between commensal and pathogenic microorganisms, and that actively participate during wound repair, regeneration and maintenance of adult tissues.

2. The planarian model system and tissue regeneration

Planarians are known for their extraordinary capacity to regenerate adult tissues. These animals can regenerate any part of their body including their entire digestive system, brain and neural connections, muscles, and connective tissues. Planarians are easy and inexpensive to maintain under laboratory conditions and are amenable to molecular, genetic, behavioral and computational analysis [1,26,31–34]. During the past 20 years, planarian research has attracted attention due to the accessibility of this model organism and the opportunities to progress our understanding in long standing biomedical problems associated with regeneration, cancer and degenerative diseases. Several tools available to aid in the study of planarians, include the *S. mediterranea* genome, proteomic data, results from high-throughput RNAi-screens and transcriptomic analysis [1,25,26,29,32,34–38]. Altogether with the availability of standard genetic and biochemical techniques, planarians present an attractive model to study wound repair and regeneration and the possible interplay of the immune system during these processes.

Detailed information about the biology of planarians and recent advances on research pertaining to its regenerative capacities has been reviewed elsewhere [1,23–25,28]. In this section, we aim at providing a brief overview of the process of regeneration in *S. mediterranea*, the most commonly used planarian species. Planarian regeneration is quick, taking about a week to reestablish form and function. Immediately following amputation, contraction around the injury reduces the damaged surface. In the first 24 h local cell death peaks, followed by neoblast proliferation and H^+/K^+-ATPase-mediated tissue depolarization around the wounded area [39–42]. The antagonistic process of cell death and proliferation around the injured area is critical for the progression of regeneration. The H^+/K^+-ATPase-mediated ion flux and consequent tissue depolarization is required for anterior tissue specification and may provide signaling that guides neoblast proliferation, migration and remodeling [5,39,40]. Decisions regarding polarity are defined within the first few hours post-amputation and differentiated tissues may provide molecular cues and guidance during regeneration [1,25,28,43]. Neoblasts, the only dividing cells in adult planarians serve as the exclusive source of new cells during the formation of the blastema (a regenerative outgrowth around the injured area).

Neoblast division gives rise to cellular progeny that migrate and differentiate within the blastema. Remodeling and integration between the new and pre-existing tissue is an active process during regeneration but little is known about the signals mediating these

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