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Integrative biology of injury in animals

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ABSTRACT

Mechanical injury is a prevalent challenge in the lives of animals with myriad potential consequences for organisms, including reduced fitness and death. Research on animal injury has focused on many aspects, including the frequency and severity of wounding in wild populations, the short- and long-term consequences of injury at different biological scales, and the variation in the response to injury within or among individuals, species, ontogenies, and environmental contexts. However, relevant research is scattered across diverse biological subdisciplines, and the study of the effects of injury has lacked synthesis and coherence. Furthermore, the depth of knowledge across injury biology is highly uneven in terms of scope and taxonomic coverage: much injury research is biomedical in focus, using mammalian model systems and investigating cellular and molecular processes, while research at organismal and higher scales, research that is explicitly comparative, and research on invertebrate and non-mammalian vertebrate species is less common and often less well integrated into the core body of knowledge about injury. The current state of injury research presents an opportunity to unify conceptually work focusing on a range of relevant questions, to synthesize progress to date, and to identify fruitful avenues for future research. The central aim of this review is to synthesize research concerning the broad range of effects of mechanical injury in animals. We organize reviewed work by four broad and loosely defined levels of biological organization: molecular and cellular effects, physiological and organismal effects, behavioural effects, and ecological and evolutionary effects of injury. Throughout, we highlight the diversity of injury consequences within and among taxonomic groups while emphasizing the gaps in taxonomic coverage, causal understanding, and biological endpoints considered. We additionally discuss the importance of integrating knowledge within and across biological levels, including how initial, localized responses to injury can lead to long-term consequences at the scale of the individual animal and beyond. We also suggest important avenues for future injury biology research, including distinguishing better between related yet distinct injury phenomena, expanding the subjects of injury research to include a greater variety of species, and testing how intrinsic and extrinsic conditions affect the scope and sensitivity of injury responses. It is our hope that this review will not only strengthen understanding of animal injury but will contribute to building a foundation for a more cohesive field of 'injury biology'.

Key words: autotomy, costs, damage, trade-offs, integrative biology, mechanical injury, metazoan, physiology, regeneration, wound healing.

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I. INTRODUCTION

Injury is a challenge that animals frequently encounter in nature and that can have profound consequences on biological systems. Mechanical injury – damage to anatomical structure that results from direct contact (hereafter simply referred to as 'injury') – threatens organismal function, homeostasis, and survival. Effects of injury can be large and are wide-ranging, spanning all levels of biological organization from the molecular to the ecological. A significant degree of conservation in responses to injury at lower levels between distantly related animal lineages (Martin & Nunan, 2015; Wenger *et al.*, 2014) suggests that injury may have long been important in animal evolution.

Although injury has been studied from many perspectives and in a wide diversity of species, and despite the high likelihood that injury effects at different levels of biological organization are interrelated, the literature on injury lacks broad synthesis and cohesion. For example, an impressive body of knowledge regarding the molecular and cellular responses to injury derives heavily from groups like vertebrates (Levesque, Villiard & Roy, 2010; Martin & Nunan, 2015; Niethammer, 2016) and insects (Razzell, Wood & Martin, 2011), but knowledge of the prevalence of injury and its potential ecological significance in these groups is far less impressive in comparison to, for example, that in marine invertebrates (Lindsay, 2010). Thus, knowledge about injury in general is highly uneven across focal areas and animal groups. Significant challenges to integration include the use of different study systems, the use of different terminologies, the different cultures of experimental design, and especially the divergent emphases and motivating questions between research communities; these all hamper dialogue across subdisciplines of research that are relevant to injury biology. A particularly deep divide exists between research motivated by biomedical goals, which mostly focuses on 'skin-in' work and seeks commonalities, and research motivated by understanding ecological and evolutionary processes, which largely focuses on 'skin-out' work and emphasizes organismal diversity. As a result, our understanding remains limited regarding how complex injury responses are linked across levels of organization, such as from changes in gene expression to whole-organism responses, or from physiology to population biology.

Developing an integrative view of 'injury biology' is challenging but necessary in order to understand animals in all their functional complexity. The 'injury response' is a complex trait, and integrative work is needed to understand how these responses are shaped by shared histories and past and ongoing natural selection. Such work can help clarify how much variation in these responses is consequential for animals, whether the source of injury matters for downstream effects, or even whether 'injury' is a meaningful way to unite diverse phenomena at any level of biology. Without synthesis, insights into prey responses to sublethal predation may lack understanding of the complex physiological processes that mediate such responses, and knowledge of the shared or divergent molecular and cellular effects of injury across animal groups may miss the ecological and evolutionary context. As another example, understanding why certain animals can and others cannot regenerate body structures requires understanding the evolutionary pattern of regeneration (Bely & Nyberg, 2010; Elchaninov, Sukhikh & Fatkhudinov, 2021), which itself requires understanding the physiological systems involved in the injury response and how their variation may be subject to selection. A similar point applies to understanding the ecological role and evolution of autotomy, the process of self-induced appendage loss (Fleming, Muller & Bateman, 2007; Higham, Russell & Zani, 2013; Maginnis, 2006*b*). Synthesis can help us determine the molecular targets of selection that are involved in adaptations to injury, which is important for understanding what aspects of injury responses are conserved *versus* convergent or divergent between species.

As a step towards developing an integrative understanding of the effects of injury in animals, this review synthesizes current knowledge about animal injury, pulling together research from disparate fields and diverse animal groups.

We begin by highlighting the prevalence of injury in nature and then review the effects of injury from across the animal kingdom and across levels of biological organization, focusing specifically on molecular and cellular effects, physiological and organismal effects, behavioural responses, and ecological and evolutionary consequences of injury. We highlight the many ways in which effects across these levels are linked and discuss the importance of stronger integration across injury biology. By assessing the general state of our knowledge, we identify important gaps that remain regarding the effects of mechanical injury in animals and general principles that are emerging from these data. We hope that this synthesis is valuable in promoting a deeper understanding of injury biology and will stimulate the generation of new hypotheses and help to guide future research.

II. INJURY IN NATURE

Injury is widespread in nature and can be caused by a variety of factors. Among the most prevalent sources of injury are predatory interactions, non-predatory biotic interactions (e.g. territorial encounters, mating rituals), damaging movements (e.g. falls, impacts), and damaging abiotic forces (e.g. crushing or shearing by physical substrates) (Archie, 2013; Crook *et al.*, 2011; Figiel & Semlitsch, 1991; Juanes & Smith, 1995; Meszaros & Bigger, 1999; Mukherjee & Heithaus, 2013; Palmer *et al.*, 2011). Injuries themselves also vary greatly in severity, from minor nicks, bumps, and abrasions to complete destruction or amputation of large body portions.

Assessing injury rates in the wild can be challenging. The sources and prevalence of injury vary greatly across animals for numerous reasons, and studies that have attempted to estimate injury rates often reveal striking findings, indicating that an injured state may be the norm for many animals. For example, an average of roughly one-third to one-half of marine benthic invertebrate populations are visibly injured at any given time, and in some populations, over 70% of individuals may be injured (Lindsay, 2010). High injury rates have been reported in groups as diverse as decapod crustaceans (an average of 25% and up to 80% with limb damage) (Juanes & Smith, 1995), pygmy octopuses (*Octopus digueti*) (over 25% with arm damage) (Voight, 1992), lizards (over 50% with tail damage) (Arnold, 1984; Fleming *et al.*, 2007), sabellid polychaetes (e.g. *Schizobranchia insignis*) (up to 100% with damage to feeding and respiratory structures) (Brown & Emlet, 2020), and anuran tadpoles (approximately 50–90% with tail damage) (Blair & Wassersug, 2000). Animal fossil records indicate that sublethal injury was prevalent in the past, with some of the best evidence coming from Paleozoic invertebrates like crinoid echinoderms, trilobites, and molluscs (Baumiller & Gahn, 2004, 2013; Bicknell & Holland, 2020; Ebbestad & Peel, 1997).

Injury is so pervasive that, for many species, every individual can be expected to sustain some kind of injury in its lifetime, and, in some species, individuals will likely experience frequent, repeated injury (Juanes & Smith, 1995; Lindsay, 2010). Furthermore, sublethal injury rates are likely underestimated in animals capable of regeneration, the process by which new tissue replaces that which is damaged or lost, resulting in new tissue that is often visually indistinguishable from the original (Bernardo & Agosta, 2005; Juanes & Smith, 1995; Lindsay, 2010). Many animals can even lose and regenerate the same body parts multiple times throughout their lives, such as clam siphons (Sasaki *et al.*, 2002; Tomiyama & Omori, 2007), polychaete palps (Zajac, 1985), hydra tentacles (Wenger *et al.*, 2014), and lizard tails (Barr *et al.*, 2019; Jacyniak, McDonald & Vickaryous, 2017). Understanding the ultimate ecological significance of the effects of injury that are discussed in Section III can be improved by developing more accurate methods of quantifying injury in the wild and in more animal groups, as we note a glaring lack of studies concerning terrestrial populations.

III. EFFECTS OF INJURY ACROSS LEVELS OF BIOLOGICAL ORGANIZATION

The effects of injury are diverse and span across levels of biological organization. At the cellular and molecular level, injuries induce complex pathways that serve a variety of functions such as sealing the wound, preventing fluid loss, combating infection, and coordinating the movements, divisions, and differentiation states of cells. At the physiological and organismal level, injuries often alter organismal function over the short to long term. At the level of behaviour, injuries may change the way animals interact with one another or with their environment in order to avoid further injury or mitigate the effects of injuries already suffered. Consequences of injury to organisms can collectively produce effects at the ecological level, affecting population or community dynamics and composition. Responses to injury are ultimately shaped by evolutionary history and also mediate ongoing selection on the injury response. Direct effects of injury are not only apparent within these aforementioned levels, but effects are also likely to involve feedbacks, linkages, and interrelated effects within and among biological levels (Fig. 1). The nature and magnitude of both direct and indirect effects depends on a broad range of factors (Fig. 2), including characteristics of the injury, the context in which injury occurs, and any recovery processes an animal might be capable of for repairing the damage (such as regeneration).

(1) Molecular and cellular effects of injury

Injury rapidly induces molecular and cellular responses with diverse functions. These include wound detection, pathogen defence, haemostasis, gene regulation, inflammation, cell proliferation, and wound healing and other end states

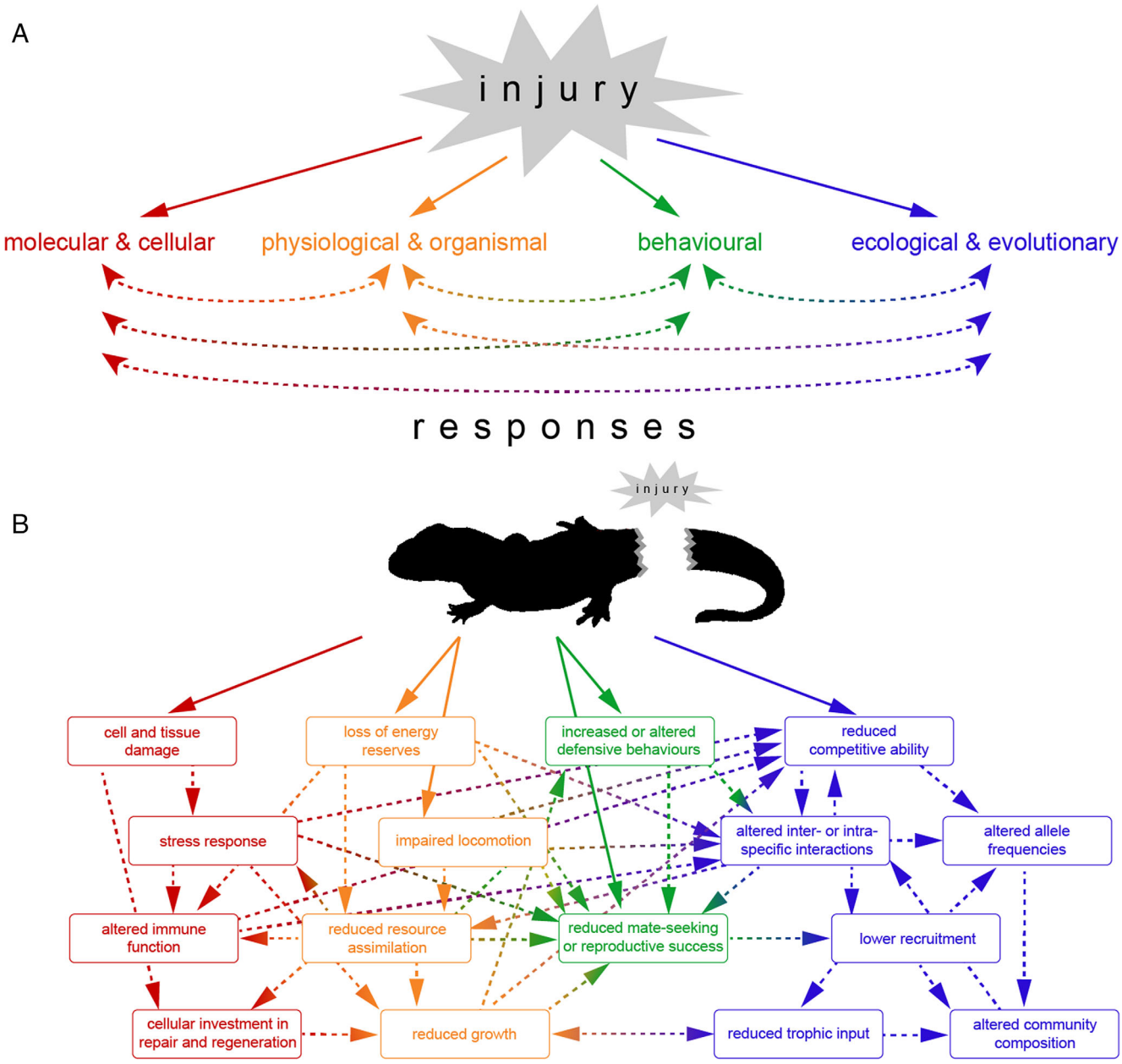

Fig. 1. Consequences of sublethal mechanical injury and interactions between effects within and among levels of biological organization. Solid arrows indicate possible immediate or direct effects of an initial injury; dashed arrows indicate any possible relationships between these downstream effects. (A) Conceptual schematic of the biological scales at which injury may lead to effects or responses and the potential linkages between responses at these levels. (B) Hypothetical example of direct and indirect consequences of injury in an animal (e.g. tail amputation in a tetrapod), based broadly on conjectured and demonstrated relationships in multiple species.

(e.g. scarring, regeneration). Much of the available information on wound responses at the molecular and cellular level comes from vertebrates, particularly model systems such as zebrafish (*Danio rerio*) and rodents (e.g. Godwin & Brockes, 2006; Gurtner *et al.*, 2008; Martin & Nunan, 2015; Niethammer, 2016; Velnar, Bailey & Smrkolj, 2009), in addition to a handful of invertebrate systems, especially *Drosophila melanogaster* (Antunes *et al.*, 2013; Belacortu & Paricio, 2011; Razzell *et al.*, 2011; Repiso *et al.*, 2011). As wound responses in these systems have been reviewed in depth, here, we provide only an overview of the key processes involved and emphasize information from outside the major model systems.

(*a*) *Wound detection and pathogen defence*

When a mechanical injury is sustained, the first step in the wound response is detection. Early wound detection involves a number of processes that are largely conserved among

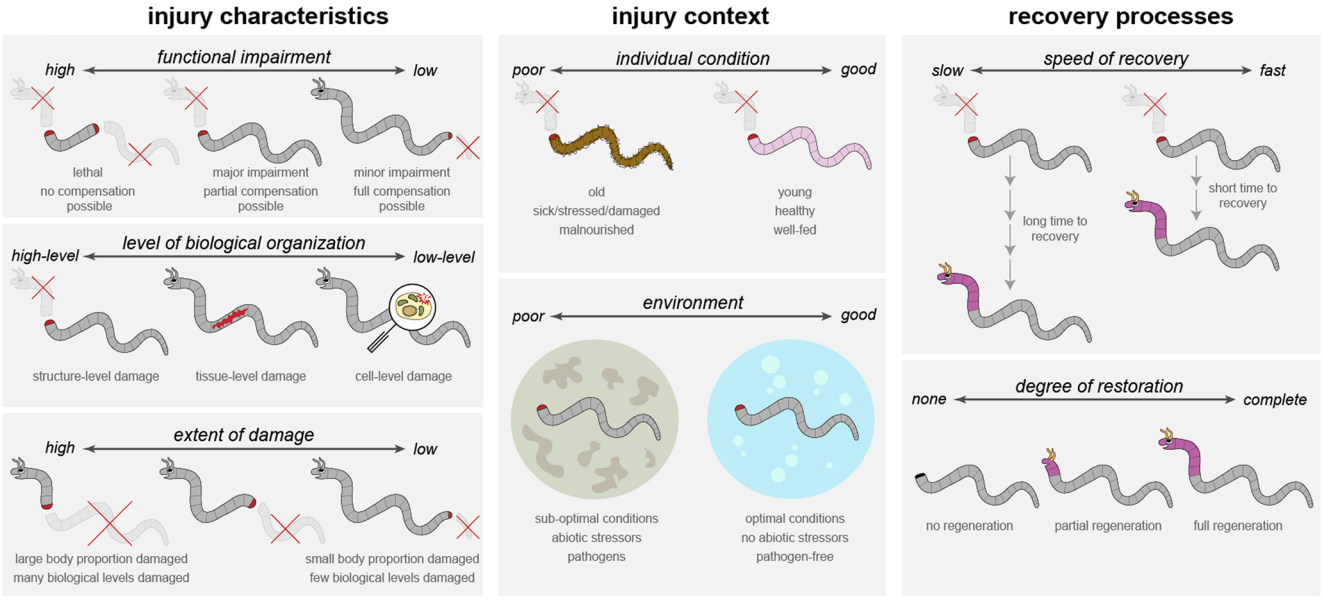

Fig. 2. Intrinsic and extrinsic factors that influence the nature and severity of injury consequences in animals. Factors may be categorized into three broad categories: (*i*) immediate injury characteristics, which includes the degree of direct functional impairment resulting from the injury, the form or level of damage inflicted (e.g. scales of biological structures damaged, such as whole-appendage *versus* cellular-level damage), and the severity or degree of damage (e.g. relative proportion of a given body part damaged); (*ii*) injury context, which includes the individual condition of the animal (e.g. nutritional status, age, parasite load, disease, pre-existing un- or partially/imperfectly repaired damage) and characteristics of the environment which may be optimal or physiologically stressful (e.g. temperature, oxygen availability, humidity, salinity, microbiota); and (*iii*) recovery processes, which includes the speed at which recovery occurs and the degree of restoration that takes place, including the potential regeneration of lost structures. Factors presented here are not exhaustive.

metazoans. Some of these even overlap substantially with damage- and pathogen-detection pathways in plants (Jones & Dangl, 2006; Newman *et al.*, 2013) and unicellular eukaryotes, including choanoflagellates (the closest relatives of animals) (Alegado *et al.*, 2012), suggesting that basic wound-healing responses have ancient origins (Wenger *et al.*, 2014). The suite of molecules released by cellular disruption that act as initial wound signals is referred to as a damage-associated molecular pattern (DAMP), which may include formylated peptides, adenosine triphosphate (ATP), free fatty acids, and calcium ions, among other molecules (Niethammer, 2016; Wenger *et al.*, 2014; Zhang *et al.*, 2010). In metazoans, many of these molecules induce transcription of pro-inflammatory gene products, and DAMPs also serve as chemoattractants for leukocytes in vertebrates (Niethammer, 2016; Wenger *et al.*, 2014; Zhang *et al.*, 2010). Comparative work in mice of contrasting regenerative abilities suggests that the strength of an initial DAMP could be important for subsequent regeneration potential (Simkin *et al.*, 2017). Calcium signalling, in particular, has been demonstrated to be crucial for cellular post-injury responses in several very different model organisms [e.g. flies, nematodes, zebrafish (Razzell *et al.*, 2013; Xu & Chisholm, 2011; Yoo *et al.*, 2012)], hinting at primordial emergence of these early pathways. Upon cellular recognition of DAMPs, various pathways activate that, although often highly variable in exact composition, ultimately function to eliminate or repair damaged cells and subcellular components, mitigate pathogenic threats, and rebuild damaged tissue; these pathways comprise animal innate immunity, a system that exists in some form from vertebrates (Romo, Pérez-Martínez & Ferrer, 2016) to non-bilaterian animals (Wenger *et al.*, 2014).

There has been intriguing recent work implicating other factors besides DAMPs in early wound responses. In particular, bioelectrical gradients and mechanical forces may serve as key early wound signals as well as be involved in subsequent coordination of wound healing and extensive structural repair in animals. Research in various animals, although most notably in planarians, has uncovered the critical role that voltage gradients altered by injury, not only across cell membranes and tissue layers but even the entire animal body, may play in activating and regulating morphogenetic pathways (Levin, 2009; Levin, Pietak & Bischof, 2019). Abrams *et al.* (2015) similarly discovered that disruption of whole-body organization itself acts as the impetus for repair in ephyrae of the jellyfish *Aurelia aurita*. Damage that disrupts body symmetry subsequently alters the forces of propulsion acting upon the swimming animal, which drive reestablishment of radial symmetry without the involvement of apoptosis, proliferation, or tissue regeneration. These findings together suggest that, although some aspects of the wound-detection response may be broadly conserved at the (sub)cellular level among different animals, the morphology

of the whole organism can be a significant factor mediating the response to injury, even from the initial stages. These findings raise the intriguing possibility that morphological diversity, in and of itself, may ultimately be responsible for significant diversity in responses to injury, driven perhaps by the functional requirements of different animals.

Preventing infection by foreign organisms is one of the primary functions of the injury response. Wounding typically includes a breach of physical barriers to the external environment, such as the skin, cuticle, or outer epithelium, which increases the risk of entry by harmful bacteria, viruses, or other invaders (Archie, 2013; Velnar *et al.*, 2009). Humoral defence mechanisms triggered by wounding have been documented in diverse animals as discussed below [the term 'humoral' here encompassing a diverse number of body fluids, such as blood or haemolymph (Monahan-Earley, Dvorak & Aird, 2013)].

Antimicrobial peptides (AMPs), structurally and functionally diverse molecules that protect injured animals against pathogens (Wang, 2010), are known to be upregulated early on following tissue damage in diverse animals including cnidarians, molluscs, annelids, nematodes, arthropods, and vertebrates (Bodó *et al.*, 2021; Chisholm, 2014; Pujol *et al.*, 2008; Romo *et al.*, 2016; Vafopoulou, 2009; van de Water *et al.*, 2015; Wenger *et al.*, 2014). In the nematode *Caenorhabditis elegans*, separate injury and infection pathways converge upon regulation of AMPs (Pujol *et al.*, 2008), indicating that the injury response is integrated with animal immunity without necessarily deriving from it. AMP expression may be complemented by expression of other molecules with antimicrobial function, such as lysozymes and lectins, as in arthropods (Liu, Ling & Wu, 2009; Rowley & Powell, 2014; von Wyschetzki, Lowack & Heinze, 2016). The presence of pathogens during wounding can increase AMP expression further, as demonstrated in bees (Erler, Popp & Lattorff, 2011; Koleoglu *et al.*, 2017). Non-sterile wounding may compromise other components of immunity. For example, Liu *et al.* (2009) found in silkworm (*Bombyx mori*) larvae that non-sterile wounding elicits fewer serine proteases, serpins, lectins, and other genes with non-pathogen-specific immune functions (e.g. which may be involved in clotting pathways) than sterile wounding, which the authors suggest may be a strategy to conserve energy and other resources to invest more heavily in pathogen defence.

An example of a conserved anti-pathogenic pathway that also has evolved in some animal lineages to play a role in wound healing is melanization. Aspects of this pathway, involving production of the pigment melanin *via* phenoloxidase, exist throughout animals but have been described most extensively in arthropods (Bilandžija *et al.*, 2017; Söderhäll & Cerenius, 1998). Melanization has pleiotropic functions in both wound healing and anti-microbial defence (Bilandžija *et al.*, 2017; González-Santoyo & Córdoba-Aguilar, 2012; Palmer *et al.*, 2011; Söderhäll & Cerenius, 1998; Theopold *et al.*, 2002). Wounding alone has been shown specifically to upregulate phenoloxidase in several insects (Bidla *et al.*, 2009; Reavey *et al.*, 2014) and crayfish (Vafopoulou, 2009), as well as in several species of coral (Palmer *et al.*, 2011; van de Water *et al.*, 2015). Evidence in zebrafish indicates that melanin may be important for wound healing in vertebrates as well (Lévesque *et al.*, 2013), where it of course has additionally evolved a function in human skin pigmentation (Mackintosh, 2001). Together, these findings serve as a case of diverse animal lineages using ancestral machinery to evolve comparable responses to injury while also facilitating other needs specific to different taxa.

(*b*) *Haemostasis*

Open wounds may leak fluids such as blood or haemolymph, which must be stopped quickly to prevent severe homeostatic disruption or fatality. The process of fluid leak cessation, known as haemostasis, is common in animals but differs with respect to the mechanisms, cellular components, and level of morphological complexity involved (Soslau, 2020). Contraction of tissue (e.g. skin, muscle) surrounding the wound and of damaged proximal vasculature, if present, can occur reflexively [*via* e.g. altered calcium flux (Niethammer, 2016; Xu & Chisholm, 2011)] to reduce wound diameter; such contractions have been described in diverse taxa including annelids (Özpolat & Bely, 2016), octopuses (e.g. *Octopus vulgaris*, *Eledone cirrhosa*) (Andrews *et al.*, 2016; Polglase, Bullock & Roberts, 1983), nematodes (Xu & Chisholm, 2011), asteroid echinoderms (Pinsino, Thorndyke & Matranga, 2007), and vertebrates (Desmouliere, Chaponnier & Gabbiani, 2005; Levesque *et al.*, 2010; Velnar *et al.*, 2009). Cnidarians are known to use a combination of cell 'crawling' and contraction of actin filaments to close wounds at the level of the epithelium depending upon the degree of damage (Kamran *et al.*, 2017), and a similar epithelial 'purse-string' process occurs in wounded embryos of *D. melanogaster* (Wood *et al.*, 2002), chicks (Lawson & England, 1998), and mammals (Redd *et al.*, 2004).

The degree or even mere occurrence of wound contraction varies, however, including among vertebrates. In *Rana* frogs, wounds contract much more rapidly in larvae than adults, but the share of the original wound area closed by contraction is less, with the remaining area restored by integumental regeneration. As development proceeds, regeneration yields to a greater proportion of contraction until disappearing entirely in adult frogs, which seal the remaining ~10% of cutaneous wound area with scar tissue (Yannas, Colt & Wai, 1996). Somewhat in contrast, adult paedomorphic axolotl (*Ambystoma mexicanum*) close a greater wound area *via* contraction than axolotl post-metamorphosis, although the latter heal more slowly overall, each without scarring (Seifert *et al.*, 2012*c*). Snakes do not exhibit any significant cutaneous wound contraction but rather form a crust over the wound area prior to re-epithelialization (Smith & Barker, 1988).

Following reflexive wound contraction, if it occurs, cellular plugs or clots often form at the wound site through a process called coagulation. This process is widespread: migratory

epithelial cells cover wound openings in octopuses (Andrews *et al.*, 2016; Polglase *et al.*, 1983), coelomocytes form clots in common sea stars (*Asteria rubens*) (Pinsino *et al.*, 2007), platelet plugs precede the formation of a fibrin mesh containing blood cells in mammals (Martin & Leibovich, 2005; Rivera *et al.*, 2009), and other (not necessarily homologous) variants of coagulation occur throughout other invertebrates (Bely, 2014; Galko & Krasnow, 2004; Palmer *et al.*, 2011; Razzell *et al.*, 2011; Theopold *et al.*, 2002, 2004). In some groups, such as nematodes (Chisholm, 2014) and crayfish (Vafopoulou, 2009), many of the mechanisms or signals of haemostasis are not well understood despite the common use of these animals as model systems. For very large wounds, especially in endotherms or other animals with high-pressure circulatory systems, haemostasis may not occur quickly enough to prevent fatal fluid loss (Soslau, 2020).

(c) *Gene expression*

Wounding and the subsequent activation of wound-healing pathways elicits significant changes in gene expression. Injury has been shown to induce differential expression of up to 9% of the transcriptome in *Cardiocondyla obscurior* ant queens (von Wyschetzki *et al.*, 2016), up to 21% in two-spotted crickets (*Gryllus bimaculatus*) (Ohuchi *et al.*, 2013), and up to 15% in the sea cucumber *Apostichopus japonicus* (Sun *et al.*, 2013). The number of differentially expressed genes following injury is over a thousand in the sponge *Aplysina aerophoba* (Wu *et al.*, 2022), in the hundreds in the sea anemone *Calliactis polypus* (Stewart *et al.*, 2017), in the thousands in the earthworm *Eisenia fetida* (Bhambri *et al.*, 2018), in the hundreds in the hemichordate *Ptychodera flava* (Luttrell *et al.*, 2016), and in the hundreds to thousands in fish (Sveen *et al.*, 2019; Wang *et al.*, 2020). The specific genes and pathways induced by wounding are diverse, typically including those with functions in signalling, cell-to-cell communication, immunity, structural composition, adhesion, cell motility, tissue growth, metabolism, and molecular synthesis, among others (Belacortu & Paricio, 2011; Erler *et al.*, 2011; Galko & Krasnow, 2004; Gurtner *et al.*, 2008; Lõhelaid *et al.*, 2014; Sveen *et al.*, 2019; von Wyschetzki *et al.*, 2016; Wenger *et al.*, 2014; Wu *et al.*, 2022).

Transcriptomic responses are complex and highly variable, often differing substantially among species, wound location, regenerative potential, and time points. Such responses have also been shown to differ depending on environmental conditions and individual factors like body size (Husmann *et al.*, 2014) and ontogenetic stage (Husmann *et al.*, 2014; Koleoglu *et al.*, 2017). However, a recent study in a sponge found little differentiation in transcriptomic responses to wounds based on wound size, frequency of damage, or the source of injury (predatory or experimental) (Wu *et al.*, 2022). Together these findings suggest that a non-specific injury response may be ancestral for animals and that responses tailored to specific wound characteristics could have arisen later in the course of animal evolution. Wu *et al.* (2022) additionally note that the pattern of post-injury gene expression resembles those of early regeneration in other animals, suggesting common origins of regeneration and wound repair. Such findings illustrate the value of comparative work on injury responses and the need for more research to understand how injury responses evolved at the molecular level.

One key aspect of the wounding response that is particularly important and generally consistent across animals is the minimal stress proteome, or cellular stress response (CSR). The CSR is a well-conserved, non-specific expression network that serves to repair cellular, protein, and nucleic acid damage, prevent further damage, regulate the cell cycle, and mobilize and reallocate energy for maintaining biological system integrity (Kültz, 2004, 2020*b*; Milisav, 2011; Sulmon *et al.*, 2015). Protein damage, resulting ultimately from the lysing of cells and the release of molecules such as reactive oxygen species (ROS) and cytokines (Basu *et al.*, 2002), serves as the primary signal for many CSR components. Following wounding, markers of oxidative stress, such as antioxidants that mitigate ROS damage, are elevated in both invertebrates and vertebrates, such as in the orb weaver spider *Larinia jeskovi* (Mouginot *et al.*, 2020) and side-blotched lizards (*Uta stansburiana*) (Hudson *et al.*, 2021), with levels of expression varying depending on wound location or severity, respectively. It should be noted that, although ROS may be deleterious if left unchecked, they are necessary for inflammatory cell recruitment to the wound site, as demonstrated in *D. melanogaster* (Razzell *et al.*, 2013) and zebrafish (Niethammer *et al.*, 2009), where they are also critical regulators of later regeneration (Yoo *et al.*, 2012).

Heat shock proteins (HSPs) are also induced by ROS and have perhaps received the most attention among CSR components in studies of wounding. HSPs, a diverse family of proteins including both common and taxon-specific members with a range of cytoprotective functions (Richter, Haslbeck & Buchner, 2010; Sørensen *et al.*, 2005), are upregulated following wounding in diverse animals including cnidarians (Stewart *et al.*, 2017; Wenger *et al.*, 2014), planarians (Sánchez Navarro *et al.*, 2009), bivalves (e.g. *Laternula elliptica*) (Husmann *et al.*, 2014), echinoderms (Matranga *et al.*, 2000; Pinsino *et al.*, 2007; Vazzana *et al.*, 2015), and fish (Li *et al.*, 2014; Sveen *et al.*, 2019). The HSPs are a particularly interesting family of genes to study in relation to injury in part because many are known to provoke a range of immune responses (Colaco *et al.*, 2013).

While many other genes comprise the CSR (Imada & Leonard, 2000; Kassahn *et al.*, 2007; Kültz, 2003, 2020*b*; Milisav, 2011; Roelofs *et al.*, 2008; Shaughnessy *et al.*, 2015; Sulmon *et al.*, 2015), many have not been examined in relation to wounding directly or have only been studied in a limited number of animal groups. Separate sets of adaptive, stressor-specific responses for restoring homeostasis often complement the CSR (Kültz, 2003), but wounding-specific stress responses distinct from the CSR have not been well characterized, limiting our ability to distinguish the potentially unique potential for injury to shape animal biology relative to stress more generally. Additionally, much of the information on expression-level injury responses are derived

from organism-wide sequencing studies, leaving a great deal to be learned regarding spatially localized expression patterns. This is necessary for better understanding of the function of specific cells and tissues in the injury response, including stem cells, which is critical for understanding variation in processes like regeneration.

(*d*) *Inflammation and cellular activity*

Inflammation is one of the classic stages of wound healing in the vertebrate literature, as detailed in several excellent reviews (Bielefeld, Amini-Nik & Alman, 2013; Godwin & Brockes, 2006; Martin & Leibovich, 2005; Martin & Nunan, 2015; Velnar *et al.*, 2009), although analogous phenomena have also been described extensively in *D. melanogaster*, an invertebrate system (Martin & Nunan, 2015; Razzell *et al.*, 2011). An essential role of inflammation in animals is the removal of debris, pathogens, and other cells from the wound area in the early post-injury phase. Inflammatory agents, such as phagocytes, are often stimulated directly by ROS in both vertebrates (Niethammer *et al.*, 2009) and invertebrates (Razzell *et al.*, 2013). ROS have also been shown to promote transcription of inflammatory cytokines in zebrafish (de Oliveira *et al.*, 2015, 2014), molecules that further attract inflammatory cells and perpetuate the process of inflammation across vertebrates (Ashley, Weil & Nelson, 2012).

As may be apparent, much of the knowledge on animal inflammatory responses following injury derives from a handful of model systems, and mostly in mammals, perhaps unsurprisingly. Yet inflammation is a feature of the post-injury response to some appreciable extent in many diverse animals [e.g. cnidarians, octopuses, annelids, arthropods, sea cucumbers, salps, snakes (Andrews *et al.*, 2016; Cima *et al.*, 2018; Liu *et al.*, 2007; Menton & Eisen, 1973; Palmer *et al.*, 2011; Reavey *et al.*, 2014; Robb *et al.*, 2014; Smith & Barker, 1988; Stein & Cooper, 1983)], although the particular cell types, cellular behaviour, and pathways involved vary considerably among these groups. This diversity might suggest that inflammation, at least at a basic level, unifies the cellular post-injury response in animals, and indeed inflammation often seems to be taken for granted as following initial injury signals. However, researchers have reported little evidence of inflammation during wound repair in several groups, including members of the cnidaria (Rodríguez-Villalobos, Work & Calderon-Aguilera, 2016), *D. melanogaster* embryos (Galko & Krasnow, 2004), and axolotls (*Ambystoma* spp.) (Levesque *et al.*, 2010). Interestingly, these animals are all known for their scarless wound-healing ability, leading to some speculation that, although inflammation appears to be quite important for the progression of wound healing in many animals, aspects of the inflammatory process may in some cases be directly responsible for fibrosis and scarring. Inflammation during wound repair is indeed known to contribute to fibrosis and scarring in some species (Bielefeld *et al.*, 2013; Levesque *et al.*, 2010), and studies in mice even suggest that some inhibition of inflammation may provide benefits for wound repair (Martin & Leibovich, 2005). Yet many animals listed above include members that exhibit post-injury inflammation as well as remarkable regenerative ability, as discussed further in this review. Inflammation is, in fact, critical for the regeneration of various tissues in several vertebrates (Aurora *et al.*, 2014; Godwin, Pinto & Rosenthal, 2013; Simkin *et al.*, 2017). The role of inflammation in wound healing thus remains difficult to generalize across animals, illustrating the need for more focused research on inflammatory processes in a greater variety of animals to understand what leads to these differences.

Regardless of the animal group, repairing an injury requires cellular changes. Cellular-level contributions to wound healing may include wound sealing, debris removal, and serving as the material itself for tissue reconstruction, in addition to haemostasis and inflammation as discussed above. Although many of these post-injury tasks will be common regardless of species, the enormous diversity across animals is reflected in their cell types, which essentially requires that the nature of cellular involvement in wound repair vary across animals. The nature of the damage being repaired and the extent of tissue reconstruction that is possible (e.g. wound healing only, complete regeneration) will also contribute to this variation. For example, injury induces significant cell proliferation in most species that have been investigated, including a wide diversity of animals (Ricci & Srivastava, 2018), but proliferation is minimal during repair in a few species and contexts (e.g. Abrams *et al.*, 2015; Galko & Krasnow, 2004; Razzell *et al.*, 2011; Tseng & Levin, 2008). Cells may also be removed during the wound-healing process, such as through apoptosis (programmed cell death), which may reshape remaining tissues and recycle resources (Greenhalgh, 1998; Palmer *et al.*, 2011; Velnar *et al.*, 2009). Apoptosis can be induced by the CSR (Kültz, 2020*a*) and appears to be an important regulator of injury-induced proliferation in diverse animals, including *Hydra*, planarians, insects, frogs, and lizards (Delorme, Lungu & Vickaryous, 2012; Ricci & Srivastava, 2018; Tseng & Levin, 2008); thus, investigating the links between variation in cell proliferation and the transcriptomic response to injury through apoptosis may be an avenue for integrative injury research. Cell migration also occurs during wound repair in many animals, having been well characterized in several vertebrate and invertebrate model systems (Bielefeld *et al.*, 2013; Levesque *et al.*, 2010; McCusker *et al.*, 2015; Ricci & Srivastava, 2018) but also observed or inferred in non-model species [e.g. corals, molluscs, sipunculids, annelids, arthropods, echinoderms (D'Ancona Lunetta, 2005; Husmann *et al.*, 2014; Meszaros & Bigger, 1999; Pinsino *et al.*, 2007; Polglase *et al.*, 1983; Tweeten & Anderson, 2008; Vafopoulou, 2009; Zattara, Turlington & Bely, 2016)]. However, which cells migrate, when, and from where, are questions with vastly different answers depending on the species.

While delving into the details of specific cell-based injury responses is beyond the scope of this review, a focus on regeneration illustrates how significant such variation can be. Even

in species that share the ability to regenerate, a process not universal in animals, the cellular sources of regenerated structures can differ widely. For example, in groups such as planarians and acoels, resident stem cells appear to be the sole source of regenerated structures (De Mulder *et al.*, 2009; Gehrke & Srivastava, 2016; Wenemoser & Reddien, 2010), while in many other groups, including such disparate animals as vertebrates and annelids, regenerated structures appear to have major contributions from heterogeneous populations of previously differentiated cells that are primarily derived from tissues close to the wound site (Bely, 2014; Fontés *et al.*, 1983; McCusker *et al.*, 2015). In sum, some general elements of cellular-level activities are found widely across animals, but substantial differences exist among species and wound contexts. Increasing understanding of how specific molecular pathways regulate distinct cellular activities following injury remains an important avenue for future research. Such work is needed to understand the diversity of cellular-level responses across animals and the evolution of post-injury outcomes across animals more broadly.

(*e*) *Wound end states: degrees of regeneration, degrees of scarring*

The conclusion of wound repair can be characterized within two end-state gradients: from complete regeneration to no regeneration, and from extensive scarring to scar-free healing. At the tissue level, regeneration and scar-free healing are essentially identical; however, at the level of larger body structures, regeneration may fail to occur following injury, even if healing occurs without forming a scar, as discussed below. This distinction is often obscure within the wound healing and regeneration literature, and adding clarity in discussions of the end states of wound repair can limit confusion as well as improve our ability to discover the mechanisms that contribute to which end states are possible in an organism. The end state of a wound ultimately may depend on many factors, including not only species but also life stage, individual condition, the location or extent of damage, and other variables.

Regeneration is the reconstruction of lost tissue or structures, such that it largely or entirely resembles the original in both form and function. Complete or near-complete regeneration has been documented across the animal kingdom and for all sorts of body structures (Bely & Nyberg, 2010; Elchaninov *et al.*, 2021; Tiozzo & Copley, 2015). Partial or imperfect regeneration occurs in some lineages, as in reptiles which regenerate tails that are not structurally identical to the original (Jacyniak *et al.*, 2017). The explicit absence of regeneration has also been documented for body parts in numerous animal groups. While regeneration occurs in a broad range of structures across animal phylogeny, current evidence indicates that there have been both evolutionary losses and gains of regeneration ability (Bely & Nyberg, 2010; Bely & Sikes, 2010; Zattara & Bely, 2016; Zattara *et al.*, 2019). This pattern, alongside comparative descriptions of the molecular, cellular, and morphological features of the regeneration process itself, suggests that instances of regeneration are not necessarily homologous among different lineages (Bely & Nyberg, 2010; Tiozzo & Copley, 2015). The variation in regeneration ability in such diverse animals nearly assures that the adaptive significance of regeneration as a response to injury varies from one lineage to another, as well as among structures within the same species. Extended discussion on regeneration exceeds the scope of the present review; we recommend that interested readers explore the vast review literature on regeneration processes and end states in animals (e.g. Bely, Zattara & Sikes, 2014; Brockes & Kumar, 2008; Goss, 1969; Imperadore & Fiorito, 2018; Murawala, Tanaka & Currie, 2012; Özpolat & Bely, 2016; Sánchez Alvarado & Tsonis, 2006; Seifert *et al.*, 2012*b*).

Scarring may also occur to varying extents after wound healing and is commonly (but not exclusively) found in animals with poor or no regeneration ability. Scar tissue permanently seals a wound but does not restore the original tissue structure and is instead fibrous, relatively inflexible, and generally less functional (Levesque *et al.*, 2010; Martin & Nunan, 2015; Murawala *et al.*, 2012). Wounds may also seal without scarring, as commonly occurs in animals that regenerate well. However, scar-free healing can occur even in non-regenerative contexts [e.g. annelids, nemerteans, arthropods, geckos (Bely, 2010; Bely & Sikes, 2010; Razzell *et al.*, 2011; Subramaniam, Petrik & Vickaryous, 2018; Townsend *et al.*, 2017; Zattara *et al.*, 2019)]. In these cases, larger structures lost to injury may not regenerate, but the wound area does not undergo fibrosis and instead is healed to resemble undamaged surrounding tissue. In a number of groups, including invertebrate and vertebrate models, the occurrence and extent of scarring is associated with inadequate remodelling of the extracellular matrix (Levesque *et al.*, 2010; Martin & Nunan, 2015; Miguel-Ruiz & García-Arrarás, 2007; Murawala *et al.*, 2012; Velnar *et al.*, 2009; Yokoyama, 2008) and the presence (or absence) and activity of certain cell types, such as macrophages (Godwin *et al.*, 2013; Murawala *et al.*, 2012). Animals with atypical regenerative and scarring abilities in comparison with their close relatives, such as spiny mice (*Acomys* spp.) which exhibit scar-free healing and regeneration of multiple tissues to an extent not found in other mammals (Brant *et al.*, 2016; Seifert *et al.*, 2012*a*), offer particularly useful systems for studying regeneration and scarring end-points and their evolution.

(2) Physiological and organismal effects of injury

Injury often causes significant changes in physiology and can impair whole-organism function. Such effects are central to the injury response, manifesting as changes at molecular and cellular levels while underlying many of the higher-level effects of injury. Some of the best-characterized physiological effects of injury are shifts in metabolism and body condition, altered investment in growth, and modified reproductive investment and output. Additionally, injury can directly impair organismal functions by compromising critical body

parts, such as those responsible for feeding, locomotion, and gas exchange.

(*a*) *Metabolism*

Injury is expected to increase metabolic rate. Energy is required for wound healing and associated processes that mobilize reserves, and if these energetic demands are high, the assimilation of additional energy may also be required (Bernardo & Agosta, 2005; Henry & Hart, 2005; Lawrence, 2010; Maginnis, 2006*b*; Starostová, Gvoždík & Kratochvíl, 2017). Whole-body resting metabolic rate has indeed been shown to increase following injury in a range of animals [e.g. annelids, planarians, insects, and brittlestars (Ardia *et al.*, 2012; Collier, 1947; Hu *et al.*, 2014; Lewallen & Burggren, 2022)], and metabolic rate during activity has also been shown to increase (e.g. in fish; Fu, Cao & Fu, 2013). However, although metabolic rate increases after injury as predicted, there are many inconsistencies among studies, and much remains to be understood about injury-induced metabolic changes. For example, the timing of increase varies substantially. Ardia *et al.* (2012) report a significant increase in metabolic rate within hours in insects, whereas Hu *et al.* (2014) report the first significant increase several days after injury in brittlestars, and Collier (1947) reports no significant increase until approximately 2 weeks post-injury in the annelid *Tubifex tubifex*. These increases occur at different relative stages of the post-injury response, including regeneration, and so absolute comparisons of the timing of metabolic shifts are not appropriate among species. Future work should attempt to link metabolism with specific underlying processes to understand why such shifts occur when they do. In some cases, injury may not accelerate whole-organism metabolism at all; one study in *Nerodia rhombifer* watersnakes reported no significant difference in metabolic rate between injured and uninjured animals (Korfel, Chamberlain & Gifford, 2015). Complicating matters is the fact that the nature of injury is inconsistent (e.g. appendage amputation, piercing, cutaneous lesions) and both feeding and handling effects are not controlled for equivalently among available studies. Additionally, most studies on the effects of injury on metabolic rate concern species with high regenerative ability, which potentially conflates metabolic changes during regeneration with those resulting from the initial injury and wound healing. As technology has advanced, the methods used to measure metabolic rate have changed, making comparisons between older and newer studies difficult. Older studies often use rough approximations of metabolic rate, such as nitrogen product excretion in crabs (e.g. *Carcinides maenas*) (Needham, 1955) and earthworms (e.g. *Eisenia foetida*, *Lumbricus terrestris*) (Needham, 1958), or body temperature in homeothermic vertebrates such as rats (Stoner, 1970). By contrast, more recent studies predominantly use respirometry (e.g. Baker *et al.*, 2018; Ferreira *et al.*, 2020; Tomlinson *et al.*, 2018). Measurements of whole-body metabolism also give little indication of changes at smaller spatial scales, such as those limited to the wound-adjacent area, limiting our understanding of what specific processes (e.g. cell proliferation, differentiation) metabolic shifts correspond to.

Any increase in metabolic rate that occurs following injury must be fuelled with energy, often by the mobilization and breakdown of energy stores. However, this need may be complicated if the injury involves the direct loss of such stores. Studies investigating animal physiological responses to injury have only included consideration of this possibility to any appreciable extent in a handful of species, specifically those that can regenerate damaged appendages that are known to be significant energy-storage sites. Recovery or other biological processes may be impacted in proportion to the degree of stores lost directly to injury. For example, this may occur in some lizard species that maintain substantial lipid stores in their tails, which are prone to being lost to sublethal predation (Bernardo & Agosta, 2005; Starostová *et al.*, 2017). Lipids are heterogeneously distributed along the tail both within and among individuals and species, thus the energetics of tail injury and recovery may depend on the extent of tail loss, but such a pattern is not observed consistently possibly due to variation in life-history traits (Chapple & Swain, 2002*a*; Dial & Fitzpatrick, 1981; Starostová *et al.*, 2017). Asteroid sea star arms are likewise often used as storage organs (Lawrence & Vasquez, 1996), yet the energetic consequences of their loss have hardly been explored. By contrast, brittlestars lack storage organs and lose body mass during regeneration at a rate based on the amount of food in the environment and the extent of any damage to digestive organs, indicating that assimilation capacity is more critical to wound recovery than storage (Dobson *et al.*, 1991; Fielman *et al.*, 1991). Future work ought to include graded injury treatments, as in the aforementioned lizard studies, in more diverse animals to seek general effects of injury depending on its direct effect on stored energy, including in non-regenerators. Insects, which often possess dedicated fat bodies separate from any regenerable limbs (e.g. Pinch *et al.*, 2021), might be a promising avenue for such research.

Injury is expected to lead to energy mobilization apparent through changes in glucose (or glycogen), lipid, or protein content. Evidence in diverse animals supports this expectation, but findings are often limited to data of circulating macromolecule levels and total body reductions in stores. Increases in body glucose are detectable within minutes following limb removal in decapod crustaceans (Manush *et al.*, 2005; Patterson, Dick & Elwood, 2007) and within hours after surgery (to insert radio transmitters) in bighead carp (*Hypophthalmichthys nobilis*) (Luo *et al.*, 2014). These findings indicate that diverse animals respond rapidly to injury, possibly *via* body-wide signalling such as the sympathetic nervous system in rats (Stoner, 1970). Lipids likely serve as longer-term fuel sources for recovery, as indicated by a decline in lipid content over the course of weeks during regeneration in annelids (Yáñez-Rivera & Méndez, 2014) and reductions in body fat months after radio-collar surgery in mule deer (*Odocoileus hemionus*) (Bleich *et al.*, 2007). Protein

has also been implicated in fuelling recovery following injury, alongside other macromolecules, in corals (see references in Henry & Hart, 2005) and brittlestars (Dobson *et al.*, 1991). The timing of these aforementioned changes varies among species, and it is not always clear where stores are mobilized from and by what methods (e.g. motile cells, circulatory systems). It is also not well known why, or if, some stores are affected in some species but not others. Yet the speed and magnitude of stored energy consumption suggests that injury can quickly have consequences for whole-animal function.

If the energetic demands of the injury response are large, it is predicted that animals capable of increasing resource assimilation will do so. This prediction is borne out by a handful of studies, predominantly in lizards. One mechanism is physiological plasticity, as in lizards that alter their digestive performance by reducing gut passage time and increasing uptake of protein after tail loss (Sagonas *et al.*, 2017). Another mechanism is increasing the frequency and amount of feeding following injury, but direct measurement of the capacity for animals to do so remains sparse. Tailless *Coleonyx* lizards increase their caloric intake relative to controls, but locomotory inefficiency due to the lack of the tail may lead to additional energetic demands, potentially diminishing the compensatory ability of this response (Dial & Fitzpatrick, 1981). Similarly, multiple polychaete species are unable to compensate for palp loss regarding food intake (Lindsay & Woodin, 1992). Together, these findings suggest that injury may affect animals to an extent not only related to the nature of the initial injury but also the plasticity of an animal's physiology and behaviour and its ecological circumstances, highlighting the need for integrative research on this topic.

Understanding how injury affects metabolism is an especially key topic for integrative injury biology given the hypothesized core role of metabolism in ecology (Brown *et al.*, 2004). The general match between predictions and data in this area thus far suggests that metabolic responses to injury are adaptive, but the considerable variation also indicates that such responses are evolutionarily shaped by complex factors. We particularly emphasize the need for work in a greater diversity of animals, particularly non-regenerating species, that attempts to link metabolic changes with fine-scale spatial and temporal processes to understand better the magnitude of sublethal impacts that injury may have on higher-order biological dynamics. In particular, there should be deeper investigation into how the nature and severity of injury affect metabolism and the links between the stage of injury repair and metabolic changes.

(*b*) *Growth and reproduction*

The loss and consumption of energetic resources associated with injury and repair often impact somatic growth and reproduction. Wound healing, and regeneration when it occurs, solicit energy and molecular building blocks (e.g. proteins, carbohydrates) to repair and rebuild damaged tissue. As these resources are limited, they must be strategically allocated among processes, leading to frequent trade-offs (Archie, 2013; Hudson *et al.*, 2021; Maginnis, 2006*b*), such as among injury recovery (e.g. regeneration), growth, and reproduction (Heino & Kaitala, 1999). The demands of injury recovery may not only reduce investment in other processes but potentially alter relative apportioning among them (Aira *et al.*, 2007; von Wyschetzki *et al.*, 2016). Understanding the effects of injury on growth and reproduction is particularly important as these can have profound consequences at higher levels of biological organization, such as by impacting individual fitness and population dynamics.

Given the energy requirements of injury responses, injury may reasonably be hypothesized to reduce somatic growth, at least in the short term. Studies in a variety of animals generally support this hypothesis, although the manner in which growth is affected varies. Reductions in growth rate following various kinds of injury have been shown in diverse animals [e.g. corals, clams, annelids, reptiles (Ballinger & Tinkle, 1979; Cameron & Edmunds, 2014; Campbell & Lindsay, 2014; Coen & Heck, 1991; Kamermans & Huitema, 1994; Korfel *et al.*, 2015; Tomiyama, 2016; Zattara & Bely, 2013)]. Understanding the specific mechanisms through which growth is impaired remains an important area of research. Some animals exhibit reduced growth only in certain areas of the body following injury, as in stick insects, where leg loss causes reduced wing growth (Maginnis, 2006*a*), and in the branching bryozoan *Bugula neritina*, where reductions in growth are restricted to the area proximal to injury, possibly due to localized impairment of nutrient translocation processes (Bone & Keough, 2005). Physiological integration, including nutrient sharing among body parts, has also been noted as a potentially important factor underlying differences in the effects of injury on growth in corals following comparative work in species that vary in the extent of colony perforation (Hamman, 2019). Growth may be reduced through injury's disruptive effects on development, as shown in tadpoles that develop more slowly following tail injury (Blair & Wassersug, 2000) and in some decapod crustaceans that experience either prolonged or accelerated intermoult periods and limited post-moult size increases following appendage loss (see references in Juanes & Smith, 1995). Growth may be reduced due to the loss of energy reserves stored in an amputated body part, such as fat in lizard tails (Dial & Fitzpatrick, 1981), which could exacerbate resource restrictions and, subsequently, growth rates. Some purported relationships between injury and growth are actually only correlative: higher injury number or frequency is often associated with smaller body size [e.g. in spiders, starfish, salamanders (Lutzy & Morse, 2008; Marrs *et al.*, 2000; Morse, 2016; Mott & Steffen, 2014)], but such studies leave open the alternative possibility that smaller individuals are simply more susceptible to injury. Altogether, the effects of injury on growth may be mediated by life history, the degree of body compartmentalization, which parts are injured, and whether parts are lost entirely in certain animals.

Despite the expectation that growth will be inhibited following injury, some studies have found no such relationship

or a relationship that is highly context dependent. Some studies on lizards have found no effect of injury on growth rate or body mass (Althoff & Thompson, 1994; Hudson *et al.*, 2021; Starostová *et al.*, 2017); in sponges and corals, injury may increase, decrease, or not affect growth (Henry & Hart, 2005); and in bivalves, the effect of siphon injury on growth rate is not straightforward and varies among species, habitats, or degrees of damage (Peterson & Quammen, 1982; Sasaki *et al.*, 2002; Trevallion, 1971), to list just a few examples. This variability suggests that simple energetic trade-offs are not sufficiently explanatory, and other mechanisms may be the cause of unexpected relationships between injury and growth.

Beyond the mechanisms described above, growth may be further negatively impacted by injury if structures used in feeding or foraging are themselves lost, damaged, or otherwise less effective, thereby decreasing resource intake. Although it is challenging to dissociate such effects from other growth-impairing effects of injury (discussed above), a few studies suggest this mechanism may be involved. In crabs, when limb loss reduces foraging efficiency, reductions in growth increment can be magnified (Smith & Hines, 1991). In scorpions, loss of the tail, which is used to subdue prey, results in reduced ability to capture larger prey items (Mattoni *et al.*, 2015), which is expected to lead to growth reductions but this has not been tested. Following siphon injury in clams, loss of foraging efficiency combined with increased energetic demands of regeneration are hypothesized to lead to reduced growth rates (Coen & Heck, 1991; Kamermans & Huitema, 1994; Peterson & Skilleter, 1994), and both factors likely contribute to reduced growth in spionid polychaetes following palp amputation (Matthews & Hentschel, 2012). More generally, if overall body condition is reduced, injury may render feeding less effective. For example, weakened body condition resulting from crushing injury in the soft coral *Gersemia rubiformis* was hypothesized to impair feeding, leading to energetic limitations and subsequent reduced growth rates (Henry, Kenchington & Silvaggio, 2003). Such an effect has also been proposed for side-blotched lizards suffering cutaneous wounds, in which wounding that has no direct impact on feeding structures can still lead to reduced food consumption (Hudson *et al.*, 2021), possibly also due to a general reduction in physiological condition.

Although injury effects on growth are primarily negative, effects of injury on reproduction are far more variable, likely reflecting the great diversity of life-history strategies among animals. For similar reasons as described above for growth, the general expectation is that injury will reduce reproductive output. Indeed, sexual reproduction is commonly suppressed following injury in a range of taxa. Wounding reduces reproductive rate in polychaetes (Zajac, 1985, 1995), six-rayed sea stars (*Leptasterias hexactis*) (Bingham, Burr & Head, 2000), ants (von Wyschetzki *et al.*, 2016), and burying beetles (*Nicrophorus vespilloides*), although the effect in the latter only manifested when injury occurred during breeding (Reavey *et al.*, 2014). In sponges and corals, sexual reproduction is commonly reduced, in favour of regeneration, in the form of lower fecundity, fertility, and offspring viability (Henry & Hart, 2005). Injury-induced decreases in reproductive rate and total fecundity can result from a variety of underlying effects, including reductions to the rate or success of mating as in *D. melanogaster* (Sepulveda *et al.*, 2008), extended brooding time as in a *Polydora* polychaete (Zajac, 1985), slowed maturation as in a *Capitella* polychaete (Hill, Grassle & Mills, 1982), and reduced gonad mass as in the purple sea urchin (*Strongylocentrotus purpuratus*) (Haag, Russell & Hernandez, 2016). Such negative effects on injury on reproduction lead to the prediction that increased severity of injury will lead to greater decreases in reproduction. This prediction has also been supported by research on diverse animals. For example, the severity or distribution of injury is linked to the degree of reproductive impact in a study of female green lynx spiders (*Peucetia viridans*), where the loss of two legs reduced the number of eggs produced, but the loss of one leg had no significant impact (Ramirez, Takemoto & Oliveri, 2017), and in a study of the bryozoan *Bugula neritina*, where more diffuse damage throughout the colony reduced the proportion that reached sexual maturity over time *versus* damage concentrated within a single branch (Bone & Keough, 2005). Offspring quality may also be expected to be impacted by injury, potentially through reductions in parental investment resulting from trade-offs with other processes. Indeed, in *Desmognathus* salamanders, a negative relationship was found between maternal injury severity and egg size (Bernardo & Agosta, 2005), but these data were observational; the authors correctly note that experimental evidence is needed to clarify whether injury leads to reduced egg size. Injury effects on reproduction may also be revealed or exacerbated by simultaneous limiting factors, such as food availability or available energy stores. For example, in a study of female *Urosaurus ornatus* lizards, minor cutaneous wounding reduced the mass of vitellogenic follicles when individuals were on a restricted diet but had no effect when they had unlimited access to food (French, Johnston & Moore, 2007). Furthermore, comparative studies across lizards and salamanders indicate that species with proportionally more caudal *versus* abdominal fat typically show greater reductions in clutch size following tail loss, suggesting an energetic restriction due to the proportionally greater amount of lipid stores lost along with the tail (Bernardo & Agosta, 2005). These latter two examples highlight the difficulty of drawing direct conclusions about the effect of an injury on growth due to the presence of confounding variables (e.g. nutritional stress, stored energy depletion), which future studies should take care to control.

However, as in the case of growth, evidence for resource limitations of reproduction following injury is not always observed. French *et al.* (2007) found there was no significant difference in follicle mass between lizards with unlimited access to food and lizards that were not fed at all; the authors hypothesize this may be due to starvation inducing a trade-off with the immune system, redirecting resources from (and thus suppressing) immunity in order to survive food

scarcity. Zajac (1985) noted that the polychaete *Polydora cornuta* (formerly *ligni*) continued to reproduce while regenerating lost segments, indicating that a total diversion of resources from reproduction to recovery does not occur. In other cases, injury can actually enhance reproduction, as in pea aphids (*Acyrthosiphon pisum*) by accelerating reproductive rate (Altincicek, Gross & Vilcinskas, 2008) and anoles (*Anolis* spp.) by increasing egg and hatchling size (Beatty, Mote & Schwartz, 2021). The particular strategy employed by injured animals is likely to be strongly shaped by life history (e.g. Bernardo & Agosta, 2005).

Some, but comparatively less, is known about the impact of injury on asexual (specifically agametic) reproduction (e.g. fission, budding). Although these effects are expected to be comparable in many ways to those on sexual reproduction, offspring produced by asexual reproduction are genetic clones of the parent, typically develop more quickly, and are substantially larger than sexually produced offspring, leading to potentially distinct effects. In forms of asexual reproduction like fission, where much or all of the offspring tissue is directly derived from the parental soma, significant tissue loss from injury would be expected to affect asexual reproduction negatively because that tissue and the resources it contains are no longer available to be allocated to viable offspring, but studies that explicitly address this expectation are needed. However, injury can also have the opposite effect on asexual reproduction. For example, injury may actually facilitate asexual reproduction if the injury severs the original individual into two or more fragments that are each capable of fully regenerating. In such a scenario, injury actually causes the asexual propagation, a mechanism suggested to occur in various animals [e.g. sponges, nemerteans, annelids, bryozoans, planarians, echinoderms (Bely *et al.*, 2014; Carter *et al.*, 2015; Coe, 1929; Martinez-Acosta & Zoran, 2015; Mladenov, 1996; O'Dea, 2006; Padua *et al.*, 2016; Wulff, 1991)] and has even been exploited in sabellid worms for commercial purposes (Murray *et al.*, 2013). In two asexually reproducing annelids (*Paranais*, *Pristina*), decapitation of fissioning individuals often leads to accelerated fission (Bely, 1999; Zattara & Bely, 2013). Interestingly, these species represent independent origins of asexual reproduction, indicating that this injury effect is repeated across evolutionary lineages and possibly adaptive. However, the opposite response – fission deceleration and even resorption – can also occur under certain conditions in *Pristina* (Zattara & Bely, 2013), suggesting that optimal resource allocation between parent and offspring can depend on the nature of the injury. In organisms capable of switching between sexual and asexual modes, injury could promote one reproductive mode over the other. In octocorals, injury has been shown to promote asexual over sexual propagation, a shift hypothesized to be partly a consequence of resource reallocation towards repair and regeneration (Henry *et al.*, 2003). Prevalence of sexual *versus* asexual reproduction may reflect adaptations to frequently disturbed environments (Meirmans, Meirmans & Kirkendall, 2012), which may include injury risks. Given the similarities and probable shared evolutionary history between asexual agametic reproduction and regeneration in many animal groups (Kostyuchenko & Kozin, 2020; Martinez, Menger & Zoran, 2005; Zattara & Bely, 2011), the effects of injury on asexual reproduction warrant special attention for their potential mechanistic and evolutionary insights.

(*c*) *Organismal function*

Beyond physiological effects, injury can directly impact organismal function through the removal or damage of structures involved in key body functions. For example, injury to structures involved in feeding impair energy assimilation and can impact growth as described above, while effects of injury to locomotory and gas exchange structures can impair movement and oxygen supply for metabolism, respectively.

Damage to or loss of locomotory structures, such as tails or limbs, can have potentially large consequences for animals. Such injuries can impair not only the ability of an animal to move about its environment but also important processes that depend on locomotion, such as feeding and reproduction. Locomotory disruption often results from directly altered biomechanics and gait following injury, as has been well established in diverse animals [e.g. crabs, lizards, dogs (Fuchs *et al.*, 2015; Jagnandan, Russell & Higham, 2014; Pfeiffenberger & Hsieh, 2021)]. While this exact mechanism is not always established, a range of motor endpoints are often negatively affected by injury to various appendages, including reduced movement speed and/or acceleration [e.g. in aquatic insects, arachnids, crabs, fish, tadpoles, and lizards (Chapple & Swain, 2002*b*; Figiel & Semlitsch, 1991; Fu *et al.*, 2013; Houghton, Townsend & Proud, 2011; Krause *et al.*, 2017; Martín & Avery, 1998; Pfeiffenberger & Hsieh, 2021; Robinson, Hayworth & Harvey, 1991*a*; Townsend *et al.*, 2017)], reduced sprint distance or stamina [e.g. in spiders, tadpoles, and lizards (Brown & Formanowicz, 2012; Chapple & Swain, 2002*b*; Figiel & Semlitsch, 1991; Martín & Avery, 1998)], and destabilized or eliminated ability to perform certain types of movements [e.g. in crabs and lizards (Fleming & Bateman, 2012; Gillis, Kuo & Irschick, 2013; Pfeiffenberger & Hsieh, 2021; Savvides *et al.*, 2017)]. Although injury to locomotory structures often affects animal movement, in some cases locomotory function is not disrupted, as has been shown for limb damage in a range of animals including wolf spiders (Brueseke *et al.*, 2001), brittlestars (Price *et al.*, 2014), and plethodontid salamanders (Hessel, Ryerson & Whitenack, 2017), or varies in a manner dependent on factors like sex (Chapple & Swain, 2002*b*). Collectively, the body of work on injury impacts on locomotion is large and reveals that the magnitude of functional impact can depend on numerous factors including the physiological costs of damage (see above), the importance of the structure to locomotion (Chapple & Swain, 2002*b*), structure redundancy (Brautigam & Persons, 2003; Pfeiffenberger & Hsieh, 2021), acclimatory ability (Fuchs *et al.*, 2015), and size and allometry (Brueseke *et al.*, 2001).

Injury to gas exchange organs may have considerable consequences for respiration and subsequent downstream effects on

animal physiology and behaviour. External respiratory structures, such as gills, are particularly prone to damage, but many animals can regenerate these structures [e.g. annelids, damselflies, fish, amphibians (Bely & Sikes, 2010; Brown & Emlet, 2020; Cadiz & Jonz, 2020; Drewes & Zoran, 1989; Eycleshymer, 1906; Mierzwa *et al.*, 2020; Robinson *et al.*, 1991*b*; Saito *et al.*, 2019; Wells, 1952)]. Siphons, which are used for pumping external water to the gills in bivalves and thus are important in respiratory function, can also often be regenerated (de Vlas, 1985; Meyer & Byers, 2005; Tomiyama, 2016). Although loss of these organs in the wild has been documented (Brown & Emlet, 2020; de Vlas, 1985; Drewes & Zoran, 1989; Robinson *et al.*, 1991*b*; Wells, 1952), few studies have investigated the functional consequences of such injuries, and these often establish only loose or indirect relationships between structure damage and effects. For example, clams with cropped siphons reduce their burrowing depth (Meyer & Byers, 2005; Zwarts, 1986). However, it is not clear whether the ability to inhale oxygenated water efficiently through the siphon is directly impeded by siphon injury or if clams reduce burrowing depth solely to compensate for reduced siphon length and maintain exposure to the overlying water. The contribution of many respiratory structures to total gas exchange is not well known under even routine conditions in many animals, and so the consequences of damage to these structures are also not well understood, highlighting the need for basic physiological research in injury-prone animals. Some existing data do indicate compromised respiration following damage to gas exchange organs, particularly in annelids. For example, amputation of posterior segments in *Branchiura sowerbyi* induces compensatory elongation of remaining filaments and formation of new filaments (Drewes & Zoran, 1989), and crown amputation leads to an 80% reduction in total respiration in a sabellid (Giangrande, 1991). Crown damage is hypothesized to differentially impact sabellid respiration based on allometry and compensatory capacity (e.g. through cutaneous or enteric gas exchange) (Wells, 1952). Other than annelids, indirect evidence of physiological impacts of respiratory appendage damage comes from larval damselflies, which reduce their habitat breadth to highly oxygenated waters following loss of lamellae (Robinson *et al.*, 1991*b*).

(3) Behavioural effects of injury

Injured animals often alter their behaviours. Many such changes have consequences for organismal physiology by affecting processes such as energy assimilation and reproduction and also appear to be adaptive, pointing to a significant role for natural selection in shaping injury responses at the behavioural level. Among the best-studied behavioural consequences of injury are impacts on foraging behaviour, social behaviour, and sensitization.

(*a*) *Foraging behaviour*

Given the central role of resource acquisition in the biology of animals, it is no surprise that injury often impacts foraging behaviour and that such changes are among the most well-documented behavioural effects of injury. Injury that affects mouthparts or limbs used for foraging often directly reduces feeding efficiency and overall food intake, as discussed above (see Section III.2.*b*). However, injury can also have significant effects on foraging behaviour, whether or not the injury is to structures directly involved in feeding.

Injury is known to induce shifts in foraging strategy in a handful of diverse animals. In several species of decapod crustaceans, damage to or loss of claws can lead to animals becoming more herbivorous (reducing predatory foraging) or taking fewer risks in predation, such as choosing softer prey (Smith & Hines, 1991). Wolf spiders missing legs are poorer at capturing larger prey (Brueseke *et al.*, 2001) and at foraging in complex environments (Wrinn & Uetz, 2008). It is notable that most knowledge in this area concerns predatory species. Understanding how and why injury affects foraging behaviour requires comparisons with herbivores as well as injury that does not involve damage to parts used for capturing or processing food or appendages that can be regenerated.

Injury may also alter foraging behaviour through changes in habitat utilization; such shifts are associated with diverse outcomes, including both increases and decreases in predation risk. For example, spionid annelids with lost palps sometimes emerge from the sediment at higher frequency to feed, which leaves them at higher risk of predation (Lindsay & Woodin, 1992). Similarly, bivalves with damaged siphons, which are used to pull food particles from the surrounding water, burrow less deeply in the sediment, increasing their exposure risk to predators (de Goeij *et al.*, 2001; Meyer & Byers, 2005). However, injured animals may also adopt foraging strategies that reduce the risk of further injury, such as by spending more time foraging in safer habitats or reducing activity levels. For example, lizards without tails alter their habitat occupation, possibly to keep out of sight of predators (Martín & Salvador, 1992, 1993), and injured salamanders that increase occupation of benthic microhabitats do not suffer any loss of foraging efficiency (Mott & Steffen, 2014). Choice of foraging microhabitats is likely to be impacted by diverse factors, including not only foraging success and predation risk but also physiological needs (e.g. Bliss & Cecala, 2017). The effect of injury on subsequent predatory encounters will certainly depend on the density and kind of predators in the injured animal's habitat as well as the animal's physiological condition, factors which require careful consideration in future studies.

Injury may also elicit a change in feeding mode itself. In spionid polychaetes, damage to feeding palps induces a switch from suspension feeding to mouth feeding. The magnitude and efficacy of this behavioural shift in feeding was found to be influenced by how many palps were damaged, corresponding to the degree of impaired function (Lindsay & Woodin, 1995). Bivalves also exhibit a switch in feeding mode from risky but rewarding deposit feeding to safer but less profitable suspension feeding following siphon damage (Peterson & Skilleter, 1994); however, the prevalence of such a shift may be dependent upon

both bivalve and potential predator density (Skilleter & Peterson, 1994). Future work ought also to consider food availability and an injured animal's physiological condition, which may each factor into its 'risk assessment'.

(*b*) *Social behaviour*

In social animals, injury has been shown to alter a range of social behaviours, particularly those relating to mating and parental care. Courtship and mating behaviours can be altered by damage to or loss of body structures that are used in such behaviours. For example, male wolf spiders (e.g. *Pardosa milvina*, *Schizocosa ocreata*) alter the frequency and intensity of a variety of courtship and mating behaviours after leg loss (Brautigam & Persons, 2003; Taylor, Roberts & Uetz, 2006) and experience reduced mating success (Brautigam & Persons, 2003). In octopuses, arm loss is posited to alter mating strategy by inhibiting the locomotory ability of males, leading to indirect female mate choice of uninjured males and shifts to 'sneaking' behaviour in injured males (Wada, 2017). In species with parental care, offspring may suffer not only from reduced direct investment of resources when their parents are injured, as discussed previously (see Section III.2.*b*), but also from behavioural adjustments in their injured parents. For example, in Hawaiian monk seals (*Monachus schauindslandi*), mothers that are injured express reduced offspring care behaviours and decreased lactation, which likely contributes to greater pup mortality (Becker *et al.*, 2008). Although available studies demonstrate that injury can affect a range of social behaviours related to reproduction, specific outcomes are likely to be highly variable, depending on a species' mating system and available mate options. More research aimed at generating and testing specific predictions about behavioural impacts on injury in social animals would be fruitful. Effects of injury on other social behaviours, beyond reproductive behaviours, have not been well described and represent an important knowledge gap to be filled.

(*c*) *Sensitization*

Behaviour may also change following injury simply as a way to avoid further noxious stimulation. Nociceptive plasticity is a sensitization response that has been demonstrated following injury in vertebrates, including humans (Woolf & Walters, 1991), as well as several invertebrates [e.g. insects, leeches, molluscs (Babcock, Landry & Galko, 2009; Crook *et al.*, 2011; Sahley, 1995; Walters, 1987; Walters *et al.*, 2001)]. Nociceptive strategies that may be elicited include being more prone to flee from a stimulus, to engage in defensive stances or actions (e.g. hissing; displaying warning coloration, teeth, claws, spines; increased aggressive behaviours), and to hiding. In longfin squid (*Loligo pealeii*), individuals are not only more likely to escape when presented with visual stimuli in the hours following injury, but they also employ crypsis more readily very shortly after an injury is inflicted (Crook *et al.*, 2011). The molecular and physiological mechanisms by which nociception affects animal behaviour have been studied in a range of animals, especially cephalopods, established invertebrate models such as *D. melanogaster*, and vertebrate models such as zebrafish and mice (Alupay, Hadjisolomou & Crook, 2014; Malafoglia *et al.*, 2013; Oshima *et al.*, 2016; Tobin & Bargmann, 2004; Tracey, 2017; Walters & Williams, 2019). However, the ecological significance of nociceptive plasticity remains poorly understood, including in relation to variable types of injury that may be experienced in the wild or in animals with less complex or less well-characterized nervous systems.

(4) Ecological and evolutionary effects of injury

Injury can have significant consequences above the organismal level. Ecological effects and evolutionary consequences of injury are common and frequently, although not exclusively, occur as a result of impacts of cell and molecular, physiological, organismal, or behavioural effects. At ecological scales, injury can affect predator–prey dynamics, competitive interactions, and, when injury is particularly prevalent, population and trophic dynamics. Injury can also affect evolutionary processes, by impacting the fitness of injured animals as well as the fitness of conspecifics and heterospecifics (such as predators) with which injured individuals interact. When injury has large individual effects or is especially common, it can be an important driver of ecological processes and influence evolutionary trajectories. Relevant research focused on injury effects at these levels includes not only empirical studies but also a significant number of modelling studies.

(*a*) *Predator–prey dynamics*

By impacting animal physiology, function, and behaviour, injury often increases the susceptibility of prey animals to subsequent predation. For example, tail loss in tadpoles increases predation by crayfish (Figiel & Semlitsch, 1991), loss of lamellae in larval damselflies increases the likelihood of being cannibalized (Robinson *et al.*, 1991*b*), and male wolf spiders with many lost legs are more frequently cannibalized by females (Brautigam & Persons, 2003). A variety of factors can be responsible for increased predation susceptibility of injured individuals. One of the most obvious is that injury can impair anti-predator defences or escape ability. For example, injury-induced impairment of locomotory ability has been shown to increase susceptibility to predation directly in a number of animal groups (Figiel & Semlitsch, 1991; Martín & Avery, 1998; Zamora-Camacho & Aragón, 2019); leg loss in crickets even elevates the risk of capture by mucilaginous plants (Cross & Bateman, 2018). Predator defences, especially physical defences, may also be impaired through physiological trade-offs with other processes. For example, soft corals produce shorter defensive sclerites after suffering damage to other tissues, possibly due to the energetic cost of regenerating those tissues, and this can lead to increased predation

(Bythell, Gladfelter & Bythell, 1993; West, 1997); and in the land snail *Satsuma caliginosa*, shell growth is delayed after foot autotomy (Hoso, 2012). In addition, injured individuals may be more easily detected or actively preferred by predators. Several studies have shown that crabs with missing chelipeds or claws are preferred by predators relative to uninjured crabs (e.g. Davenport *et al.*, 1992; Juanes & Smith, 1995). However, although the idea that predators pick out vulnerable – including wounded – prey is commonplace in ecological literature and popular accounts of animal behaviour, this hypothesis has been formally tested only rarely (Krumm *et al.*, 2010). Thus, understanding the ecological consequences for injured prey will benefit from studying the behaviour of their predators (see Section III.3.*a*).

As discussed above, injury can cause important changes to an individual's behaviour, and these changes can have complex effects on subsequent predation risk. It is not straightforward to formulate predictions about the impact of injury on susceptibility to predation; outcomes are expected to be highly dependent on the specifics of the animal's biology and the environmental context in which it exists. Indeed, available data suggest that injury-induced changes in behaviour may make animals more likely or less likely to be preyed upon subsequently. For example, in marine clams, siphon cropping, which can be very common, forces clams to bury themselves at shallower depths in order to avoid suffocation (de Vlas, 1985; Zwarts, 1986), which in turn increases their risk of predation, primarily by decapods (Meyer & Byers, 2005; Zwarts & Wanink, 1989). Similarly, a study of harvestmen found that individuals that had lost legs climbed slower and occupied lower perches, effects that are expected to raise future predation risk (Houghton *et al.*, 2011). And in sardines (*Sardinella aurita*), injuries inflicted by predators reduce swimming performance and drive spatial sorting in schools, such that injured individuals are more exposed to possible further predation (Krause *et al.*, 2017). However, injury can also lead to behavioural changes that decrease predation risk, likely as adaptive behavioural responses to mitigate the heightened vulnerability of animals when in an injured state. These changes often take the form of decreased activity levels, heightened predator sensitization, and increased time in habitats with lower predation risk. For example, lizards that have lost their tails reduce the length of their daily active periods (Martín & Salvador, 1995), flee more readily from predator cues despite having impaired movement (Downes & Shine, 2001), and spend more time in habitat types that offer more opportunities to hide, perhaps as compensation for reduced locomotory performance (Martín & Salvador, 1992, 1993). Injured individuals spending more time in certain habitats may then indirectly impose increased predation pressure upon other prey individuals in those or other habitats, potentially affecting community ecological interactions. Behavioural sensitization may also heighten predator avoidance following injury, as with injured longfin squid, which become hyper-responsive to visual stimuli, although this may lead to the respective animals making themselves more conspicuous (Crook *et al.*, 2011). Injury may also affect the specific anti-predation strategies used by animals. For example, crayfish with missing limbs switch from burrowing to tail-flipping behaviour to avoid predators, which has the added effect of increasing water turbidity (Dunoyer, Coomes & Crowley, 2020).

Particularly in aquatic habitats, chemical cues emitted by injured individuals can be important in mediating injury effects on predator–prey dynamics. For example, injury cues can serve as a warning signal to other individuals, eliciting antipredator or avoidance behaviours and even inducible physical defences in prey species. Chemically mediated injury signalling to conspecifics has been documented in a variety of animals including clams, gastropods, annelids, flatworms, crustaceans, aquatic insects, and fish (Alemadi & Wisenden, 2002; Gall & Brodie, 2009; Kaliszewicz, 2015; McCarthy & Dickey, 2002; Smee & Weissburg, 2006; Wasserman *et al.*, 2014; Wisenden, Chivers & Smith, 1997; Wisenden, Pohlman & Watkin, 2001; Wisenden & Millard, 2001). Some animals can even learn to respond to injury signals released by heterospecifics subject to a similar class of predators. For example, tadpoles can learn to respond to chemical cues released by injured amphipods, apparently because these cues indicate a potential predation risk to the tadpoles themselves (Pueta & Perotti, 2016). Inducible anti-predator defences are known to exist in a variety of invertebrate taxa, and the cues for these inducible defences include injury cues. For example, blue mussels (*Mytilus edulis*) exposed to chemical cues from wounded conspecifics develop thicker, stronger shells (Leonard, Bertness & Yund, 1999). However, chemical cues alone may be insufficient for inducing anti-predator defences in some animals, as in the bryozoan *Membranipora membranacea*, which only grow defensive spines after suffering mechanical damage from (nudibranch) predation. These spines do not appear following similar yet experimentally induced injury, suggesting this species is adapted to respond in this manner specifically to predatory injury (Harvell, 1984). A wholly different and unusual strategy for responding to conspecific injury cues occurs in some meiofaunal annelids (e.g. *Stylaria lacustris*, *Nais christinae*), which lack obvious antipredator physical defences and instead accelerate rates of asexual fission while also increasing the size of both parent and offspring worms when exposed to such cues (Kaliszewicz, 2015). Injury signals from a wounded animal can also attract opportunistic conspecific or heterospecific predators, further compounding the detrimental effects of injury. For example, starved blue crabs (*Callinectes sapidus*) are more likely than non-starved crabs to track olfactory injury cues emitted by conspecifics, presumably to prey upon them (Moir & Weissburg, 2009), and crayfish respond to injured snail prey cues by increasing their activity, although this does not seem to improve their prey capture success (McCarthy & Dickey, 2002).

(*b*) *Competitive interactions*

Relatively few studies have directly investigated how injury modulates inter- or intraspecific competitive interactions,

but based on the known effect of injury on organismal physiology, function, and behaviour, it is likely that injury effects on competition are common and substantial. As discussed earlier, functional impairment from wounding can impact foraging strategies, prey preference, habitat occupation, mating success, growth, and other factors, and such impacts are thus likely to bring injured animals into more frequent or contextually altered contact with one another in competition for food, physical space, mates, or other resources. This remains an open area of investigation, but a handful of studies have examined the relationship between injury and competitive ability or its likely correlates. Numerous studies in corals suggest that wounding may reduce inter- or intraspecific competitive ability as a result of increased fouling of lesions, increased risk of sublethal predation, and impaired growth, which reduces occupation of habitat space (see references in Henry & Hart, 2005). To give one specific example, damaged corals are significantly more susceptible to being overgrown, and ultimately killed, by certain sponge species as opposed to maintaining 'standoff' interactions (Aerts, 2000). Another study in edible crabs (*Cancer pagurus*) has found that induced claw injury reduces competitive ability among conspecifics (McCambridge, Dick & Elwood, 2016).

Studies that experimentally assess competitive impacts of injury are challenging to do in the wild for a number of reasons, and it is subsequently difficult to attribute findings to injury. For example, the presence of siphon-nipping fishes in experimental cages produces greater intraspecific competition in clams (Skilleter & Peterson, 1994). This is posited to be due to the reduction of viable feeding modes to those with less siphon exposure, but it is not made clear that injury itself induces this change, rather just that a source of injury is present. Designs using treatments such as predator cues without the presence of actual predators can help clarify the mechanisms responsible for prey behaviour. In another study, Mott & Steffen (2014) found correlations between sublethal injury severity and both body size and habitat selection in salamanders, but the authors were unable to determine whether more injury in fact leads to reductions in body size and greater cryptic habitat use or *vice versa* due to limitations of the observational design. While either may hypothetically reduce intraspecific competitive success in salamanders or other various animals, there are scant data supporting injury as a factor in shaping non-predatory interactions. These examples illustrate the importance of linking observational and experimental findings to injury effects at organismal and lower levels; for example, the latter study may be followed by an experiment that inflicts sublethal injuries on salamanders and observes their growth and performance in a mesocosm.

A noteworthy pool of studies has concerned the direct and indirect effects of sublethal predation upon infaunal polychaetes in soft-sediment ecosystems, animals which are of particular importance due to their role as sedimentary engineers. As these animals are capable of rapidly and substantially altering physical properties of their environment, their activity has a considerable effect on the frequency and nature of sediment-mediated interactions, and injury especially of parts subject to cropping by browsing predators (e.g. fish, crustaceans) can modify activity patterns and thus competitive interactions within the sediment (Wilson, 1991). Experimental (Woodin, 1984), observational (Lindsay & Woodin, 1996), and modelling work (Lindsay, Wethey & Woodin, 1996) suggests that sublethal predation injury, *via* its impacts on sediment-engineering behaviours, indeed has the capability to shape community dynamics within these vast and abundant ecosystems. More research of this kind would be of great value to parsing the ecological consequences of injury, especially concerning non-predatory interactions within and among species, in other types of ecosystems, especially freshwater and terrestrial ones.

(*c*) *Population dynamics*

Injury is very common in wild populations, as detailed above, and when sufficiently prevalent can affect population dynamics. In most cases, injury is expected to decrease population growth rates, as negative impacts on reproduction are already well evidenced in many species (Bernardo & Agosta, 2005; Henry & Hart, 2005; Ramirez *et al.*, 2017; Reavey *et al.*, 2014; Sepulveda *et al.*, 2008; von Wyschetzki *et al.*, 2016; Zajac, 1985, 1995), as discussed above (see Section III.2.*b*). For example, models of population dynamics in mudflats suggest that sublethal cropping of polychaetes can reduce their population growth rates (although less than if the predation was lethal) (Zajac, 1995), and in some clams, siphon cropping, which is a common occurrence, is often so effective at facilitating subsequent lethal predation that cropped clams are considered 'as good as dead' (Meyer & Byers, 2005). Mortality risk likewise increases in amphibians with sublethal predation: tail injury by predators in salamander larvae reduces survival prior to metamorphosis (Segev, Mangel & Blaustein, 2009), and predation-driven missing-limb abnormalities increase mortality in frogs, which is expected to have significant ecological consequences (Bowerman, Johnsonfi & Bowerman, 2010). In environments where injury is common, repeated injury in the same individual is likely also common, with potentially important implications for population dynamics. Modelling of these effects is especially needed, as has been long recognized (Lindsay, 2010). Although injury is generally expected to decrease population growth, its role in governing population size is likely determined by many complex factors. For instance, injury can increase population growth rate if it causes individuals to be fragmented into multiple viable pieces of which two or more can subsequently regenerate to complete individuals, as discussed above. This situation is most likely in highly regenerative animals, such as sponges and annelids, and colonial animals, such as cnidarians and bryozoans, and has been documented in a number of aquatic animals in response to abiotic forces, such as wave action and storms (see Section III.2.*b*). Modelling by Wethey *et al.* (2001) shows that intermediate levels of sublethal browsing predation on adults of the clam *Macoma balthica* may actually be

necessary for maximizing equilibrium population density by promoting a balance between adult occupancy and larval recruitment.

(*d*) *Trophic transfer*

Sublethal predation, in which a predator consumes part of a prey individual's body, is a form of injury that can be very common in some habitats. A key question is whether sublethal predation contributes significantly to trophic energy transfer. Work in this area suggests that the frequency of sublethal predation is indeed great enough to constitute a major input to food webs. The cropping of body parts by predators, such as fish and decapods, is particularly common among benthic invertebrates, including bivalves and annelids, in soft-bottomed aquatic environments such as mudflats and sandflats (de Vlas, 1985; Lindsay, 2010; Meyer & Byers, 2005; Peterson & Quammen, 1982; Skilleter & Peterson, 1994; Tomiyama, Omori & Minami, 2007). The injured animals often regenerate tissues lost to cropping and may do so many times in their lives. For example, Sasaki *et al.* (2002) estimated that the bivalve *Nuttalia olivacea* may regenerate their siphons an average of 26 times in a single season, and another study found that clams are estimated to suffer cropping damage to their siphon tips several times a day during summer (de Vlas, 1985). Tissue cropping and subsequent regeneration can be so prevalent that cropped tissues can serve as major sources of secondary production (de Vlas, 1979*b*, 1985; Henry & Hart, 2005; Lindsay, 2010; Sasaki *et al.*, 2002; Tomiyama *et al.*, 2007; Zajac, 1995). For example, juvenile stone flounder (*Platichthys bicoloratus*) are able to meet the majority of their nutritional needs by cropping the siphons of clams (Sasaki *et al.*, 2002), one study found that up to 70% of the diet of plaice (*Pleuronectes platessa*) in tidal flats consisted solely of siphon tips (de Vlas, 1979*a*), and another study found that the trophic transfer of cropped brittlestar arms alone in one community accounted for secondary production on a scale comparable to that of other communities in their entirety (Pape-Lindstrom *et al.*, 1997). However, there is a need for similar work in terrestrial systems and a better understanding of the proportional energy flux provided by sublethal predation in trophic networks.

(*e*) *Evolutionary consequences*

As reviewed in previous sections, injury can have substantial effects on many components of fitness, including an individual's growth, mating success, reproductive output, and survival, and can thus ultimately have important evolutionary consequences. If injury frequency and magnitude of effect are sufficiently large as to represent a significant selection pressure, and if there is heritable variation in injury responses among individuals, organismal responses to injury will evolve over time. The costs of injury (or autotomy), for example, may drive adaptive switches towards better morphological defences that reduce the chance of injury (Hoso, 2012) or towards more effective recovery pathways, such as compensation or regeneration (Bely & Nyberg, 2010).

Despite the importance of understanding injury as a selective force, the evolutionary role of injury remains the topic most in need of focused research. Although variation in injury responses among species is extensive and well described, variation in injury responses within species has not been well documented, and this represents a significant knowledge gap to fill for understanding the evolutionary consequences of injury. There is also a need to understand better the frequency of injury in the wild, which is challenging for many reasons, including cryptic or absent indicators of past injury, particularly in regenerating species (Lindsay, 2010). Multigenerational studies are especially warranted, for example, to determine whether variation in traits related to wound healing, the CSR, or metabolism are affected by injury pressure from different sources. However, acknowledging these gaps in understanding, many injury responses in animals can be reasonably interpreted as adaptations either to avoid injury or to reduce the negative fitness consequences of injury. Thus, wound healing, injury-induced immune responses, organismal-level compensatory responses to injury, injury-induced behaviours, physical defences, predator avoidance behaviours, autotomy, and regeneration abilities may all be evolved responses to injury, at least in some contexts and animal lineages. Sublethal predation pressures could even have stimulated major transitions in animal mobility, as proposed for Paleozoic crinoids (Baumiller *et al.*, 2010). Collectively, the widespread presence of injury-reducing or injury-responsive phenomena suggest that injury has imposed strong and taxonomically widespread selection pressures that have impacted the evolution of animals.

As yet, limited work has focused on understanding the evolutionary forces that have shaped injury responses, but available data suggest that many possible factors merit consideration. For instance, autotomy has evolved many times across animals (Bateman & Fleming, 2009; Cromie & Chapple, 2013; Fleming *et al.*, 2007; Maginnis, 2006*b*), but the factors driving its evolution are likely multi-faceted. Experimental evidence in insects suggests that autotomizing damaged limbs significantly reduces various potential costs of injury (Emberts *et al.*, 2017). Thus, autotomy may be beneficial not only as a way to avoid full predation but also as a way to decrease injury costs. Disentangling the relative importance of these two effects will be important for understanding the evolution of this injury response. Organismal features such as size, rate of aging, and life-history strategy will also affect how organisms respond to injury and the likelihood of survival following injury, thus affecting the evolutionary consequences of injury (Bely & Nyberg, 2010; Seifert *et al.*, 2012*b*; Webb, 2006). For example, the fitness cost of losing a head is dramatically higher in a species that reproduces exclusively sexually and requires head structures to survive and reproduce than in a species that reproduces asexually by fission, in which the loss of the head may not preclude the production of offspring by fission. This scenario has been proposed as a possible evolutionary explanation for the

loss of head regeneration ability in a group of fissioning annelids: several such species have been shown to be able to reproduce asexually even if anteriorly amputated, suggesting a very low cost to anterior amputation that would decrease selection for maintaining anterior regeneration ability following injury (Bely, 1999; Bely & Sikes, 2010). Among lizards and salamanders, short-lived species tend to have poorer regenerative ability than species with greater longevity while exhibiting fewer negative consequences for reproduction; this may similarly represent a scenario in which life history modulates investment trade-offs related to injury (Bernardo & Agosta, 2005). Which traits are selected for under injury pressure may thus vary or even conflict with one another in a number of ways, such as trade-offs between evolving greater ability to escape injury *versus* evolving cumbersome but effective defensive structures. Vermeij (1982) argued that, in the case of injuries caused by sublethal predation, selection for traits involved with injury recovery or defence ought to be stronger than for those involved with avoidance when the incidence of sublethal predation is high, that is, when rates of detection and capture are also high. Selection may even act on diverging strategies within the same structure or trait. For example, studies in damselfly larvae indicate a link between lamellar joint allometry and environmental predation risk, where smaller, weaker joints are correlated with increasing predation risk (Gleason, Fudge & Robinson, 2014), presumably reflecting past and ongoing selection to facilitate autotomy or breakage by direct predation, whereas larger, stronger joints enhance swimming in low-predation risk environments (Bose & Robinson, 2013). Injury-related phenomena that have evolved repeatedly across animals, such as autotomy and changes in regenerative ability, provide particularly powerful frameworks for disentangling the many factors that shape the evolution of injury responses.

IV. INTEGRATION AND FUTURE RESEARCH

Data on injury biology are broad and deep, spanning animal phylogeny and the spectrum of biological levels of organization (Fig. 3). As highlighted throughout this review, this breadth and depth enables some integration to begin to understand the multi-level effects of injury as well as how injury effects at one level can affect other levels. Integration is strongest where the effects of injury have been studied across multiple levels of organization in the same taxon. Lizards, dipteran insects, decapod crustaceans, and bivalve molluscs stand out among the groups best studied across levels of biological organization, providing the clearest pictures thus far of the multi-level effects of injury. The body of work in lizards is particularly large and diverse in scope. Collectively, studies in anoles, skinks, and geckos, focused predominantly on tail loss but also on cutaneous injury, have revealed the cellular and immune dynamics involved in wound healing, the developmental processes of tail regeneration and scarring, the impacts of tail loss or other injury on physiology (including relative investment in various organismal processes), the consequences of injury for locomotion and several types of behaviour, and the influence of injury on intra- and interspecific interactions, as well as some cross-talk among these levels. In insects, the primary emphasis has been on the molecular, cellular, and developmental responses to injury, which have been studied with a high level of detail owing primarily to work in *D. melanogaster*. Studies at other levels in insects, especially ecological scales, are sparse or lacking, precluding broad integration. Both decapod crustaceans and molluscs are common subjects of work at the levels of behaviour and population and community ecology, in part due to their commercial and ecological relevance. In these groups, lower-level responses to injury are understood to some extent, but genetic and organismal knowledge particular to pathways and processes involved in injury and regeneration, including especially how these relate to higher-order phenomena, is still developing.

Although better-studied groups such as lizards, arthropods, and molluscs provide information on the multi-level effects of injury, most studies still focus predominantly on endpoints at narrow biological scopes. Very little work has investigated correlative or causal links between injury effects at multiple levels of organization within species despite the critical value of understanding such relationships. For example, consider a case where injury induces an increase in reproductive output in one species but not another. While this is unlikely to be an easy question to answer, work in lizards (Bernardo & Agosta, 2005; Dial & Fitzpatrick, 1981) provides a testable hypothesis concerning the role of life-history differences, such as lifespan. If this is suspected to be a general principle underlying injury-induced reproductive changes, comparative work in animals only distantly related to lizards, such as insects, may be useful. If such a pattern exists between closely related species in multiple taxa, researchers might look for analogous genetic components associated with variation in lifespan, mating system, or other life-history traits. This work might be followed by, for example, evolutionary studies to determine where such variation arose, functional studies to validate the links between candidate molecular targets and injury-induced changes in reproduction, and field studies in the species of interest to quantify the prevalence and patterns of injury in the wild. Such a research program would require collaborations between biologists of disparate disciplines, highlighting the need for establishing common scientific ground among groups interested in injury. The few examples of already existing integrative research reveal important connections between injury effects at different levels. For example, injury-induced shifts in gene expression are associated with altered reproductive output in ants (von Wyschetzki *et al.*, 2016), and injury-induced post-embryonic developmental effects have been shown to affect predator–prey interactions in toads (Zamora-Camacho & Aragón, 2019). These examples, along with our example scenario, may serve as a guide for how to conduct work that integrates research across levels of

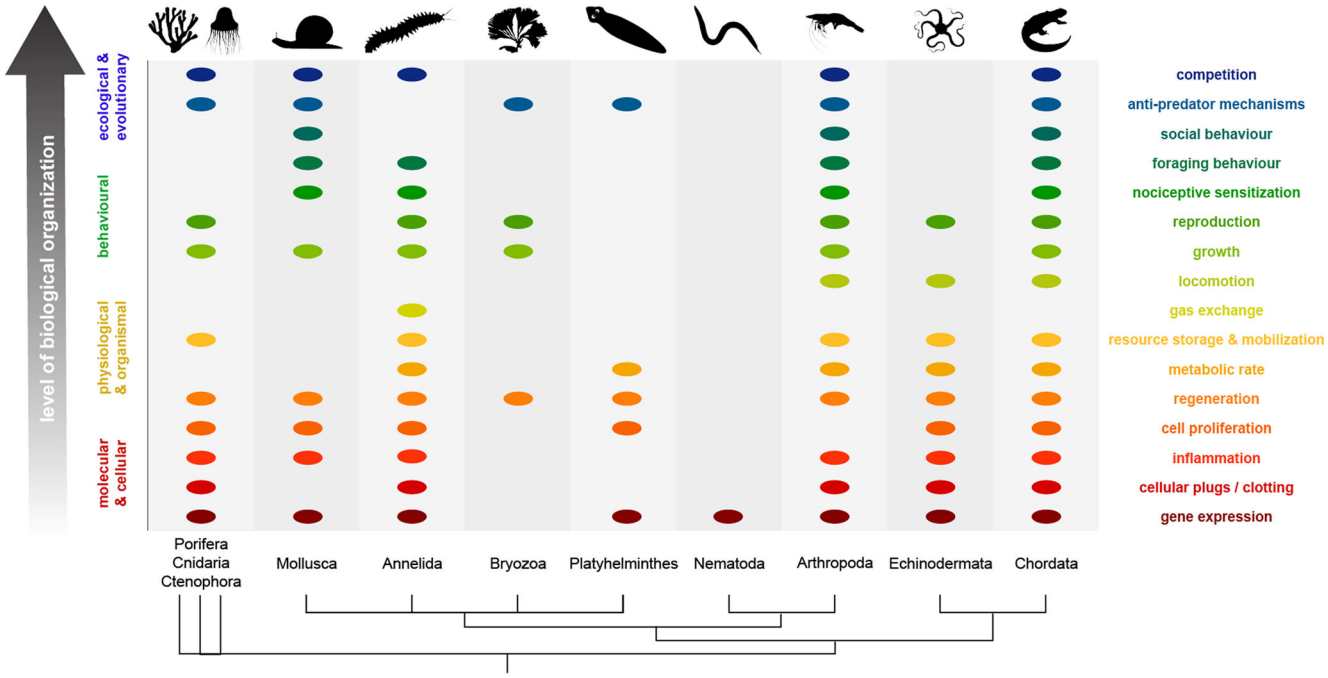

Fig. 3. Graphical representation of research findings on the effects of injury across levels of biological organization and across animal phylogeny. Colour scheme used indicates where various endpoints studied (right) roughly fall within broader levels of organization (left). Relative ordering of endpoints is arbitrary. Coloured ovals indicate the existence of literature cited in this review that reports direct or suggested effects, either positive or negative, resulting from mechanical injury on the corresponding endpoint (row) within the corresponding animal phylum or group of phyla (column). Absence of an oval does not mean the absence of an effect in nature, only the absence of effects reported in the reviewed literature, indicating areas of research opportunity. Phylogenetic relationships are based on Giribet *et al.* (2007), but we acknowledge that both the placement of non-bilaterian taxa and relationships among the Lophotrochozoa remain subjects of debate. See text for references and additional details. Silhouette attributions: sponge – image by Mali'o Kodis, photograph by Derek Keats; cnidarian – image by Qiang Ou; annelid – image by Noah Schlottman, photograph by Casey Dunn; bryozoan – image by Noah Schlottman, photograph by Hans de Blauwe; platyhelminth – image modified from Andreas Neudecker; *arthropod – image by Almandine, vectorized by T. Michael Keesey*; chordate – image by Matt Reinbold, modified by T. Michael Keesey.

organization either within single studies or across studies to answer complex questions regarding animal responses to injury.

A critical task for injury researchers going forward is to clearly demarcate several similar yet distinct phenomena, in particular endogenously *versus* exogenously induced injury, and wound healing *versus* regeneration. Endogenously induced injury, namely autotomy, differs from exogenously induced injury in that it is induced by the animal upon stimulation at pre-existing fracture planes, which serves partly to reduce damage and fluid loss. While it might be hypothesized that the negative effects of autotomy would be diminished compared to typical injury, only scant attention has been devoted to investigating these differences. By comparison with autotomy, exogenously induced injury has been found to reduce intraspecific competitive ability in crabs (McCambridge *et al.*, 2016) and increase blood loss in lizards (Delorme *et al.*, 2012); more investigations such as these, comparing exogenously and endogenously induced injuries, are needed. A complicating issue is that many studies claim to assess the effects of 'injury' when they actually focus specifically on induced autotomy, which may have different consequences at one or more biological levels; it will be beneficial to improve clarity of language and avoid using these terms interchangeably. As with exogenous injury and autotomy, the effects of wound healing and regeneration are often conflated with one another; these are more appropriately considered separate but partly overlapping processes (Brockes & Kumar, 2008; DuBuc, Traylor-Knowles & Martindale, 2014; Jacyniak *et al.*, 2017), ones that may even exhibit trade-offs with one another in some contexts, such as mammals (Wang *et al.*, 2020). Even different instances of regeneration in diverse species may represent convergent evolution (Bely *et al.*, 2014; Lai & Aboobaker, 2018; Zattara *et al.*, 2019), complicating the task of generalizing how and why regeneration evolves and what costs it imposes upon animals. Not only are wound healing and regeneration often not well delineated, but our knowledge of injury responses in general is strongly skewed toward species that can regenerate well, including many which also autotomize their body parts, such as crabs, salamanders, and lizards (Fleming *et al.*, 2007; Juanes & Smith, 1995; Maginnis, 2006*b*), potentially

introducing significant biases. Increasing the diversity of species in injury research to include those that cannot autotomize or regenerate, or that exhibit a gradient of injury responses, is necessary to clarify the origins – both proximate and ultimate – and mechanistic underpinnings of these responses. Important insights are likely to come from research on species in which often-confounded processes can be dissociated, such as the insect *Narnia femorata*, which can either automize or regenerate its limbs but cannot do both (Emberts *et al.*, 2017), or certain annelids which fully regenerate at one end of the body but only wound heal at the other (Bely, 2006; Bely & Sikes, 2010). Drugs or other molecular disruptions that selectively inhibit certain processes [e.g. inhibiting only autotomy or regeneration (Arnoult & Vernet, 1995; Coomber, Davidson & Scadding, 1983)] may also prove useful.

Two additional important factors remaining underexamined in injury research are injury history and the nature of the injury itself. Although it is common for animals to sustain multiple injuries either at once or over time, most experimental work concerns the effects of single discrete injuries. The cumulative effects of repeated injury and regeneration on animal physiology, fitness, or subsequent rate or success of repair are not well known, as previously highlighted by Lindsay (2010). A small number of studies have reported such effects, including increased susceptibility to further damage and potential resource limitation in corals (Henry & Hart, 2005), reduced body growth in bivalves (Tomiyama & Omori, 2007) and (alongside reduced activity levels) in polychaetes (Campbell & Lindsay, 2014), and the regeneration of smaller limbs with reduced innervation or failure to regenerate in axolotl (Bryant *et al.*, 2017). However, a lack of effects has also been reported following repeated lens regeneration in newts (Eguchi *et al.*, 2011), and repeated spinal cord transection has virtually identical outcomes for animal functional recovery and tissue repair in sea lamprey (*Petromyzon marinus*) (Hanslik *et al.*, 2019). Repeated injury may even be beneficial, as suggested by a study showing that repeated injury and regeneration can extend lifespan in the freshwater annelid *Paranais litoralis*, possibly as a consequence of inducing repair mechanisms conferring longevity (Martinez, 1996). Given the often substantial (and likely underestimated) rates of injury documented in the wild, it is important to expand experimental treatments to ecologically relevant frequencies of injury. More work is also needed to assess the impact of the nature of injury on the injury response; most research on injury employs controlled, 'clean' injuries, such as total amputation of appendages or body extremities, standardized cutaneous incisions, or piercing wounds. Wound types beyond these, such as crushing, abrasion, or partial amputation, are uncommon in experimental studies, but may be highly relevant in the wild. Wound severity, including lesion size or degree of amputation, is also rarely manipulated experimentally, despite these characteristics being far from consistent in natural injuries. Injuries of different sizes or qualities may require different amounts of investment in repair, may vary in the amount of time that repair takes, and may elicit quantitatively and qualitatively different responses and compensatory changes, potentially leading to variable downstream impacts of injury. For example, different species of coral vary in growth rate reduction and recovery speed following different types of injury in a manner that may be mediated by morphology (Cameron & Edmunds, 2014), and a study in the planarian *Schmidtea mediterranea* found different spatial and temporal patterns of stem cell proliferation between puncture and amputation wounds (Wenemoser & Reddien, 2010). Therefore, future research should consider incorporating gradients of damage whenever possible rather than single, homogeneous injuries. More generally, expanding the design scope of experimental work on injury will benefit our understanding of its biological consequences.

Although injury represents a special type of insult to the body, it is theoretically and practically useful to recognize the ways in which injury affects animal biology as a stressor. Like other typical stressors, such as thermal stress or pollutant stress (Kassahn *et al.*, 2009; Killen *et al.*, 2013; Sulmon *et al.*, 2015), sublethal injury often disturbs homeostasis, reduces fitness, and induces the CSR (Kassahn *et al.*, 2009; Killen *et al.*, 2013; Makrinos & Bowden, 2016; Matranga *et al.*, 2000; Mydlarz *et al.*, 2008; Sulmon *et al.*, 2015). And as is the case with other physical stressors (Gianguzza *et al.*, 2014; Sulmon *et al.*, 2015; Vasquez *et al.*, 2015), non-summative effects result from combinations of injury and other stressors [e.g. osmotic, thermal, nutritional, sedimentation, pollution, parasites (Denley & Metaxas, 2015; Grdisa, 2010; Henry & Hart, 2005; Hickey, 1979; Jensen *et al.*, 2015; Johnson *et al.*, 2006; Stueckle, Shock & Foran, 2009)]. Trade-offs between wound healing and environmental stress resistance have been documented, and these trade-offs can be mediated by factors like nutrition, social status, and seasonality (Archie, 2013; Juanes & Smith, 1995; Maginnis, 2006*b*), underlining the importance of not only studying injury at a mechanistic level but also within the broader ecological context of particular animals. Additionally, as injury is known to stimulate the CSR, it will be valuable to assess whether mild injury could have beneficial hormetic effects or confer cross-tolerance, as evidence suggests can occur with other stressors (Costantini, Metcalfe & Monaghan, 2010; Kültz, 2003; McClure *et al.*, 2014). A great example of a synthesis in this area is a review on the interactive effects of predatory injury and anthropogenic stress in corals by Rice, Ezzat & Burkepile (2019). Given the frequency of injury in nature and the likelihood of more extreme environmental stress scenarios in the future because of anthropogenic impacts on biological systems, it will be important to understand the interactions between injury and these stressors across levels of organization in diverse species.

While the present review concerns injury in animals, we would be remiss to conclude without noting the considerable work concerning injury in plants, which helps provide a broader perspective on eukaryotic wound responses. Similar phenomena comprising animal injury responses that we

cover herein have been described in diverse plant species, such as complex wound signalling pathways (Bergey, Howe & Ryan, 1996; León, Rojo & Sánchez-Serrano, 2001; Savatin *et al.*, 2014; Schilmiller & Howe, 2005; Suzuki & Mittler, 2012; Vasyukova *et al.*, 2011; Zebelo & Maffei, 2015), regulated self-injury (autotomy) (Shtein *et al.*, 2019), injury-induced chemical cues (Kalske *et al.*, 2019; Karban *et al.*, 2006; Pearse *et al.*, 2012), effects on growth and reproduction (Buchanan, 2015), effects on metabolism (Chitarrini *et al.*, 2017; Macnicol, 1976), and regeneration (Ikeuchi *et al.*, 2019). A review of this literature provides insight into the remarkable ways in which members of different kingdoms of life converge upon similar solutions to problems posed by injury, even if the components of such solutions differ themselves, as well as which solutions may actually be derived from ancestrally shared foundations.

V. CONCLUSIONS

(1) Mechanical injury is common in nature, and a broad range of injury responses have been documented in diverse animal groups. Injury affects animal biology across biological levels of organization, from lower-order molecular and cellular processes to large-scale ecological and evolutionary dynamics. (*a*) At molecular and cellular levels of organization, commonalities in early injury responses are evident between even distantly related species. In particular, the immediate molecular wound signals appear highly conserved, while divergence in responses becomes more pronounced as diverse cell types are engaged, including those involved in innate immunity. Both intrinsic and extrinsic factors mediate the specific responses at these levels, as well as the links between proximate molecular and cellular mechanisms and downstream organismal consequences. (*b*) Wound healing is widespread and ancient in animals, although specific mechanisms vary across groups. Regeneration ability differs substantially across species, body regions, and contexts, ranging from zero to total restoration of lost tissue. Evolutionary increases and decreases in regenerative ability have likely been widespread. (*c*) Injury is generally detrimental to organismal function, but diverse compensatory responses and variability in numerous factors (e.g. life history, environment) produce complex effects such that predicting injury impacts is not straightforward. In some cases, certain biological processes can be enhanced by injury. (*d*) Injuries may significantly affect ecological dynamics and organismal fitness. Injury impacts on foraging, movement, and biotic interactions are increasingly well understood, but the relative roles these outcomes play in large-scale phenomena beyond the level of the individual or of small populations remain largely hypothetical. Nevertheless, many injury responses in animals appear to be adaptations either to avoid injury or to mitigate potential negative fitness consequences of injury.

(2) Synthesis of injury responses, both within species across levels of biological organization and comparatively among species, is limited but expanding. Such synthesis is challenging because injury responses are variable, because work at different scales often makes use of different species, and because relevant work regards injury (whether as a factor or an endpoint of interest) in relation to a broad assortment of research questions. A fuller understanding of how animals respond to injury, including the links between injury effects at various levels and across species, will be aided by focused, integrative research programs on the matter of injury itself in a greater variety of species. There will be substantial benefits from establishing a more cohesive field of injury biology.

(3) Proximate and mechanistic understanding of relevant phenomena, such as wound healing, regeneration, and autotomy, remains limited, even in some well-studied model systems, precluding a thorough understanding of their effects in animals generally. Further investigation of these processes at proximate scales is needed, while including a greater variety of study species to uncover novel genes, molecular pathways, cellular components, and evolutionary insights.

(4) The context of work investigating injury responses to date is largely limited to optimal conditions, controlled and uniform injuries, and a few endpoints at a time in healthy, adult animals. A better understanding the mechanistic underpinnings, physiological dynamics, and long-term organismal consequences of injury necessitates expanding the design of studies to include factors like simultaneous stressors, different types and frequencies of injuries, and various ontogenetic stages and phenotypes, as well as expanding the endpoints assessed simultaneously when possible. Experimental designs will also require careful ethical considerations to maximize intellectual development while minimizing suffering in subject organisms.

(5) Current injury research is biased towards mammalian and other model systems with medical significance, species that regenerate well, species that autotomize, and species with commercial importance. Many taxa with ecological significance are not well represented or have not been the subjects of injury research. Although taxonomic coverage in injury-related studies is improving, more concentrated efforts to address taxonomic biases will improve our ability to predict how injury shapes animal biology broadly, including to what extent injury may act as an important variable in future ecological scenarios and as an evolutionary driver.

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