Bridging the regeneration gap: insights from echinoderm models

In their Review¹, Sánchez Alvarado and Tsonis present an interesting discussion of “...the model systems that are currently used to dissect the molecular and cellular bases of regeneration, with a focus on *in vivo* models”.

Surprisingly, echinoderms received little attention. Regeneration potential is expressed to a maximum extent in echinoderms². Larval and adult echinoderms from each of the five classes exhibit natural, rapid regeneration of entire lost parts following predation or other traumatic events (FIG. 1). As adults, echinoderms can regenerate many organs, including limbs, disc, gut, spines and podia and, in some species, regeneration is used for asexual reproduction^{2,3}. Moreover, the process has been studied extensively at molecular, cellular, tissue and ecological levels (for example, REFS 2–7).

All the regenerative strategies that are currently described in animals are represented in echinoderms. Arm regeneration in ophiuroids and crinoids is an epimorphic blastemal process, by which new tissues arise from active proliferation of migratory undifferentiated cells (amoebocytes and coelomocytes), which accumulate at the end of the nerve cord as a blastema. In sea stars and sea urchins, morphallaxis is the main regenerative process, involving cells derived from existing tissues by differentiation, transdifferentiation or migration^{2,3}. Importantly, echinoderms are deuterostomes and an average of 70% of echinoderm genes have human homologues⁸. Therefore, the processes involved in echinoderm regeneration are more likely to be extended to mammals than those observed in other classical models such as *Hydra* or planarians, which are more distantly related to chordates.

A

B

Figure 1 | **Two echinoderm models for regeneration studies.** **a** | A sea star, *Asterias rubens*, with three regenerating arms. **b** | A brittlestar, *Amphiura filiformis*, with six scars that indicate sites of regeneration.

Recent studies demonstrate that echinoderms have the potential to offer viable and tractable models for molecular and cellular research on regeneration. First, a growing amount of molecular information about the regeneration process is available. Echinoderms show nerve-dependent regeneration^{2–7}, and regeneration in these organisms has been shown to involve growth factors. For example, the bone morphogenetic protein/transforming growth factor- β (BMP/TGFB)-signalling pathway has been shown to function in regeneration in brittlestars and crinoids^{5,9,10}, the HOX-signalling pathway in brittlestars and seastars⁶, and the Ependymin pathway in the sea cucumber⁷. These molecular pathways are repeatedly encountered during regeneration throughout the animal kingdom¹. Second, all of the classical cellular and molecular tools are available for these models: EST libraries, not to mention the complete genome of the sea urchin *Strongylocentrotus purpuratus*⁸,

immunohistochemistry^{4,6,9}, *in situ* hybridization^{5,10}, real-time PCR^{7,10}, microarrays¹¹, proteomics and so on. Echinoderm models allow analysis both *in vivo* and *in vitro* (for example, cell and tissue explant cultures¹²). Finally, Sánchez Alvarado and Tsonis¹ emphasized the importance of model organisms such as the protostome planarians to ultimately help in the design and implementation of stem-cell therapies in mammals. Echinoderms can be promoted as an alternative deuterostome model in this respect. In a recent study, we have demonstrated that cell proliferation and differentiation rates can be readily manipulated *in vivo* in the brittlestar *Amphiura filiformis*, allowing the study of the stem-cell niche during regeneration¹³.

In consequence, echinoderm models have the potential to contribute significantly to the understanding of regeneration at the molecular and cellular levels, are good models for *in vivo* research on regeneration and, owing to the shared ancestry of echinoderms with chordates, findings from these models are likely to have a positive impact on mammalian regeneration research.

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