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Recent Advances in Invertebrate Regeneration & Stem-Cell Biology

Mudbe PK and Mudgal MB

Department of Zoology, GES's, H.P.T. Arts and R.Y.K. Science College, Nashik.
*Corresponding Author Email: amimudgal@gmail.com

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Abstract

Invertebrates exhibit remarkable regenerative capabilities, ranging from whole-body regeneration in flatworms, cnidarians, echinoderms to complex tissue restoration in annelids, molluscs and crustaceans.. Recent technological advances in molecular biology, single-cell transcriptomics, lineage tracing, computational modelling, and in vivo manipulation are transforming our understanding of stem-cell biology in model systems such as planarians, hydra, echinoderms, annelids, cephalopods (Mollusca), and crustaceans cellular sources and also molecular signaling, and evolutionary strategies underlying regeneration. This review summarizes key findings over the past few years (mainly from 2015–2025), focusing on stem-cell identity, dedifferentiation, senescence-driven reprogramming, signaling pathways and organismal models like annelids and cnidarians. For the completion of review free access research articles are used. We also highlight emerging themes, current challenges, and translational implications for regenerative medicine.

Key words: Regeneration, stem cell, Invertebrates.

1. Introduction

Regeneration is the ability to reconstitute missing or lost body parts after injury is distributed unevenly across the animal kingdom. Invertebrates, especially certain taxa, present some of the most astonishing regenerative feats. For decades, planarians (flatworms) and hydra (cnidarians) have served as archetypal models to explore regeneration, but recent advances in molecular and cellular biology are broadening the landscape. Understanding how different invertebrates regenerate not only improves our fundamental knowledge of stem-cell biology, but also offers potential strategies for regenerative medicine. There are some questions about regeneration which should be addressed as cellular source of regeneration, molecular signaling pathways behind regeneration, evolutionary prospective, methods driving recent advances.

This review synthesizes recent progress (mainly from 2015–2025) on these fronts due to Single-cell RNA sequencing (scRNA-seq), High-resolution imaging, CRISPR/Cas9 gene editing, Comparative genomics, Epigenomic profiling etc. These technologies have clarified the molecular basis of regeneration and enabled cross-species comparisons of conserved regeneration programs.

2. Cellular Sources of Regeneration in Invertebrates

a) Planarian Neoblasts: Pluripotent Stem Cells:

Planarian flatworms (e.g., *Schmidtea mediterranea*) are known for their neoblasts- adult stem cells responsible for their regenerative capacity. These cells proliferate and differentiate into virtually all cell types, forming a blastema at wound sites. Traditionally, neoblasts were considered a homogeneous population, but recent studies using single-cell transcriptomic have revealed considerable heterogeneity among them, suggesting subtypes with different lineage potentials and stress responses. Recent scRNA-seq studies revealed ~12–15 distinct neoblast subpopulations, including pluripotent clonogenic neoblasts (cNbs) and lineage-committed progenitors for neural, epidermal, intestinal, and excretory tissues [1,2].

Furthermore, recent research has questioned the traditional "niche" concept for neoblasts. A 2025 study revealed that planarian stem cells might not depend solely on adjacent cells for their identity. Instead, they react to signals from distant tissues, like the intestine, indicating a more widespread regulatory network [3].

This redefinition of the niche paradigm can reshape how we view stem-cell regulation in regenerative systems.

b) Annelids: Dedifferentiation and Lineage Restriction:

A recent breakthrough in the marine annelid *Platynereis dumerilii* combined single-cell RNA sequencing and mosaic transgenesis to dissect the cellular dynamics of posterior regeneration [4]. The study discovered that, after amputation, distinct cell populations re-express stem cell–associated genes (such as piwi, myc) and contribute to the blastema. Importantly, different lineages (epidermal vs. coelomic/mesodermal) produce distinct posterior stem cells (PSCs), indicating that regeneration is not driven by a single pluripotent source but involves dedifferentiation (or reprogramming) of more differentiated cells [4].

c) Cnidarians (Hydractinia): Senescence-Induced Reprogramming:

One of the most fascinating recent findings is in the cnidarian *Hydractinia symbiolongicarpus*. Here, researchers discovered that transient senescent cells, which appear at the wound site shortly after amputation, secrete factors that reprogram neighbouring differentiated cells into pluripotent i-cells (stem cells) [5]. These newly generated i-cells then drive whole-body regeneration. Genetic or pharmacological inhibition of senescence blocks regeneration, while artificially inducing senescence (via optogenetics) accelerates stem-cell formation and regenerative outgrowth [5].

d) Regeneration in Mollusca:

Mollusca are also having capacity of regeneration. Cephalopods as Octopus and cuttlefish have regeneration capacity in arms, they regenerate arms via: proliferative zone formation, Neuronal regeneration via SoxB1 and NeuroD, Pax6 [6].

e) Regenration in crustacea:

Crustaceans, such as the crustacean *Parhyale*, possess the ability to regenerate their limbs thorogh blastema formation. Recent insights include. Embryonic and regenerating legs of *Parhyale* differ in their gene expression dynamics, they ultimately produce mature structures that appear similar. The regeneration process is remarkably precise, replicating the complex microanatomy and spatial distribution of external sensory organs and fully restoring their sensory function [7].

While the insulin-like androgenic gland hormone (IAG) is widely accepted as the main regulator of male sexual differentiation in crustaceans, recent transcriptomic analyses show this is not the full picture. The discovery of multiple other sex-related genes, such as *CFSH*, *Dsx*, and *Foxl2*, reveals that the process of sexual differentiation in crustaceans is more complex and involves a wider range of genetic factors than previously understood [8].

This reveals senescence, conventionally regarded as harmful or aging-related, as an ancient and positive regulator of plasticity in certain invertebrates.

3. Molecular Signaling Pathways Behind Regeneration:

a) Wnt/β-Catenin Signaling:

The Wnt pathway remains one of the most conserved and critical regulators of regeneration. In planarians, modulation of Wnt/β-catenin activity determines the head vs. tail fate of the blastema: low Wnt signals lead to head regeneration, while high Wnt promotes tail formation [9].

A 2023 review consolidated these insights and highlighted how wound-induced Wnt activation, combined with chromatin remodelling, directs positional identity in regenerating tissues [10].

b) Cellular Senescence Signaling:

As described above, in Hydractinia, senescent cells emerge transiently after amputation and secrete factors reprogramming surrounding cells [5]. Molecular profiling shows upregulation of senescence-associated genes (such as Cdki1, a cyclin-dependent kinase inhibitor) at early timepoints post-injury [5]. This suggests a tightly regulated role for senescence in triggering regeneration, rather than simply being a byproduct of damage.

In a broader context, recent reviews on inflammatory and regenerative biology note that senescence-induced reprogramming via SASP (senescence-associated secretory phenotype) factors (like IL-6) can enhance reprogramming efficiency in vivo [11].

c) Positional Identity, Dedifferentiation, and Regrowth:

In the annelid Platynereis, single-cell data reveal that after amputation, not only do PSCs reappear, but positional identity genes (for example, cdx, foxa) are reactivated, guiding the blastema toward appropriate patterning [4]. This re-expression hints at a mechanism where body-axis information is re-established dynamically during regeneration.

4. Comparative and Evolutionary Perspectives:

a) Conserved Regeneration-Related Genes Across Metazoans:

Chereddy et al., [12] A compelling comparative-genomic study analyzed genes conserved across species known for high regenerative potential (e.g., planaria, cnidarians) but reduced or absent in low-regeneration species. They identified several candidate genes — including those with homeodomain transcription elements — that may represent a "regeneration toolkit" preserved in highly regenerative lineages [12].

b) Differences Between Invertebrate and Vertebrate Stem Cells:

Invertebrate adult stem cells differ markedly from stem cells in vertebrates. According to a 2022 MDPI volume Advances in Aquatic Invertebrate Stem Cell Research, aquatic invertebrate stem cells are often pluripotent or even totipotent, distributed widely in the body, and sometimes do not reside in a fixed niche [13]. These characteristics contrast with vertebrate stem cells, which are often lineage-restricted and niche-bound.

5. Methods Driving Recent Advances:

a) Single-Cell Transcriptomics & Lineage Tracing:

The use of single-cell RNA sequencing (scRNA-seq) has been transformative, especially when applied during different stages of regeneration. For example, in Platynereis, scRNA-seq data across timepoints revealed how new PSCs emerge and how cell identity changes after injury [4]. Coupled with mosaic transgenesis (labelling individual cells and their progeny), researchers have mapped lineage restrictions in vivo.

b) Computational & Theoretical Models:

Recent theoretical work is bridging gene-regulatory networks with stem-cell behavior. A computational framework by Li, Liang, and Lei (2024) integrates gene regulatory network (GRN) dynamics with epigenetic inheritance models, allowing simulation of how heterogeneous stem-cell populations self-renew and differentiate.

Further, AI-driven approaches have been proposed to modulate bioelectric signaling in real time (e.g., using deep reinforcement learning) to guide tissue patterning and regeneration, potentially in systems like planaria [14].

c) In Vitro & Culture Systems:
The MDPI volume Advances in Aquatic Invertebrate Stem Cell Research compiles methods for isolating and culturing adult stem cells (ASCs) from invertebrates [15]. These include protocols for marine cell lines, assays for stemness, and molecular markers common to vertebrate stemness (e.g., piwi, vasa).

6. Challenges, Open Questions, and Future Directions

- Defining "stemness" across taxa: Given the diversity of invertebrate stem cells (pluripotent, lineage-restricted, dedifferentiated), how should we define stemness in a comparative way?
- Regulatory niche vs. systemic signaling: The discovery in planaria that stem-cell fate can be dictated by distant signals (rather than a fixed niche) raises questions about how widespread this phenomenon is.
- Regenerative loss in evolution: Why have many animals (especially vertebrates) lost regenerative capacity? Comparative genomics might help identify "regeneration-gene deserts" in non-regenerative taxa.
- Manipulating senescence: The role of senescence in reprogramming is exciting, but how universal is it? Could transient senescence be used therapeutically in other systems?

Translational applications: Can invertebrate insights — such as positional reprogramming and systemic signaling — be applied to human regenerative medicine? Also, how can we build in vitro models (cell lines, organoids) for invertebrate stem cells to test therapeutic ideas?

7. Conclusion

This study successfully demonstrates that leaf extracts of *Achyranthes aspera* and *Ficus racemosa* from the Amravati region possess significant antimicrobial properties against a range of pathogenic bacteria and fungi. The phytochemical profile confirmed the presence of antimicrobial compounds, and the bioactivity was found to be dependent on the extraction solvent. The findings validate the ethnomedicinal use of these plants and position them as promising candidates for the development of novel plant-based antimicrobials. Future work should focus on the bioassay-guided fractionation of the active extracts to isolate and characterize the specific bioactive compounds, determine their minimum inhibitory concentrations (MIC), and evaluate their safety and efficacy in in vivo models.

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Correspondence and requests for materials should be addressed to **Mudgal MB**

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