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Insights into regeneration tool box: An animal model approach

Abijeet S. Mehta [a], Amit Singh [a,b,c,d,e,*]

[a] Department of Biology, University of Dayton, Dayton, OH, 45469, USA
[b] Premedical Program, University of Dayton, Dayton, OH, 45469, USA
[c] Center for Tissue Regeneration and Engineering at Dayton (TREND), University of Dayton, Dayton, OH, 45469, USA
[d] The Integrative Science and Engineering Center, University of Dayton, Dayton, OH, 45469, USA
[e] Center for Genomic Advocacy (TCGA), Indiana State University, Terre Haute, IN, USA

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* Dedicated to Prof. Panagiotis A. Tsonis (1953–2016)

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ABSTRACT

For ages, regeneration has intrigued countless biologists, clinicians, and biomedical engineers. In recent years, significant progress made in identification and characterization of a regeneration tool kit has helped the scientific community to understand the mechanism(s) involved in regeneration across animal kingdom. These mechanistic insights revealed that evolutionarily conserved pathways like Wnt, Notch, Hedgehog, BMP, and JAK/STAT are involved in regeneration. Furthermore, advancement in high throughput screening approaches like transcriptomic analysis followed by proteomic validations have discovered many novel genes, and regeneration specific enhancers that are specific to highly regenerative species like Hydra, Planaria, Newts, and Zebrafish. Since genetic machinery is highly conserved across the animal kingdom, it is possible to engineer these genes and regeneration specific enhancers in species with limited regeneration properties like *Drosophila,* and mammals. Since these models are highly versatile and genetically tractable, cross-species comparative studies can generate mechanistic insights in regeneration for animals with long gestation periods *e.g.* Newts. In addition, it will allow extrapolation of regenerative capabilities from highly regenerative species to animals with low regeneration potential, *e.g.* mammals. In future, these studies, along with advancement in tissue engineering applications, can have strong implications in the field of regenerative medicine and stem cell biology.

1. Introduction

Regeneration is a phenomenon where species can regrow their damaged or missing body parts. The fascination for regeneration can be traced back to the Greek and Indian mythology. According to Greek mythology, Hercules, son of Zeus, destroyed the monstrous, multi-headed mythological animal, which they named Hydra. The creature "Hydra" was able to grow back two heads after losing one. Moreover, Greek mythology has an account of liver regeneration when Prometheus's, a Greek God, immortal liver was feasted upon every day by Zeus' eagle (Maden, 1992; Power and Rasko, 2008). To date, humans still have the capability to partially regenerate hepatic cells (Michalopoulos, 2013). This raises the possibility that ancient Greeks knew about the amazing capability of liver to regenerate. Mythologies are mere stories, a coincidence, or a knowledgeable fact has not been validated. Similarly, according to Indian mythology, Ravana, a devotee of Lord Shiva, lived for almost 12000 years, since he had the power to regenerate his head. He regenerated his head ten times in his life. Present day humans only have the capability to regrow neurons from stem cells in two discrete regions of the brain: the hippocampus (Ernst and Frisén, 2015), and axon regeneration in peripheral nervous system (PNS) (Seifert and Muneoka, 2018).

According to our current understanding, regeneration can occur by either one or a combination of the following three modes: (1) Rearrangement of pre-existing tissues, (2) Use of adult somatic stem cells (3) Dedifferentiation and/or transdifferentiation of cells (Fig. 1) (Sanchez Alvarado and Tsonis, 2006). All of these modes result in re-establishing the polarity, structure and final form of the tissue/organ or organism (Fig. 2A) (Sanchez Alvarado and Tsonis, 2006). Therefore, animals with regenerative potential typically utilize either one or a combination of modes to promote regeneration (Poss, 2010; Sanchez Alvarado and Tsonis, 2006; Tanaka and Reddien, 2011). Based on our present understanding, regeneration can be classified into the following five groups: (a) Whole body regeneration, (b) Structural regeneration, (c) Organ regeneration, (d) Tissue regeneration, and (e) Cellular regeneration (Bely and Nyberg, 2010) (Fig. 1). In whole body regeneration, an animal can

* Corresponding author. Department of Biology, University of Dayton, Dayton, OH, 45469, USA.
E-mail address: asingh1@udayton.edu (A. Singh).

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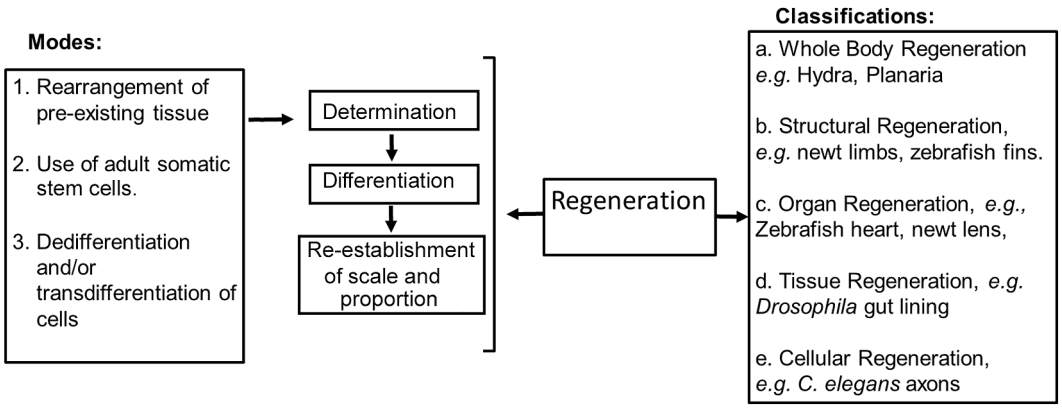

Fig. 1. Modes and different classes of regeneration. Regeneration can occur by either one or combination of these three modes (1) Rearrangement of pre-existing tissue, (2) Use of adult somatic stem cells (3) dedifferentiation and/or transdifferentiation of cells. Regeneration is classified into five different types. In vertebrates, the regeneration response is activated by both stem cell proliferation, and dedifferentiation or transdifferentiation of the cells present adjacent to the amputated stump. The amputated stump responds to the stimulus to regenerate and eventually cells nearby undergo determination, differentiation, and scale up to the appropriate polarity to replace the missing tissue in same proportion.

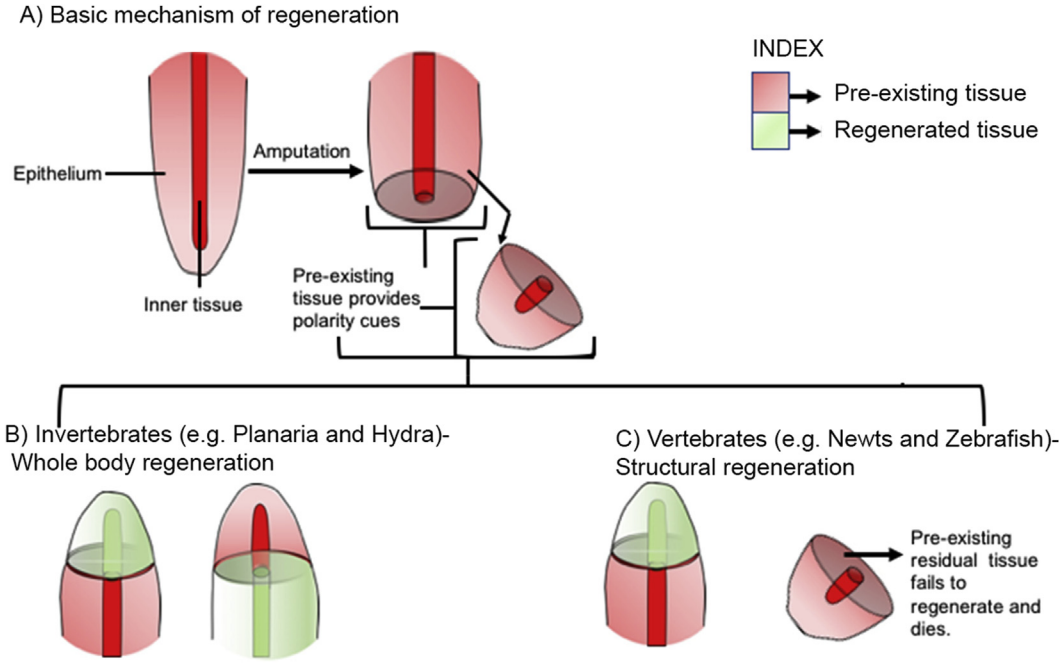

Fig. 2. Mechanism of regeneration. (A) The basic mechanism of how regeneration takes place. (B) In invertebrates (Planaria, and Hydra) whole body regeneration takes place, while as in (C) vertebrates (Newt limb, and Zebrafish fin regeneration) structural regeneration takes place (Sanchez Alvarado and Tsonis, 2006).

regenerate every part of the body *e.g.* Hydra, or Planaria can regenerate entire organism from head or foot/tail fragments (Fig. 2B) (An et al., 2018; Baguñà, 2012; Chera et al., 2009; Galliot and Chera, 2010; King and Newmark, 2012; Sánchez Alvarado, 2006; Tanaka and Reddien, 2011). Structural regeneration allows an organism to regenerate multi-cellular structures (Fig. 2C) excluding regeneration of internal organs, *e.g.,* regeneration of limbs in Newts (Arenas Gomez et al., 2017; Brockes and Kumar, 2008; da Silva et al., 2002; Geng et al., 2015; Stocum, 2017; Tanaka et al., 2016), and fins in Zebrafish (Gemberling et al., 2013). Organ regeneration restores the organ size, which often includes multiple lineages of cells, *e.g.* heart regeneration in Zebrafish (Gonzalez-Rosa et al., 2017; Poss, 2010; Poss et al., 2002), lens regeneration in Newts (Eguchi et al., 2011; Henry and Tsonis, 2010; Roddy et al., 2008; Sousounis et al., 2015). Tissue regeneration is required to close gaps in homogeneous cell population *e.g.* epidermis, and gut lining regeneration in *Drosophila* (Belacortu and Paricio, 2011; Liu and Jin, 2017; Worley et al., 2012). Cellular regeneration allows regeneration of severed axons *e.g.* axon regeneration in *C. elegans* (Basu et al., 2017; Byrne and Hammarlund, 2017; Ghosh-Roy and Chisholm, 2010; Hisamoto and Matsumoto, 2017).

Regeneration is non-uniformly widespread among all the animal phyla (Bely, 2010; Bely and Nyberg, 2010; Sanchez Alvarado and Tsonis, 2006; Slack, 2017) (Fig. 3A). Many evolutionarily conserved pathways are present in the highly regenerative species (Fendrich et al., 2008; Hadzhiev et al., 2007; Rink et al., 2009; Sanchez Alvarado and Tsonis, 2006; Slack, 2017; Tian and Jiang, 2017; Tian et al., 2015) (Table 1). For example, Wingless/Wnt/β-catenin pathway has been found to regulate head regeneration in Planaria (Gurley et al., 2008), and Hydra (Chera et al., 2009; Galliot and Chera, 2010). It has also been found to play role during Zebrafish fin regeneration (Stoick-Cooper et al., 2007), *Drosophila* wing repair, (Smith-Bolton et al., 2009), retina regeneration in fish and chicks (Meyers et al., 2012; Ramachandran et al., 2011; Zhu et al., 2014),

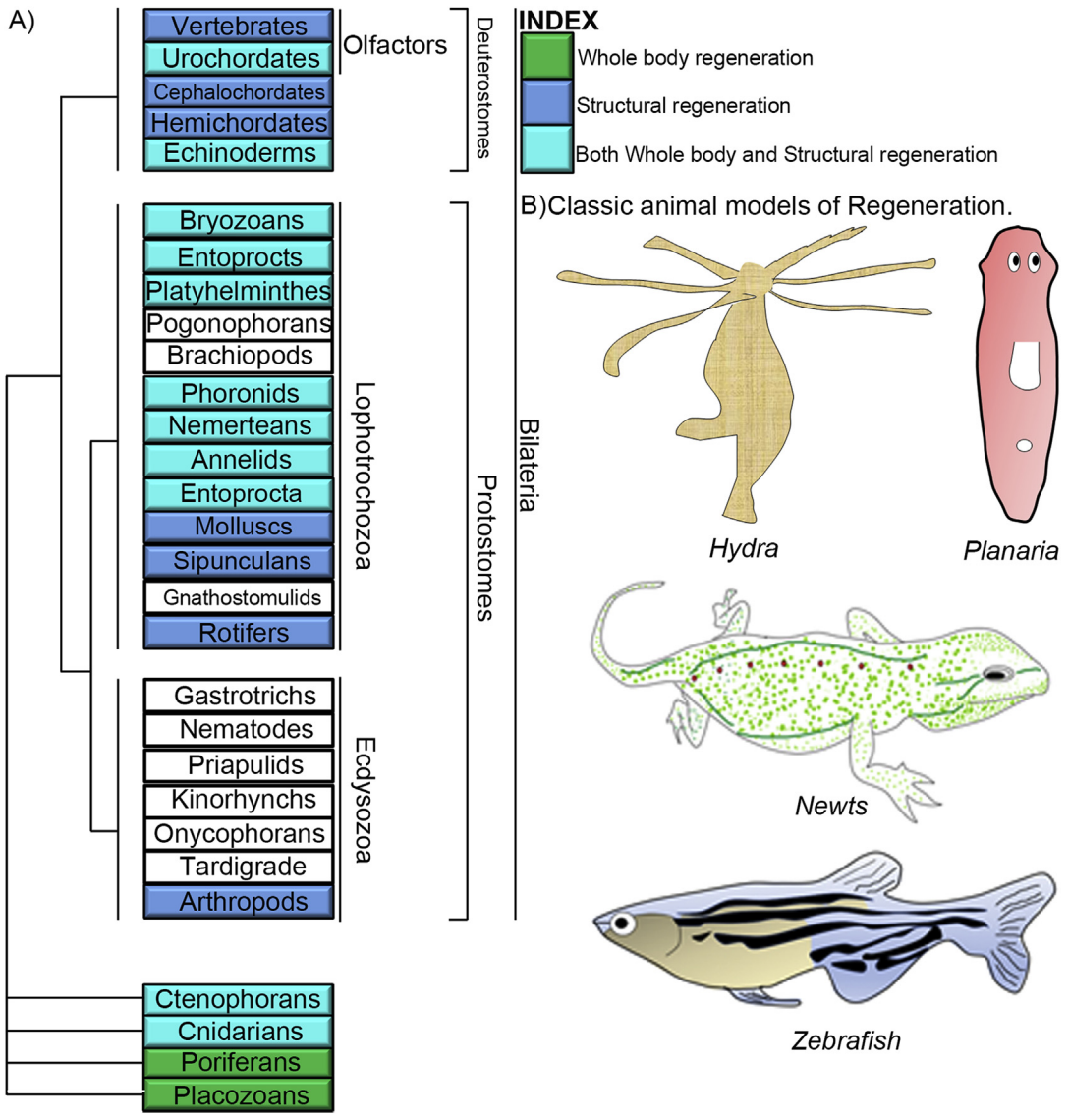

Fig. 3. Regeneration response is non-uniformly distributed throughout the animal kingdom- Phylogenetic distribution and corresponding model species. (A) The taxa which contains at least one species that are capable of regeneration are shown in colored background. The taxa that show whole body regeneration are shown in green. The taxa that show structural regeneration are shown in Blue, and the taxa that show both whole body as well as structural regeneration are shown in Cyan. For the remaining taxa where regeneration has not been reported or the species where its presence is unknown. (B) The diverse animal phylogeny showing regeneration include animal models like, Hydra, Planaria, Newts, and Zebrafish (Classic animal models of regeneration) (Sanchez Alvarado and Tsonis, 2006).

Table 1
Evolutionarily conserved signaling pathways known to be regulated during regenerative response shown by corresponding species or groups.

Signaling pathway	Species or group					
	Hydra	*Planaria*	*Newts*	*Zebrafish*	*Drosophila*	*Mouse*
Wnt pathway	Yes (Galliot and Chera, 2010)	Yes (Gurley et al., 2008)	Yes (Singh et al., 2012b)	Yes (Stoick-Cooper et al., 2007)	Yes (Smith-Bolton et al., 2009)	Yes (Sodhi et al., 2005)
Hedgehog	Not reported	Yes (Rink et al., 2009)	Yes (Tsonis et al., 2004b)	Yes (Hadzhiev et al., 2007)	Yes (Tian et al., 2015)	Yes (Fendrich et al., 2008)
Notch	Yes (Münder et al., 2013)	Yes (Wenemoser et al., 2012)	Yes (Ghai et al., 2010)	Yes (Münch et al., 2013)	Yes (Ohlstein and Spradling, 2007)	Yes (Lin et al., 2011)
Bmp/Dpp	Yes (Rentzsch et al., 2007)	Yes (Molina et al., 2007)	Yes (Grogg et al., 2005)	Yes (Smith et al., 2006)	Yes (Tian and Jiang, 2017)	Yes (Yu et al., 2010)
JAK/STAT	Not reported	Not reported	Yes (Godwin and Rosenthal, 2014)	Yes (Elsaeidi et al., 2014)	Yes (Amoyel and Bach, 2012)	Yes (Doles and Olwin, 2014)

and human liver regeneration (Russell and Monga, 2018). In humans, misregulation of same pathways can cause cancer in differentiated cells (Taciak et al., 2018). Additionally, humans have developed defense mechanisms as an evolutionary adaptation against excessive cell division to prevent cells from becoming cancerous in nature (Carbone and Minna, 1993; Labi and Erlacher, 2015). Previously, it has been reported that cell division of quiescent precursor cells can promote regeneration (Heber--Katz et al., 2013) Therefore, it is possible that this regeneration response in humans might have been downregulated or lost in recent evolutionary past as a preventive measure against uncontrolled growth as seen in cancer (Lambrou and Remboutsika, 2014; Oviedo and Beane, 2009). If regeneration is an intrinsic property of all living beings, then a simple way to understand it in humans would be to restore component(s) that regulate conserved pathways like Wnt, Notch (N), Bone Morphogenetic Protein (BMP), JAK/STAT during regeneration (Amoyel and Bach, 2012; Doles and Olwin, 2014; Elsaeidi et al., 2014; Ghai et al., 2010; Godwin and Rosenthal, 2014; Grogg et al., 2005; Lin et al., 2011; Molina et al., 2007; Münch et al., 2013; Münder et al., 2013; Ohlstein and Spradling, 2007; Rentzsch et al., 2007; Smith et al., 2006; Tian and Jiang, 2017; Yu et al., 2010).

This review highlights the history of regeneration and the modern techniques employed in different regenerative animal models to track conserved pathways. In addition, it explores novel elements found in highly regenerative species that could restore the dormant state of regenerative potential in mammals. Furthermore, it also elucidates the limitations/challenges associated with each animal model system and future directions that can help researchers address these challenges.

2. History of regeneration

Initial studies on regeneration date back to 1712, when Reaumur studied regeneration in crayfish (Reaumur, 1712). In 1740, Abraham Trembley performed remarkable experiments with fresh water polyps, by cutting polyps along different planes into many pieces. He found that each piece of the polyp had the capability to regenerate into a new polyp (Maden, 1992; Morgan, 1901; Okada, 1994; Vergara et al., 2018). Furthermore, he observed that if the polyp head with its tentacles is cut off, it develops into an entire new animal. He named the animal “Hydra” after the Greek mythological creature. Reaumur repeated Trembley's experiment of cutting Hydra and found similar results. He also found that fresh water worms, and terrestrial Earthworms also have regeneration potential [for review see (Maden, 1992)]. Meanwhile, Bonnet conducted similar experiments with fresh water worms including *annelid lumbriculus*. He demonstrated that when a worm is cut into anterior and posterior pieces, a new tail develops from the anterior piece, and new head from the posterior piece (Morgan, 1901). Bonnet also found that if a worm was cut into one, two, three, four, or even fourteen pieces, each piece could regenerate into a new worm (Morgan, 1901). Later, Spallanzani performed experiments on a variety of animals to test their regeneration potential (Maden, 1992; Morgan, 1901; Spallazani, 1768). He worked on various species of Earthworms. He found that when a worm was cut into two pieces, then each piece could regenerate into two new worms. The anterior headpiece regenerates a new tail whereas the posterior half of the cut piece produces a short head; however, the remaining missing part of the animal was never fully restored. Spallanzani also worked with several species of Salamanders. Among all the Salamander species he tested, he observed limb regeneration as a ubiquitous property. He also found that Salamanders possess a remarkable capability to regenerate new tail and new vertebrae (Maden, 1992; Morgan, 1901). Many important facts pertaining to regeneration were discovered by the work of these four naturalists: Trembley, Reaumur, Bonnet, and Spallanzani. They furnished the basis for present-day understanding of regeneration; however, certain terminologies regarding regeneration remained unclear.

During the early part of his career, Morgan studied regeneration and emphasized the importance of adopting a clear and consistent terminology, which helped him classify regeneration (Sunderland, 2010). He used epimorphosis to refer to regenerative phenomena where development of the new part involved cellular proliferation, for example, limb regeneration in Salamanders (Morgan, 1901; Sanchez Alvarado and Tsonis, 2006). On the other hand, morphallaxis was referred to the regeneration resulting from the remodeling of existing material without cellular proliferation, such as regeneration in Hydra (Morgan, 1901; Sanchez Alvarado and Tsonis, 2006; Worley et al., 2012). This basic subdivision of regeneration into two general categories, epimorphosis and morphallaxis, still holds true (Luttrell et al., 2018; Sanchez Alvarado and Tsonis, 2006; Seifert and Muneoka, 2018; Tanaka and Reddien, 2011). These categories underlie the foundation of research programs that study why and how different modes of regeneration are used in different cases. For example, why regeneration occurs via growth from specialized tissue as compared to the remodeling that occurs during morphallaxis? How do molecular pathways contribute to these different modes? (Sanchez Alvarado and Tsonis, 2006). The development of new genetic tools in traditional animal models of regeneration (Fig. 3B), and including genetically amenable models, like *Drosophila melanogaster* (Fig. 8A), added to the list of species in which regeneration can be studied. These approaches can provide answers to some key questions.

3. Modern techniques to study regeneration in animal models

Invention of different experimental tools and recognition of regenerative prowess of different animal models has been instrumental in improving our understanding of regenerative phenomena (Table 2). For example, regenerative capability of Hydra and Planaria can now be studied using double-stranded RNA-mediated interference (dsRNAi) approach (Poss, 2010). The mechanistic inputs into regeneration can be obtained from transgenic Axolotls, and Zebrafish (Tanaka and Reddien, 2011). Similarly, *Drosophila* imaginal disc models can be used to screen conserved regenerative pathways (Harris et al., 2016).

3.1. Hydra

Hydra, a fresh water hydrozoan with cosmopolitan distribution, belongs to the phylum Cnidaria, and is a sister group to all bilaterians (Fig. 4). The animal is radially symmetrical, organized along a single oral–aboral axis, and is divided into three distinguishable anatomical parts: (i) foot for adhesion to the substrata, (ii) a body column that serves as a gastric cavity, and (iii) a head region comprising of tentacles surrounding a primitive mouth (Siddall, 2004). This simple body plan contains two germ layers: ectoderm and endoderm. These two germ layers are separated by an extracellular matrix called the mesoglea. In Hydra, existing epithelial cells divide to give rise to new epithelial cells, whereas other cell types arise from interstitial stem cells (David and Murphy, 1977). These interstitial stem cells are located in the interstitial spaces of the ectodermal layer (Galliot, 1997) (Fig. 4A). These multipotent interstitial stem cells can be differentiated into various cell types such as neurons (David and Murphy, 1977), secretory cells (Bode et al., 1987), gametes (Bosch and David, 1987), and nematocytes (David and Murphy, 1977).

3.1.1. Regeneration mechanism in Hydra

Hydra is the first animal where regeneration was formally described during the mid-eighteenth century (Gibson, 1966; Williams, 2010). It is considered to be negligibly senescent (Martínez, 1998) due to its amazing capability to regenerate missing tissues and replace cells that are lost during normal physiological turnover (Martínez, 1998). Regeneration in Hydra can occur through both morphallactic and epimorphic modes, which is initiated by three cell-types: ectodermal epithelial, endodermal epithelial and interstitial stem cells (Galliot and Chera, 2010). Hydra when bisected at mid gastric level regenerate into two separate Hydras. The upper half will regenerate the foot through cellular rearrangement and transdifferentiation (morphallactic regeneration) (Fig. 4D); while

Table 2
Genetic tools associated with model systems to study regeneration.

Specie or Group	Hydra	Planaria	Newts	Zebrafish	*Drosophila*	Mouse
Key tissue assessed in regeneration studies	Whole Animal	Whole animal, germ cells, nervous system	limbs, tail, heart, lens, spinal cord, brain, jaw, retina, and hair cells of the inner ear	amputated fins, lesioned brain, retina, spinal cord, heart, and other tissues	Midgut, germ cells, Wing disc, Leg disc, eye disc	Liver, Pancreas, Digit Tip, Skin
RNAi	Yes	Yes	Yes	Yes	Yes	Yes
Transgenesis	Yes	No	Yes	Yes	Yes	Yes
Real time imaging of regeneration	Yes	Yes	No	Yes (Larvae)	Yes	Yes
CRISPR/Cas9	Yes	Yes	Yes	Yes	Yes	Yes
Gal4/UAS system	No	No	No	Yes	Yes	Yes
Genome sequencing finished for at least one specie of the group.	Yes	Yes	Yes	Yes	Yes	Yes
Limitations	Complexities involved with loss/gain of function experiments	Lack of transgenesis	Long life cycle, and enormous genome size	Genome duplication, and multiple misalignments	Limited regeneration potential	Limited regeneration potential

the lower half will regenerate the head called as basal head regeneration (Fig. 4C). This regeneration in Hydra occurs through compensatory proliferation induced as a response to apoptosis following epimorphic-like regeneration (Chera et al., 2009; King and Newmark, 2012). However, post decapitation head regeneration is different and named as apical head regeneration (Technau and Holstein, 1995). This particular regeneration follows the morphallactic route (Fig. 4B). Therefore, Hydra provides an animal model where three different types of tissue regeneration can be studied: (i) foot regeneration, (ii) basal head regeneration, and (iii) apical head regeneration.

3.1.2. Toolkit to study regeneration in Hydra

In the early 21st century, many molecular and cellular tools were generated to study mechanism of regeneration in Hydra. The double-stranded RNA-mediated interference (dsRNAi), achieved by feeding the animals with bacteria, provides an amenable method for transiently silencing gene expression in organisms (Buzgariu et al., 2008; Chera et al., 2006). Another highly dependable method for gene silencing in Hydra includes transgenic expression of RNA hairpins (Boehm et al., 2012; Brooun et al., 2019; Franzenburg et al., 2012; Juliano et al., 2014b). Moreover, a robust gene silencing technique involving *in vivo* electroporation of double-stranded RNA into Hydra polyps has also been used (Bosch et al., 2002; Lommel et al., 2017; Vogg et al., 2019b). Initially electroporation was also used to efficiently transfect Hydra polyps to express Green Fluorescence Protein (GFP) reporter *in vivo* (Miljkovic et al., 2002), but the first stable transgenic Hydra strain expressing GFP was reported in 2006 (Wittlieb et al., 2006). The transgenic lines were generated by microinjection in the embryo, which provided a platform to study real-time determination of cellular dynamics during regeneration (Juliano et al., 2014a; Wittlieb et al., 2006). Additionally, RNAi and transgenic approaches in Hydra allowed both loss-of-function (Buzgariu et al., 2008; Chera et al., 2006; Lohmann et al., 1999) and gain-of-function studies (Juliano et al., 2014a; Khalturin et al., 2007; Wittlieb et al., 2006). These studies expanded our understanding of the dynamic role of Wnt–β-catenin pathway, Notch, BMP etc. during regeneration in Hydra (Table 1). Wnt–β-catenin pathway is regulated differently during apical head regeneration after decapitation (Fig. 4B) with respect to basal head regeneration after mid-gastric bisection (Fig. 4C). For example, regulation of Wnt pathway depends upon the cellular niche that is undergoing regeneration (Lengfeld et al., 2009; Philipp et al., 2009). After decapitation, Wnt3 signaling is restricted only to the epithelial cells. Regeneration of the apical head is induced by remodeling of the pre-existing tissue. Previously it is reported that in mid-gastric bisection there is an immediate induction of apoptosis and burst of Wnt3 secretion among interstitial cells at the regeneration site in the head region (not in foot). This Wnt3 secretion is localized in the apoptotic cells that promote compensatory proliferation and induce basal head regeneration that favors epimorphosis (Chera et al., 2009; Galliot and Chera, 2010). At the site of injury, basal head regeneration in Hydra is abolished after silencing Wnt3 (using an RNAi approach), which inhibits the proliferative burst (Chera et al., 2009; Galliot and Chera, 2010). Interestingly, it has been reported by the same group that transcriptional changes are identical in head and foot regeneration for the first four hours after mid-gastric bisection (Wenger et al., 2019). These studies reveal the importance of evolutionarily conserved canonical Wnt signaling pathway in head regeneration in Hydra (Vogg et al., 2019a) raising the possibility that the molecular mechanisms that are activated during Hydra regeneration might have relevance to tissue regeneration in humans. However, something is missing in humans that could modulate such conserved pathways to promote regeneration in a regulated fashion. Recently, *Hydra vulgaris* genome was sequenced and compared to the human genome (Chapman et al., 2010). Also a peptide project in Hydra identified roughly 500 novel peptides (Fujisawa, 2008). These peptides may provide insights into Hydra's amazing regenerative capabilities.

3.1.3. Limitations

Hydra has been the paradigm to study regeneration. Despite having developed many genetic tools for Hydra regeneration model, there are some limitations with respect to carrying out loss-of-function and gain-of-function studies. Furthermore, double-stranded RNA-mediated interference (dsRNAi), achieved by bacteria feeding approach requires treatment for up to 18 days and ultimately leads to starvation and cell death (Technau and Steele, 2011). Similarly silencing of gene achieved by *in vivo* electroporation of dsRNAi results in 50% mortality rate (Technau and Steele, 2011). Other methods to perform loss-of-function experiments like using morpholino treatment to knock down gene expression is only possible with marine cnidarians (Momose et al., 2008). Recently, CRISPR-Cas9 has been utilized for knock-out experiments in *Hydra Vulgaris* (Lommel et al., 2017) and knock-in experiments in *Hydractinia symbiolongicarpus* (Sanders et al., 2018). However, this approach is still in its early stages of development in Hydra species. Due to these limitations associated with Hydra, it is not yet a well-developed genetically tractable animal model.

3.2. Planaria

Free-living fresh water Planaria (Fig. 5) are triploblastic bilaterians belonging to the phylum Platyhelminthes, and order Tricladida. Among hundreds of Planarian species available worldwide *Schmidtea mediterranea* and *Dugesia japonica* are well studied and possess amazing capability to regenerate almost all body parts within days after injury

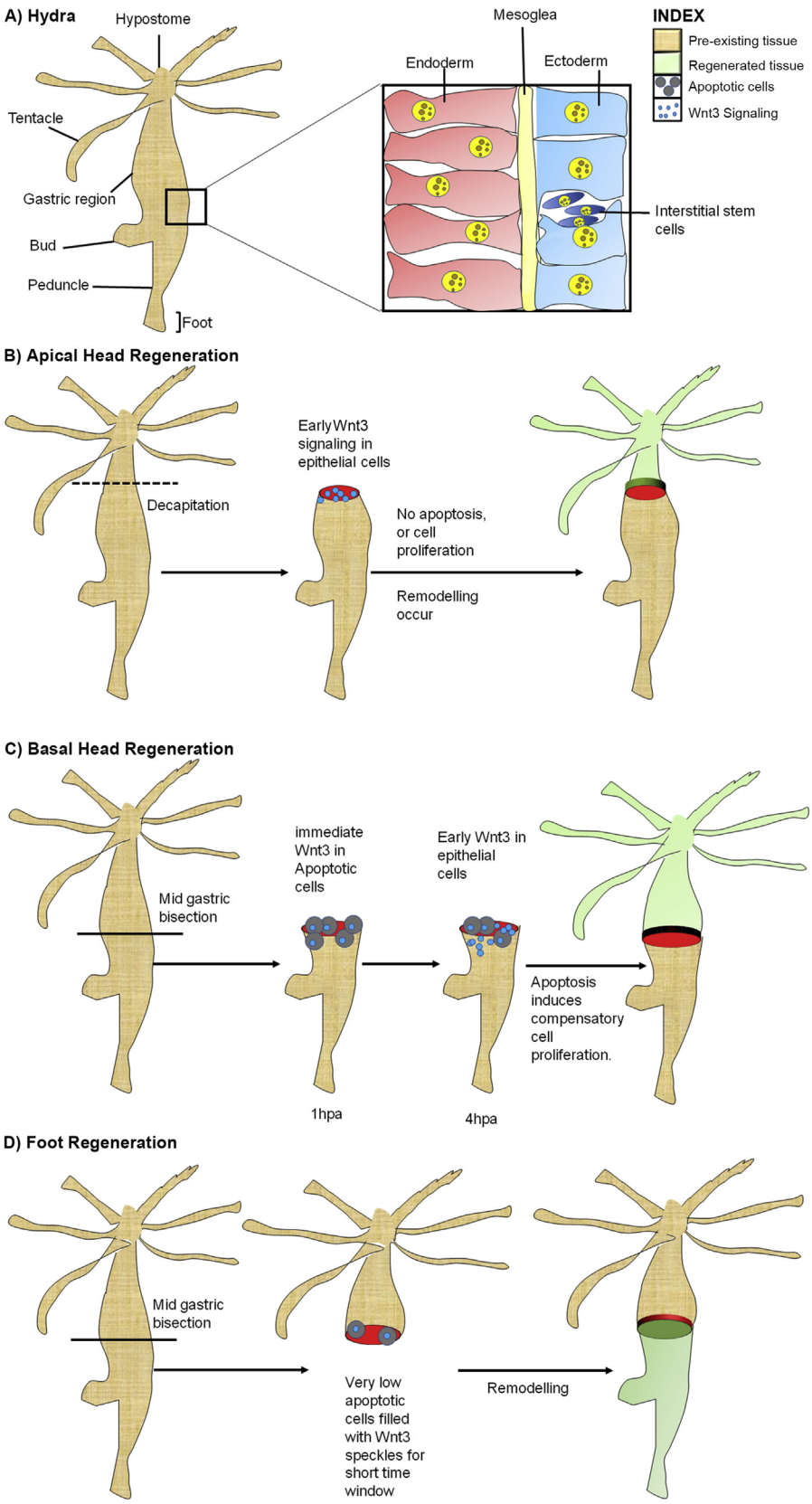

Fig. 4. Regeneration in fresh water polyp, Hydra (*Hydra vulgaris)*. (A) Nomenclature used to describe different body parts of Hydra anatomy. Head (Hypostome) region is decorated by tentacles surrounding primitive mouth, a body column serves as gastric cavity, peduncle is the lower quarter of the body column that stores most of gastro vascular fluid and pumps it into rest of the cavity (Shimizu and Fujisawa, 2003), foot is used to adhere to the substrate, bud is used to accomplish asexual reproduction. Hydra regeneration is accomplished by three different stem cell populations: endoderm epithelia, ectoderm epithelia, and interstitial stem cells. (B–D) Role of Wnt signaling pathway during three different types of regeneration that can be studied in Hydra (B) Apical head regeneration (C) Basal head regeneration (D) Foot regeneration.

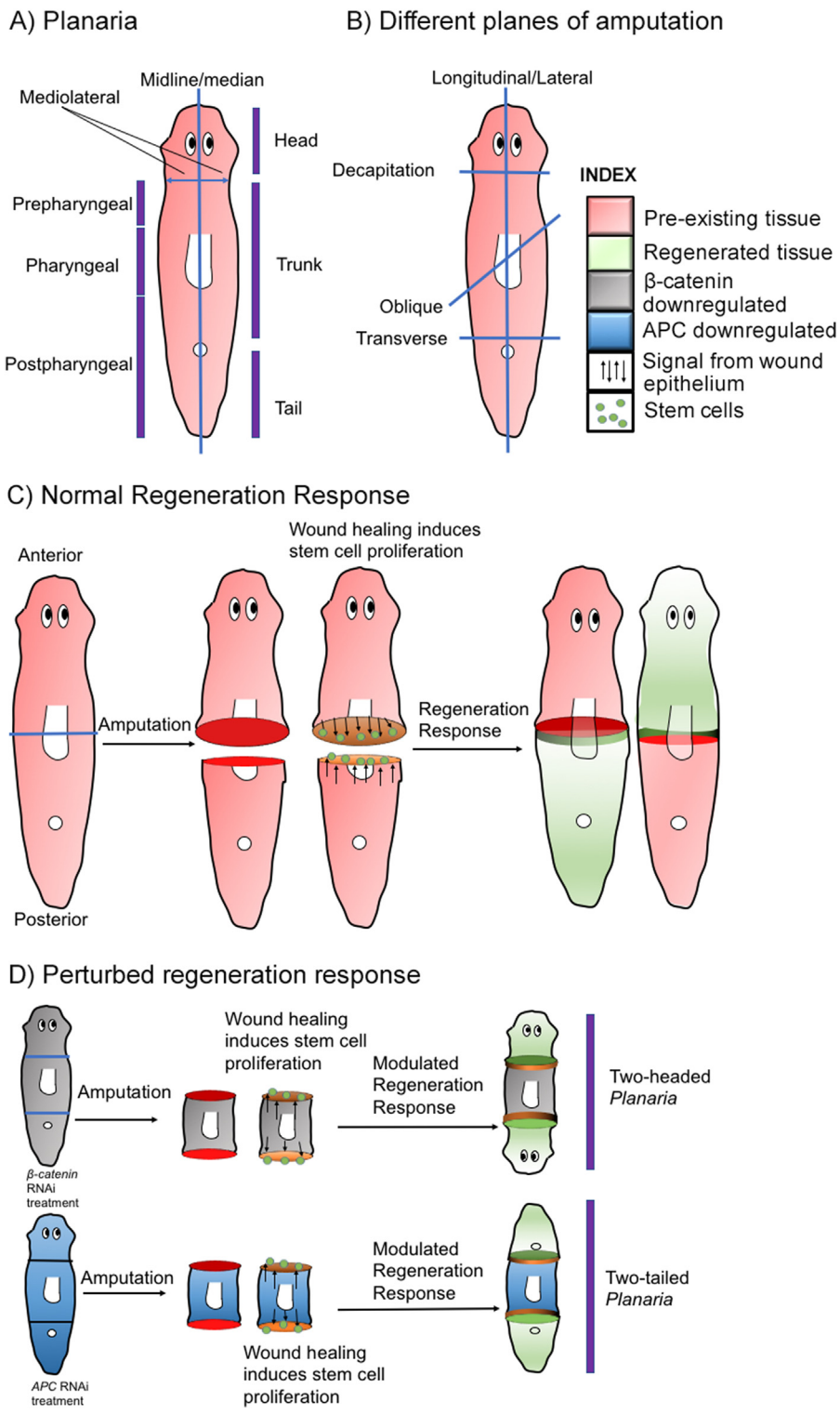

Fig. 5. Fresh water Planaria, *Schmidtea mediterranea*, exhibits regeneration response. (A) Nomenclature used to describe different body parts of planarian anatomy, (B) Types of amputations to study regeneration response in Planaria, (C) Normal regeneration response in Planaria. Wound epithelium formed after amputation sends signal that promote stem cell proliferation and regeneration response. (D and E) Perturbed regeneration response (D) *β-catenin RNAi* treated Planaria induce posterior blastema to regenerate into head. (E) RNAi of APC, a negative regulator of Wnt-*β-catenin* signaling pathway, in Planaria induce anterior blastema to regenerate into tail.

(Fig. 5B) (Reddien and Alvarado, 2004). Planarians have a central nervous system, protonephridial excretory system, and can reproduce sexually as a hermaphrodite or asexually by transverse fission (Reddien, 2018; Reddien and Alvarado, 2004).

3.2.1. *Regeneration mechanism in Planaria*

Recently, there has been an increased interest in Planaria as a model for regeneration (Newmark and Alvarado, 2002; Zeng et al., 2018). Unlike Hydra, Planaria after injury will assemble into a proliferating pool of cells called the blastema from which the missing structure regenerates (Fig. 5C). Blastema arises from proliferation of preexisting somatic cells called as neoblasts (Nb). These cells have been studied for centuries (Baguñà, 2012). They are 5- to 10-μm in diameter with a high nucleus to cytoplasm ratio, have a lot of free ribosomes, few discernible organelles, and prominent chromatoid bodies. Alejandro Sanchez Alvarado and his team isolated single neoblast cell, Tetraspanin-1^{+} (TSPAN-$1^{+)}$ Nb2, which is pluripotent in nature and can rescue lethality in irradiated animals (Zeng et al., 2018). Generating transgenic Planaria is still a missing

milestone, and one can think that genetically engineering this single cell *in vitro* and then transplanting it into the lethally irradiated Planaria can be a novel approach in generating transgenic animals.

3.2.2. Toolkit to study regeneration in Planaria

The tool kit for Planaria includes organism-wide RNAi screening (Sánchez Alvarado and Newmark, 1999), 5-bromo-2′ deoxyuridine (BrdU)-labeling (Newmark and Sánchez Alvarado, 2000), whole mount BrdU staining (Cheng and Alvarado, 2018), whole mount *in situ* hybridization (WISH) (Pearson et al., 2009; Umesono et al., 2003), Fluorescence-Activated Cell Sorting (FACS) in stem cell population (Romero et al., 2012), and next generation sequencing techniques (Dattani et al., 2018; Friedländer et al., 2009; Sandmann et al., 2011; Zeng et al., 2018). An unbiased RNAi screen was carried out and over 1000 genes were screened to find their role in regenerative processes (Cebrià et al., 2002). This novel screen found that 85% of the genes that exhibited regeneration phenotypes in Planaria (*S. mediterranea*) RNAi screen were also conserved in other animals. Using the same knock-down RNAi approach, the role of many conserved pathways (Table 1) including Wnt pathway components: *β-catenin*, *disheveled (dsh) and Adenomatous Polyposis Coli (APC)*, were found in head regeneration in Planaria (Fig. 5D) (Gurley et al., 2008). These classical experiments validated the observation made by T.H. Morgan 100 years ago. While working on Planarian regeneration, Morgan observed two headed Planaria and coined the term for these animals as "Janus Heads". He suggested that "something in the piece itself determines that a head shall develop at the anterior cut surface and a tail at the posterior cut surface" (Morgan, 1901). Alejandro and his team found the Wnt pathway component *β-catenin* acts as a molecular switch to maintain antero-posterior (A/P) identity during regeneration in planarians (Gurley et al., 2008). Therefore, as seen in Hydra, the evolutionarily conserved Wnt pathway also plays a role in Planarian regeneration. This again raised the question, what modulates the Wnt pathway to regulate regeneration in Planaria? However, the same pathway in humans when misregulated can cause cancer (Taciak et al., 2018).

Furthermore, *S. mediterranea* genome has been sequenced, and a database, SmedGD 2.0 is being maintained (Guo et al., 2016; Robb et al., 2015; Ross et al., 2016). Like Hydra, many new proteins and peptides have also been discovered in Planaria. Recently, Newmark lab performed a gene expression-guided functional screen to identify factors that regulate diverse aspects of neural regeneration in *S. mediterranea* (Roberts-Galbraith et al., 2016). Their screen revealed molecules that influence neural cell fates, support the formation of a major connective hub, and promote reestablishment of chemosensory behavior. They also identified genes that encode signaling molecules with roles in head regeneration. These results raised an open-ended question that needs to be resolved - Can these proteins, which are not present in humans, modulate Wnt and other conserved pathways to regulate regeneration in Mammals?

3.2.3. Limitations

In Planaria, development of techniques to manipulate gene expression has always been a challenge. In Planaria, loss-of-function experiments using RNAi approach has many limitations including higher mortality rate (Rouhana et al., 2013). Injection of dsRNA is highly effective but the physical damage caused to animal during the injection process is not desirable when studying wound healing and regeneration (Rouhana et al., 2013). Generally, RNAi approaches also suffer limitations of leaky phenotype. In addition, lack of transgenesis in Planaria considerably hampers its use as a genetically tractable animal to study regeneration.

3.3. Zebrafish

Zebrafish (*Danio rerio*), a teleost (bony fish), is found in the river basins of east India. It was first used as a laboratory animal model by Streisinger and colleagues in the 1970's to study vertebrate development (Streisinger et al., 1981). Since then Zebrafish, a lower vertebrate, has offered an excellent opportunity to study regeneration (Woods et al., 2005). Zebrafish has the capability to regenerate plethora of tissues, *e.g.* amputated fins, brain lesion, retina, spinal cord, heart *etc.* (Fig. 7A) (Gemberling et al., 2013). Specifically, the potential of Zebrafish to regenerate heart is commendable. When a ventricular resection of up to 20% is performed, cardiomyocytes at the leading epicardial edge of the regenerating myocardium proliferate and replace the lost part within two months (Poss et al., 2002).

3.3.1. Regeneration mechanism in Zebrafish

Like other regenerative animal models, Zebrafish has also conserved pathways like, Wnt, Hh, BMP, Notch etc. that have been reported to play role in regeneration (Table 1). During Zebrafish fin regeneration, Wnt pathway plays a role in blastema formation, and proliferation of progenitor cells (Fig. 7B and C) (Stoick-Cooper et al., 2007). Despite the conservation of regenerative pathways like Wnt across the animal kingdom, the regenerative capacity has diminished in vertebrate evolution. Thus, comparison between Zebrafish and higher vertebrates could potentially provide the missing link. In comparison to other classic regenerative animal models, Zebrafish also expresses novel proteins that have roles in regeneration, and organogenesis (Behra et al., 2009; Pei et al., 2008). Similarly, other fishes, like Medaka, *Oryzias latipes,* express six candidate genes that are involved in blastema formation and fin regeneration (Katogi et al., 2004). Studying these novel factors of Zebrafish, and Medaka holds the potential to revolutionize the field of regenerative medicine.

3.3.2. Toolkit to study regeneration in Zebrafish

Zebrafish can be reared easily in the laboratory set up (Streisinger et al., 1986), and their developmental time is short (Kimmel et al., 1995). Genetic screens have resulted in numerous mutants including some that affect regeneration (Patton and Zon, 2001). In addition, its genome is now mapped. Approximately 70% of human genes have at least one obvious Zebrafish orthologue (Howe et al., 2013b). Microarray analyses are possible in this model (Mathavan et al., 2005). In addition to transgenesis (Udvadia and Linney, 2003), knockdown technology using morpholinos (Patton and Zon, 2001), and CRISPR Cas9 (Irion et al., 2014) is readily available.

3.3.3. Limitations

Importantly, Zebrafish when compared to Hydra and Planaria, represents one of the best available genetic regenerative model system (Gemberling et al., 2013; Gonzalez-Rosa et al., 2017; Liu et al., 2018; Poss, 2010). However, it still has some limitations. The life cycle of zebrafish is about 10–12 weeks (Kimmel et al., 1995; Streisinger et al., 1981, 1986). Furthermore, the Zebrafish model lack a large repository of mutants and transgenic animals are also not readily available (Howe et al., 2013a). These limitations make genetic studies using Zebrafish a bit challenging. Additionally, enormous gene duplications has been found in the annotated genome of Zebrafish (Lu et al., 2012; Postlethwait et al., 2000), which also has multiple misalignments (Howe et al., 2013b; Woods et al., 2000). This complicates gene knock out experiments using Zebrafish.

3.4. Newts

Urodeles (Salamanders and Newts, evolved during the Permian period, the last period of the Paleozoic era, ~300 million years ago) are among the group of vertebrates who have remarkable regeneration capabilities (Fig. 6A) (Stocum, 2017). Newts can regenerate a gamut of tissues including limbs, tail, heart, lens, spinal cord, brain, jaw, retina, and hair cells of the inner ear (Brockes and Kumar, 2008; Sanchez Alvarado and Tsonis, 2006) throughout their life (Eguchi et al., 2011).

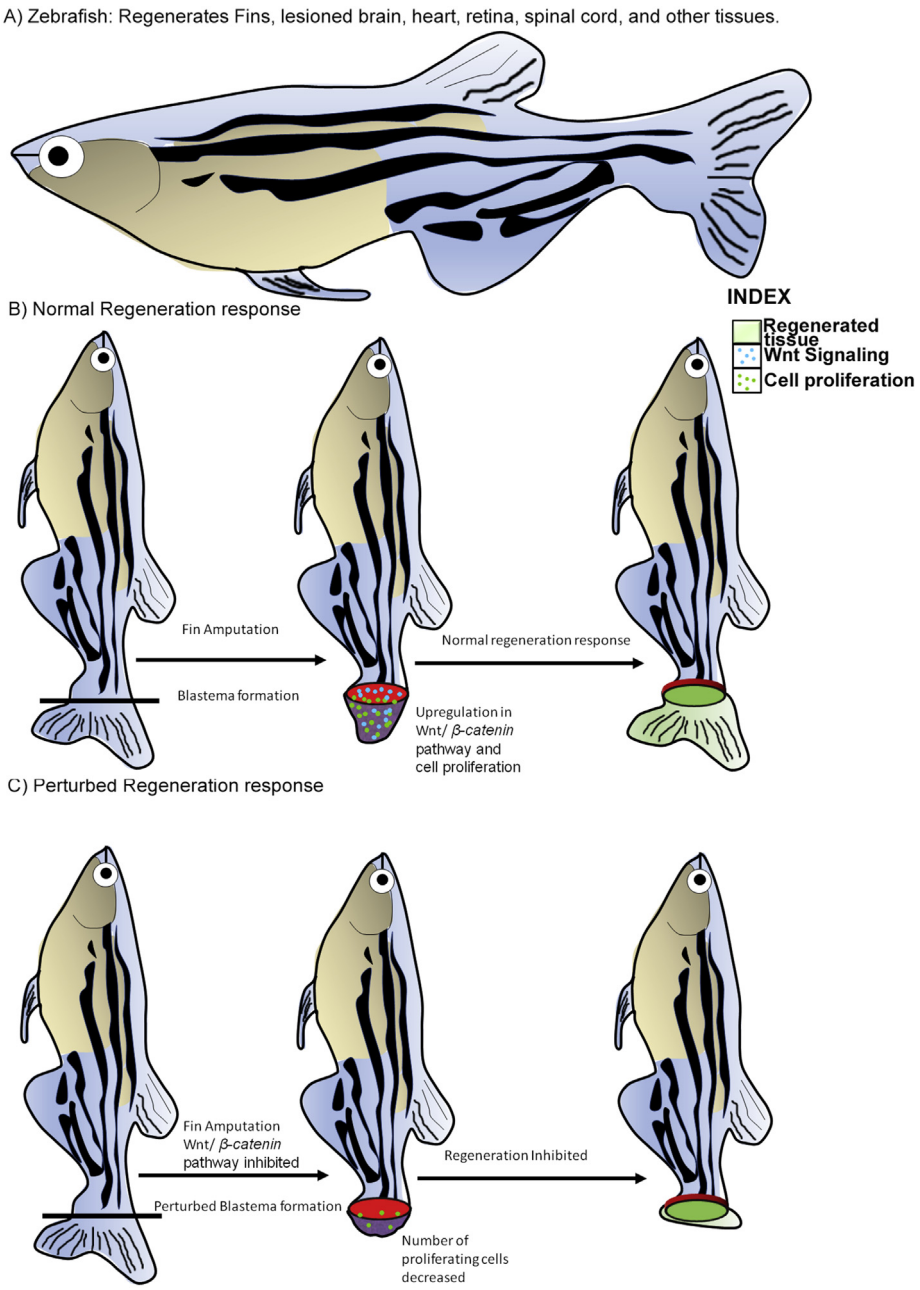

Fig. 6. Regeneration response of Zebrafish (*Danio rerio*), a teleost (bony fish). (A) Zebrafish model exhibits regeneration potential, (B) In Zebrafish, Wnt-*β-catenin* pathway gets upregulated during fin regeneration, (C) Wnt- *β-catenin* pathway when inhibited perturbs blastema formation, and blocks fin regeneration.

3.4.1. Regeneration mechanism in Newts

Regeneration in Newts takes place both by stem cell proliferation (Zielins et al., 2016), dedifferentiation (Tanaka et al., 2016), and/or transdifferentiation of the cells that lie adjacent to the plane of amputation (Bhavsar et al., 2011; Shen et al., 2004; Stone and Sapir, 1940). Dr. Panagiotis A. Tsonis (1953–2016), one of the pioneers in the field of Newt Regeneration, was deeply fascinated by their amazing regeneration capability (Singh, 2016).

In his early days, Tsonis studied effects of carcinogens on limb regeneration (Structural regeneration) (Tsonis and Eguchi, 1982). Later he was more focused on studying lens regeneration (Organ regeneration) using *Notopthalmus viridescens* as an animal model (Vergara et al., 2018). Lens regeneration is a classic example of how cells regenerate a complete organ. Lens regeneration in Newt was first reported independently by Collucci (1891), and Wolff (1895) (Vergara et al., 2018). Based on their pioneer work on lens induction, the process of lens regeneration is often called Wolffian regeneration (Henry and Tsonis, 2010; Vergara et al., 2018). Collucci was the first to report that Newts can regenerate their ocular lens even as adults. Wolff independently reported that the pigmented epithelial cells (PEC) of the iris were the cellular resource for lens regeneration. Lens regeneration in Newts occurs by process of transdifferentiation (a switch of cell fate) where a fully differentiated somatic tissue reprograms and becomes a different one (Grogg et al., 2005; Stone and Sapir, 1940). Lens is exclusively induced from the dorsal part of the iris pigmented epithelium (IPE), and never from the ventral part (del Rio-Tsonis and Eguchi, 2004; Henry and Tsonis, 2010; Madhavan et al., 2006; Okada, 1994; Tsonis et al., 2004a; Tsonis et al., 2004b). It has always intrigued researchers in this field that two different domains of the same cell type (iris), derived from same germ line, have different regeneration potential. Tsonis started looking at the mechanism of lens induction in *Notopthalmus viridescens*, and successfully identified the role of fibroblast growth factors (FGFs) in lens regeneration from the dorsal

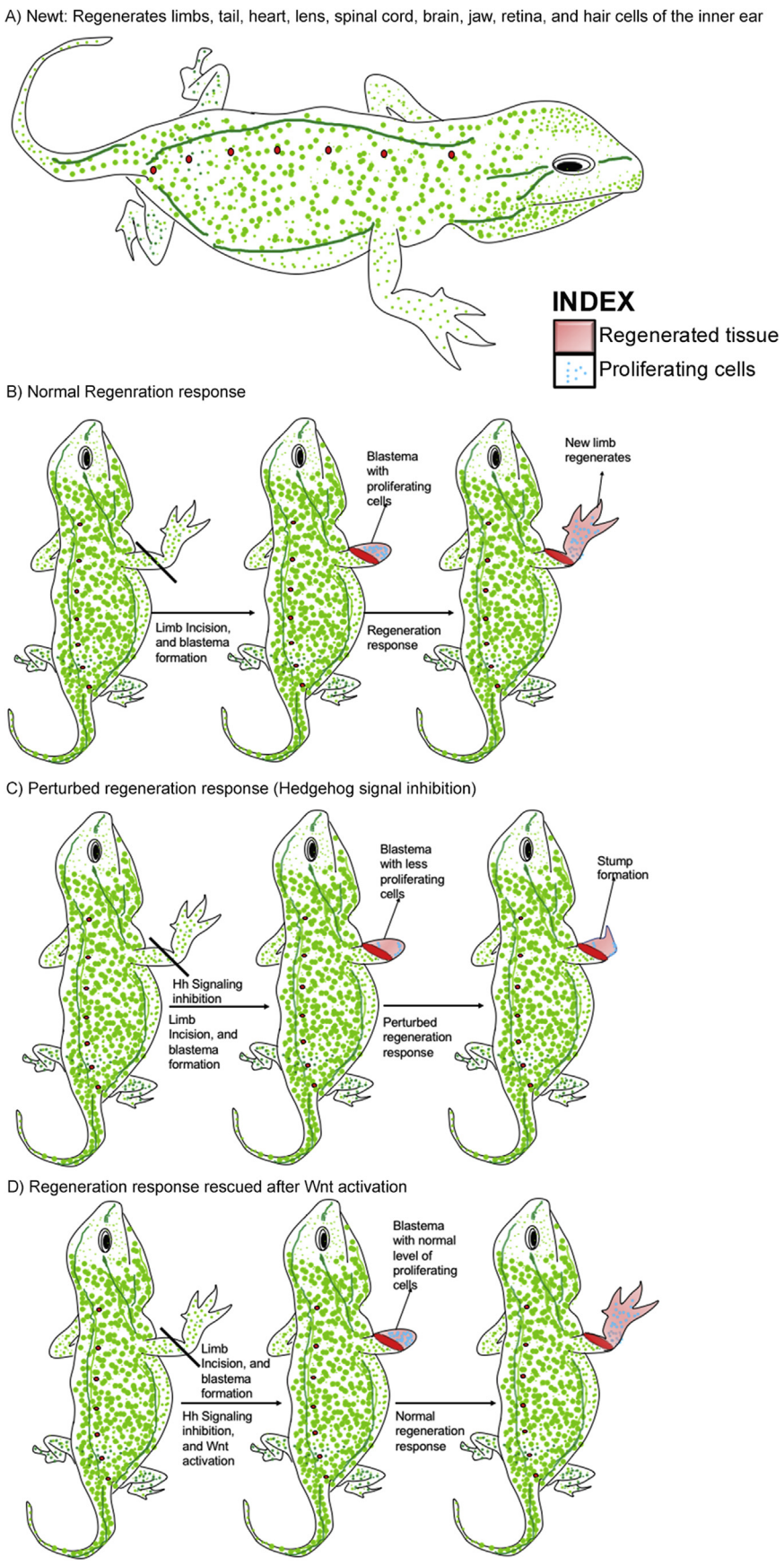

Fig. 7. Regeneration mechanism in Newts. (A) *Notopthalmus viridescens* exhibits strong regeneration potential, (B) Limb regeneration in Newt is a classic example of normal (epimorphic) regeneration response. The cell at the site of amputation promote blastema formation without drastic rearrangement of remaining tissue. Blastema initiates regeneration response. (C, D) The cross talk between evolutionary conserved pathways, Hedgehog (Hh) and Wnt regulate limb regeneration in newts.

iris. Inhibition of FGF receptor signaling significantly inhibited lens regeneration in Newt (Del Rio-Tsonis et al., 1998), whereas ectopic expression of FGF led to induction of a second lens from the dorsal iris (Del Rio-Tsonis et al., 1997). It suggests that FGFs play important role in lens induction from the dorsal iris. Other important factors that modulate lens regeneration include Retinoic acid (Tsonis et al., 2000), Hedgehog (Tsonis et al., 2004b), Complement components (Kimura et al., 2003), Pax6 (Madhavan et al., 2006), and Wnt (Hayashi et al., 2006). Although, none of these molecules and signaling pathways associated with them were able to induce a lens from the ventral iris. Tsonis and his group successfully demonstrated the induction of lenses from ventral irises under certain *in vitro* conditions. This milestone was achieved by over-expression of the transcription factors Six3 along with Retinoic acid treatment and BMP pathway inhibition (Grogg et al., 2005; Singh and Tsonis, 2010). They followed it with transcriptomic analysis of dorsal versus ventral iris during the process of lens induction to generate insights into genetic machinery responsible for lens regeneration (Sousounis et al., 2013). In this analysis, a class of genes were highly enriched in the dorsal iris. These included cell cycle, immune response, and cytoskeletal genes, while the ventral iris showed enrichment of transposon transcripts. In future, with the advancement of technology, it is possible to uncover the molecular path that will unlock the regenerative capability of ventral iris. Such studies will be an advancement towards switching on the dormant factors in mammals to induce regeneration. This could have remarkable implications in regenerative medicine.

3.4.2. Toolkit to study regeneration in Newts

Recently, many new genetic tools have been developed to study regeneration in Newts, and Axolotls, another Salamander with great regenerative abilities (Haas and Whited, 2017). The genetic tools include gene knockout/knock down using morpholinos (Madhavan et al., 2006; Tsonis et al., 2011) or CRISPR/Cas9 (Flowers et al., 2014), transgenic newts (Casco-Robles et al., 2011; Hayashi et al., 2013), and Axolotls (Sobkow et al., 2006). These experimental tools can unravel cellular contributions during regeneration (Fei et al., 2017; Tanaka et al., 2016; Umesono et al., 2003). Furthermore, the Axolotl: *Ambystoma mexicanum* (Nowoshilow et al., 2018), and the Newt: *Pleurodeles waltl* (Elewa et al., 2017) genomes have been sequenced, assembled, annotated, and analyzed, which provides a rich biological resource for development, regeneration, and evolutionary studies.

On analyzing the Axolotl genome, all three Hedgehog (Hh) paralogues as well as a full set of vertebrate Wnt genes have been identified (Nowoshilow et al., 2018). Previously, Hh and its hierarchal correlation with Wnt signaling pathway has been found to play important role during Newt limb regeneration (Fig. 6 C, D) (Singh et al., 2012b). The proliferation and migration of dedifferentiated cells depend upon Hh signaling. Inhibition of Hh results in reduced Pax7 positive cells and regeneration fibers. Activation of Wnt signaling rescues Hh inhibition phenotype in Newts by enhancing proliferative signals. Thus, this work demonstrates the hierarchical network between conserved pathways that play roles in inducing regeneration in Newts. Recently, conserved Hedgehog (Hh)-Gli1-Mycn network has been reported to promote cardiomyocytes proliferation and heart regeneration in Newts as well as in mammals. Using a genome wide screen, Hh signaling was shown to play an important role in Newt heart regeneration. Role of Hh signaling was further characterized in neonatal, adolescent, and adult mouse heart regeneration, and in the proliferation of human induced pluripotent stem cells derived cardiomyocytes (hiPSC-CM). These findings support the existence of conserved pathways and their role in tissue regeneration among vertebrates (Singh et al., 2018). Thus, there is a need to identify novel elements that could modulate such pathways (otherwise dormant in other organisms with limited regeneration potential) to regulate regeneration in mammals, including humans. Previously, many such novel proteins have been discovered in Newts. For example, Prod 1, a Newt specific protein, was identified as a cell surface protein implicated in the local cell-cell interactions mediating positional identity during limb regeneration in Newts (da Silva et al., 2002; Geng et al., 2015). Similarly, using *de novo* assembly of the Newt transcriptome followed by proteomic validation, five new genes were discovered in *Notopthalmus viridescens* that do not have any homologs or orthologs in other species (Looso et al., 2013). Moreover, recently a novel gene, *Newtic1,* has been identified in Japanese Newts, which has robust expression in a subset of erythrocytes that form a novel clump (EryC) (Casco-Robles et al., 2018). In addition, this gene is upregulated in blastema formation and limb regeneration. It is clear that similar to Planaria and Hydra, Newts have novel factors in their gene pool that promote regeneration, and thus can have important implications in the field of regenerative medicine.

3.4.3. Limitations

Newts as compared to Hydra and Planaria are difficult to breed under laboratory conditions due to their long-life cycle (Brockes, 2015). Therefore, genetic studies with Newts (Notopthalmus viridescens and Cynopus pyrrhogaster) are challenging. Also, the enormous genome size of Newts has exacerbated the scientific efforts to discern molecular pathways involved during regeneration (Looso et al., 2013). However, recent efforts are focused on the more genetically amenable Newt, the spanish Newt (*Pleurodeles waltl*), which has a shorter life cycle and its genome has been recently sequenced (Elewa et al., 2017). These Newts are also amenable to transgenesis and CRISPR Cas9 gene editing (Elewa et al., 2017; Joven et al., 2015).

3.5. Mammals

Mammals, homeothermic vertebrate animals of the class Mammalia, are located at the topmost hierarchy of animal kingdom. They are characterized by having hair or fur, produce milk and typically give birth to live young (Foley Nicole et al., 2016). These characteristics distinguish them from reptiles and birds, from which they diverged in the late Triassic (201–227 million years) period (Baker and Solari, 2007). There are around 5400 species of mammals that are divided into two subclasses: Prototheria, which contains the egg-laying monotremes (platypus and echidna), and Theria, which contains the placental and marsupial clades (Szalay, 1999). Mammals have limited regenerative ability as compared to salamanders, but have potential to regenerate injured tissues (Iismaa et al., 2018). These include bone, skeletal muscle, intestine, skin, peripheral nerve, and urinary bladder (Seifert and Muneoka, 2018). A remarkable example of mammalian regeneration include deer and moose antlers, which can grow at a rate of over an inch per day at the peak (Price and Allen, 2004). Blood vessels also exhibit tremendous regenerative growth at the site of necrosis (Zhang et al., 2014). Some internal organs, such as the liver (Michalopoulos, 2007, 2013), spleen (Bradshaw and Thomas, 1982; Tavassoli et al., 1973), and pancreas (Kopp et al., 2016) also have remarkable powers of regeneration.

3.5.1. Regeneration mechanism in mammals

Regeneration mechanism in mammals involve two different paths: Physiological regeneration and Reparative regeneration. Physiological regeneration also called as tissue homeostasis refers both to the regular and repeated renewal of a particular structure or tissue throughout the life of an organism. A primary example of physiological regeneration in mammals is the seasonal replacement of deer (cervid) antlers (Kierdorf et al., 2007). In most cervids, androgen levels play important role in antlers regeneration. Before rutting there is a surge in testosterone levels causing full mineralization of antler bone. After the rut, testosterone levels fall leading to antler shedding that is followed by regeneration of new antlers. However, unlike limb regeneration in Urodeles, antler regeneration in cervid does not involve blastema-mediated epimorphic regeneration but rather an atypical stem-cell-based epimorphic-like regenerative process that is independent of cellular dedifferentiation or transdifferentiation. Other examples of physiological regeneration include replacement of epidermis, endometrium,

blood cells, and gut lining. Homeostatic cell replacement in adult organs involves either stem cell differentiation, or the replication or transdifferentiation of existing cells (Kopp et al., 2016). On the other hand, Reparative regeneration involves restoration of injured tissue or lost body parts. Reparative regeneration is triggered by injury signals, and can be either incomplete, with only partial restoration of structure and function, or complete, parallel to that observed during development. Examples of the former include regeneration of digital tips of fetal and juvenile mice, and fingertips of children. These processes involve blastema formation that is critically dependent on the nail organ, a keratinized ectodermal appendage unique to the tips of digits (Han et al., 2003; Illingworth, 1974; Lehoczky and Tabin, 2015). Complete reparative regeneration is a rare property possessed by mammals. It is limited to regeneration after whole-thickness skin injury in certain species of mice (African spiny mice, *e.g., Acomys kempi*) and rabbits (lagomorphs, *e.g.*, *Oryctolagus cuniculus*) (Gawriluk et al., 2016; Seifert et al., 2012). This type of injury involves loss of connective tissue, blood vessels, nerves, cartilage and the entire dermis. In *Acomys kempi*, all apart from skeletal muscle are regenerated, akin to their formation during development.

3.5.2. Toolkit to study regeneration in mammals

Among all the Mammals, *Mus musculus,* a house mouse has been used as a primary model organism since the early days of genetics. Many experiments made with this small mammal have regularly contributed to enrich our knowledge of mammalian biology and pathology, ranging from embryonic development to metabolic disease, histocompatibility, immunology, behavior, cancer, and regeneration (Guenet, 2005). *Mus musculus* can be easily reared in the laboratory (Abolins et al., 2017), and its genome has been sequenced (Guenet, 2005). Over the past two decades, a variety of genetic tools has been developed. Some of these tools are gene knockout/knock down using dsRNAi (Wianny and Zernicka-Goetz, 2000; Yang et al., 2001), morpholinos (Leong et al., 2009), CRISPR/Cas9 (Modzelewski et al., 2018), Knockin(s) using CRISPR/Cas9 (Platt et al., 2014), transgenics (Cho et al., 2009), and targeted gene expression using Gal4/UAS system (Ornitz et al., 1991).

These genetic tools have proved handy in studying regeneration in mouse, in particular liver regeneration that is the prototype for mammalian organ regeneration. The liver regenerates by the proliferation of the existing tissues. Surprisingly, the regenerating liver cells do not fully dedifferentiate when they reenter the cell cycle, and no blastema is formed. However, five types of liver cells: hepatocytes, duct cells, fat-storing (Ito) cells, endothelial cells, and Kupffer macrophages divide to produce more of themselves. Each type of cell retains its cellular identity, and the liver retains its ability to synthesize the liver-specific enzymes necessary for glucose regulation, toxin degradation, bile synthesis, albumin production, and other hepatic functions (Michalopoulos, 2007, 2013). Like other animal models discussed above, the evolutionarily conserved pathway such as Wnt also play role in promoting liver regeneration of mouse (Nejak-Bowen and Monga, 2011). Recently, Brahma related gene 1, Brg1 has been found to interact with β-catenin to potentiate Wnt signaling and promote hepatocyte proliferation. (Li et al., 2018).

3.5.3. Limitations associated with mammals as a regeneration model

Mouse among all the mammals is well studied, and is one of the best genetic tools available. However, it has limited regenerative potential. Regenerative organs, such as the skin and gastrointestinal tract, use resident stem cells to maintain tissue function. Organs with a lower cellular turnover, such as the liver and pancreas, mostly rely on proliferation of committed progenitor cells. In many organs, injury reveals the plasticity of both resident stem cells and differentiated cells. The ability of resident cells to maintain and repair organs diminishes with age, whereas, paradoxically, the risk of cancer increases (Wells and Watt, 2018).

3.6. Drosophila melanogaster

Insects exhibit varying range of regeneration potential during development (Kango-Singh et al., 2001; Singh et al., 2007; Yang et al., 2016). The genus *Drosophila,* one of the members of Ecdysozoa, contains over 1600 species (O'Grady and DeSalle, 2018). Among them *Drosophila melanogaster*, also called as fruit fly, has been extensively studied. *Drosophila* do not have a robust regenerative capability like classic regeneration models discussed above. However, it is important to point out that *Drosophila* larvae possess regeneration capability under certain conditions (Wildermuth, 1970). The transplantation experiments with *Drosophila* larval imaginal disc have been put forward as regeneration model (Fig. 8A) (Sustar and Schubiger, 2005). In addition, *Drosophila* is emerging as a remarkable model to study wound healing (Belacortu and Paricio, 2011; Weavers et al., 2018). Recently a team of scientists at the University of Toronto lead by Rodrigo Fernandez-Gonzalez have uncovered a mechanism to generate scar free wound healing in *Drosophila* embryos (Zulueta-Coarasa and Fernandez-Gonzalez, 2018). The focus of their research was on mechanical and bioelectric forces that could play crucial role in generating scar free wound healing. Previously, it has been reported that scar free wound healing can initiate limb regeneration in vertebrates (*Xenopus laevis*) under non-regenerative conditions (Herrera-Rincon et al., 2018). Therefore, adding *Drosophila* will complement the list of animal models (discussed above in the review) that are used to study regeneration.

3.6.1. Regeneration mechanism in Drosophila

A series of classic experiments by Ernst Hadorn and his colleagues from the mid-1940s to the 1970s laid the groundwork for our current understanding of regeneration in *Drosophila* imaginal discs. Hadorn and his colleagues used an *in vivo* culture system that was developed by Ephrussi & Beadle (Ephrussi and Beadle, 1936). They implanted disc fragments into mature third-instar larvae immediately prior to pupation and recovered the adult structure generated by the implant from the abdomen of the adult fly. Adult structures that corresponded to the portions of originally implanted disc are referred to as autotypic, and structures appropriate to other discs are referred to as allotypic (Hadorn, 1965). Allotypic structures found in the regenerated portions was interpreted as change in the cell fate from one type of disc to another. Hadorn coined the term "transdetermination" to describe such phenomena (Fig. 9) (Hadorn, 1965).

The discs sub-cultured (implanted) several times revealed various striking properties of these transdetermination events: (a) Certain types of transdetermination events are more frequent than others, (b) only some transdetermination events seem to be reversible, and (c) transdetermination events appear to occur in a specific sequence (Hadorn, 1965; Schubiger et al., 2010; Tata and Rajagopal, 2016). For example, cultures derived from genital discs could switch to a leg or antennal fate. However, a switch in the opposite direction was almost never observed. Similarly, cultures that generated wing structures could switch to making thorax (notum), but a switch in the opposite direction was rare. In contrast, the cultures that generated legs could switch to antennal fate and *vice versa*. Thus, there was a trend in long-term cultures derived from the genital disc to reach a dorsal thorax (notum) identity (Fig. 9) (Hadorn, 1965; Schubiger et al., 2010; Tata and Rajagopal, 2016; Worley et al., 2012).

Unlike transdetermination, regeneration response in *Drosophila* is well studied only in wing-, leg- (Hariharan and Serras, 2017), and eye-imaginal disc (Fig. 8A) (Meserve and Duronio, 2018). Like other animal models, the evolutionarily conserved Wnt pathway, also plays a role during *Drosophila* imaginal disc regeneration (Fig. 8B) (Schubiger et al., 2010; Smith-Bolton et al., 2009). Wing discs show robust regeneration until early third instar stage, when levels of Wingless (Wg), one of the members of Wnt family, is enriched in the regenerating pouch region. As imaginal disc gets older, Wg can no longer induce proliferation, and the regeneration response is diminished. Later, it was found that

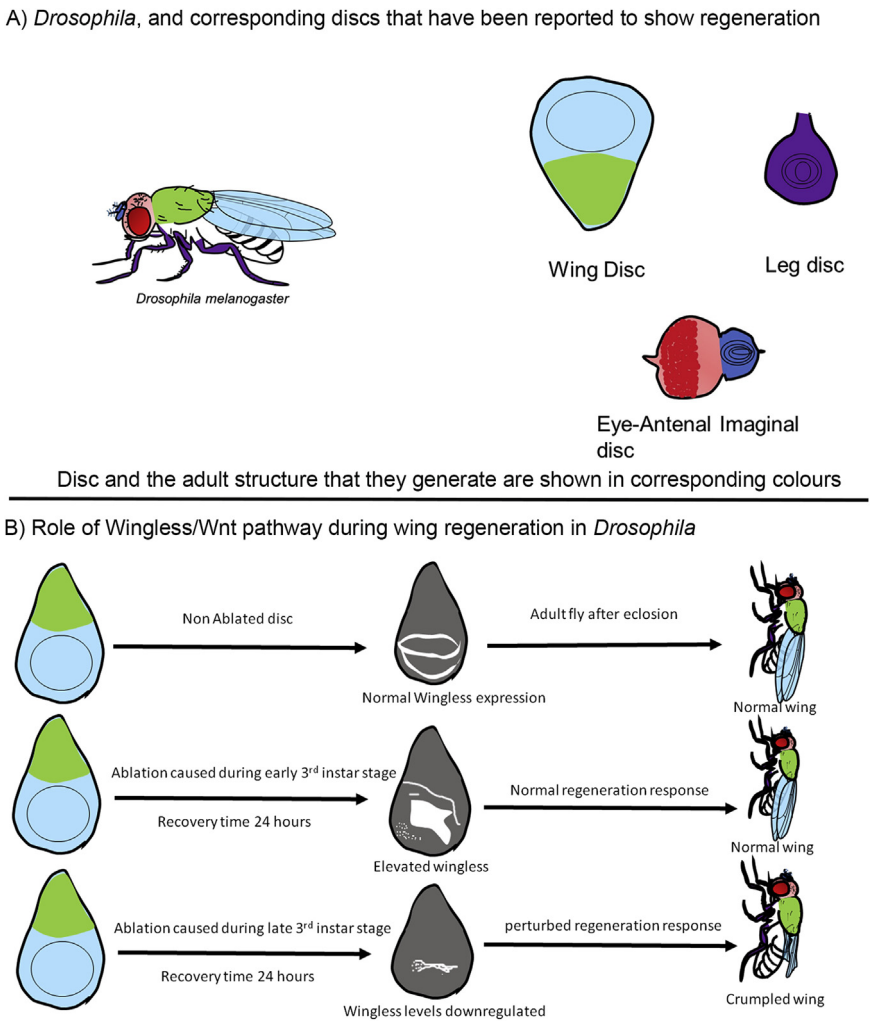

Fig. 8. Regeneration response in *Drosophila melanogaster* model system. (A) *Drosophila* larval imaginal discs exhibit regeneration. The imaginal disc, and the adult structure that they regenerate, are shown in corresponding colors. (B) Effect of Wingless (Wg, orthologue of vertebrate Wnt1 in *Drosophila*) on wing regeneration (early vs late developmental stage) in *Drosophila*. Wg follows the canonical *β-catenin* signaling pathway.

damage-responsive expression of *wg* depends upon its bipartite enhancer whose activity is locally silenced as wing disc undergoes through developmental stages (Harris et al., 2016). It is an important finding and could be of considerable interest to find if loss of regenerative capacity through evolution is due to such selective epigenetic silencing of damage-responsive enhancers that regulate orthologues of *Drosophila* Wnt gene members *e.g.* Wingless (Wnt1).

Apart from regeneration response studied in wing-, and leg-imaginal discs (Hariharan and Serras, 2017), the developing eye imaginal disc, have also been investigated as a regeneration model (Meserve and Duronio, 2018). Targeted misexpression of *head involution defective (hid)*, pro-apoptotic protein that triggers cell death, in the differentiating retinal neurons results in neurodegeneration in *Drosophila* eye. Targeted misexpression in differentiating retinal neurons was accomplished using Glass Multiple Repeat (GMR) enhancer (Moses and Rubin, 1991). This system was used as a paradigm to study regeneration (Meserve and Duronio, 2018). Tissue damage was genetically induced in posterior half of the eye imaginal disc, which activated normally dormant cells posterior to the second mitotic wave to re-enter cell cycle. Previously, it has been reported that cell cycle re-entry of quiescent precursor cells can promote regeneration (Heber-Katz et al., 2013). In the developing *Drosophila* eye imaginal disc regeneration response was found following genetically induced tissue damage (Meserve and Duronio, 2015, 2018). Tissue damage was caused by targeted misexpression of hid using GMR enhancer (GMR-hid). However, this regeneration response was limited only to the accessory cell types in the *Drosophila* retina. The photoreceptor cells were not restored. It suggests that *Drosophila* eye disc has regeneration potential; however, it is missing genetic factors that can regenerate all cell types in the *Drosophila* retina. This raises very important question: Could genetic factors from highly regenerative animal models have the capability to promote regeneration of all the cell types in *Drosophila* eye?

3.6.2. *Toolkit to study regeneration in Drosophila*

Earlier surgical experiments to study regeneration using *Drosophila* imaginal discs were laborious (Ephrussi and Beadle, 1936). To overcome the drawback, a genetic model for studying regeneration following tissue ablation was developed (Smith-Bolton et al., 2009). This system involves wing imaginal disc utilizing yeast transcription factor Gal4 (Brand and Perrimon, 1993) to overexpress pro-apoptotic genes (*eiger* or *rotund*) in the pouch of the wing using regulatory elements of the *rotund* gene. Gene encoding yeast transcription factor, Gal4, was inserted in the *Drosophila* genome that can be expressed in wide variety of tissue/cells using diverse array of genomic enhancers. This strategy allowed selective activation of genes (cloned downstream to Gal4 binding site) in those cells where Gal4 is expressed. It allows selective expression of the gene of interest in spatio-temporal manner. The above Gal4/UAS system for studying regeneration in *Drosophila* (Smith-Bolton et al., 2009) was further

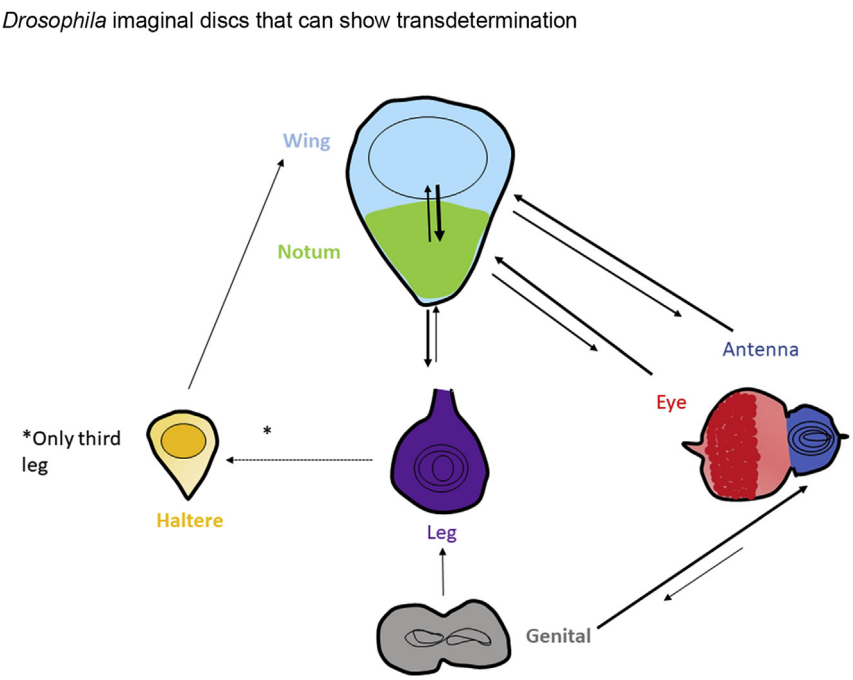

Fig. 9. Transdetermination response in *Drosophila*. Certain transdetermination events are more probable than others (Worley et al., 2012). The thickness of the arrow is used to indicate the relative likelihood of the event.

fine-tuned using temperature sensitive, Gal80^{ts}, to control activity of Gal4 (McGuire et al., 2003). Using temperature sensitive Gal80, which binds to Gal4, further fine-tunes the temporal factor to the already established Gal4/UAS system. This experimental strategy made this regeneration model unique to control ablation experiments along spatio-temporal axis.

3.6.3. *Limitations*

Although *Drosophila* has a limited regeneration response comprising epidermis, gut lining regeneration (Belacortu and Paricio, 2011; Liu and Jin, 2017; Worley et al., 2012), and imaginal discs regeneration (Harris et al., 2016). It is a highly versatile genetic model. *Drosophila* has a short life cycle of 12 days (Hales et al., 2015; Jennings, 2011; Singh et al., 2012a), and a large repository of mutants and transgenic animals (Drysdale and FlyBase, 2008; FlyBase, 2003). This makes *Drosophila* a suitable animal model for cross specie studies where we can ascertain the mechanism behind the regeneration potential of genes from highly regenerative species (discussed above) that have limited genetic tools, and have long life cycle *e.g.* Newts.

4. Future directions

Although since the beginning of 21st century there has been a generous growth in the development of new genetic tools to solve the mystery behind regeneration properties exhibited by classic regeneration animal models, key questions pertaining to regeneration are still unanswered. For example, what evolutionary and biological reasons could be utilizing distinct modes in different cases to promote regeneration? How do molecular pathways contribute to these different modes? What are the differences and similarities between regeneration and normal development? Studies have suggested that pathways that have roles in regeneration are conserved throughout the animal kingdom. For example, the evolutionarily conserved Wnt/β-catenin signaling pathway promotes regeneration, growth, and differentiation in a variety of organisms. In Hydra, Wnt signaling pathway promotes head regeneration, and regulation of Wnt pathway depends upon the cellular niche that is undergoing regeneration (Lengfeld et al., 2009; Philipp et al., 2009). In Planaria, Wnt signaling pathway component, *β-catenin,* acts as a molecular switch to maintain anteroposterior (A/P) identity during regeneration in planarians (Gurley et al., 2008). In Zebrafish, Wnt pathway has been reported to play role in blastema formation, and proliferation of progenitor cells to regenerate fin (Stoick-Cooper et al., 2007). In Newts, Hh and its hierarchal correlation with Wnt signaling pathway has been found to play an important role during newt limb regeneration (Singh et al., 2012b). Apart from these classical animal models of regeneration, Wnt signaling pathway promotes regeneration in animals with limited regeneration potential *e.g.* promotes wing imaginal disc regeneration in *Drosophila* (Harris et al., 2016), and promote cell proliferation during regeneration of mammalian muscle, liver and bone (Polesskaya et al., 2003; Sodhi et al., 2005; Zhong et al., 2006). Therefore, it raises the possibility that regulating such pathways can promote tissue regeneration in humans. Researchers are continuously searching for such elements that can regulate evolutionarily conserved pathways like Wnt, in a manner to promote regeneration in animal models that have limited regeneration potential. The advancement of high throughput screening to study transcriptome of animal models like Newts (Looso et al., 2013), Planaria (Sandmann et al., 2011), Hydra (Chapman et al., 2010) and Zebrafish (Howe et al., 2013b) has made it possible to screen for novel genes/genetic pathways that can play a crucial role in tissue regeneration. Interestingly, such novel elements have been found in regenerative animal models throughout animal kingdom like Hydra (Fujisawa, 2008), Planaria (Robb et al., 2015), Zebrafish (Behra et al., 2009; Pei et al., 2008), and Newts (Looso et al., 2013). If we want to extrapolate the usage of these novel genes for tissue regeneration in humans, then we need to know their function in other animals that do not have profound regenerative capability, like mammals, *Drosophila*, *etc.*

Drosophila melanogaster is a well-defined genetically tractable animal model available to the biological community (Bier, 2005; Jennings, 2011; Singh and Irvine, 2012) that has been used before to study the function of foreign genes (Hughes et al., 2012; Sarkar et al., 2018; Tare et al., 2011). In addition, just like highly regenerative animal models, many evolutionarily conserved pathways have been reported to promote growth and regeneration (Grusche et al., 2011; Harris et al., 2016; Schubiger et al., 2010; Smith-Bolton et al., 2009) in *Drosophila* larvae (Table 1). Therefore, *Drosophila* can be used to address questions about regeneration that could be difficult or time consuming using highly

regenerative animal models (Singh and Irvine, 2012; Singh et al., 2012a; Tare et al., 2013). Additionally, such studies will not only identify missing links between highly regenerative (Planaria, Hydra, Newts, Zebrafish), and low regenerative animals (Human), but could also bridge such gaps. Our group attempted to use *Drosophila* as a genetic tool to screen the function of newly identified Newt gene family (Looso et al., 2013). These newly identified Newt genes may have the ability to switch on the regeneration potential in *Drosophila* as well as higher vertebrates, and humans.

In humans, low regeneration potential has also led to alternative approaches like tissue engineering applications (Dzobo et al., 2018; Mehta et al., 2014; Shafiee and Atala, 2017; Snigdha et al., 2016). Tissue engineering is the combination of engineering techniques like fabrication of scaffolds, mathematical modeling, computational simulation, and natural science to understand and mimic the processes by which a single cell develops into functional biological structures (Mehta et al., 2015; Sachlos and Czernuszka, 2003; Shafiee and Atala, 2017; Zhang et al., 2018). Thus, the idea of this approach is to regulate the process by which cells and tissues organize into structures to generate organs (Minton, 2013). This process is called morphogenesis, which is orchestrated by coordinated communication of genetic machinery with following three stimuli: chemical, mechanical and electrical. (Nelson and Gleghorn, 2012). These stimuli can influence cell survival, proliferation, migration, and differentiation (Chen, 2008; Khang, 2015; Levin, 2012; Mammoto and Ingber, 2010; Tyler, 2017). Among these three, the electrical stimuli also called as endogenous bioelectric signaling, is considered as the master regulator of morphogenesis (Levin, 2009, 2012; Levin et al., 2018; Mathews and Levin, 2018; Sullivan et al., 2016; Tyler, 2017). Bioelectric signaling is a voltage mediated communication and control system that has profound control over organ sculpting, and its function (Feng et al., 2017; Ferreira et al., 2016; Levin et al., 2017; Mathews and Levin, 2018; Nakajima et al., 2015). During regeneration, *in vivo* modulation of bioelectricity has been used to induce entire organ. For example, eye made out of a gut tissue (Pai et al., 2012), regeneration of tail and limb under non-regenerative conditions (Ferreira et al., 2018; Herrera-Rincon et al., 2018). These data showed that bioelectricity can modulate encoded regeneration set points in an animal that has otherwise normal genomic sequence. Such regenerative set points are encoded in the pattern memory of the organisms, which is a read out to achieve final goal of matching the current anatomy to the pattern memory (French et al., 1976; Lau et al., 2015; Munjal et al., 2015; Pezzulo and Levin, 2016). In future, it will be possible to coax an organism to revive or initiate regeneration responses by editing such set points using bioelectricity (Levin et al., 2018; Sullivan et al., 2016). For example, a single cell from a human patient can be edited to design a complete organ that could be transplanted with 100 percent compatibility. Therefore, current advances in regeneration studies including identification of novel regeneration factors, along with development in tissue engineering as a technology, may promote regeneration of organs and structures in humans.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ydbio.2019.04.006.

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