Comparative Study in Zebrafish and Medaka Unravels the Mechanisms of Tissue Regeneration

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Tissue regeneration has been in the spotlight of research for its fascinating nature and potential applications in human diseases. The trait of regenerative capacity occurs diversely across species and tissue contexts, while it seems to decline over evolution. Organisms with variable regenerative capacity are usually distinct in phylogeny, anatomy, and physiology. This phenomenon hinders the feasibility of studying tissue regeneration by directly comparing regenerative with non-regenerative animals, such as zebrafish (*Danio rerio*) and mice (*Mus musculus*). Medaka (*Oryzias latipes*) is a fish model with a complete reference genome and shares a common ancestor with zebrafish approximately 110–200 million years ago (compared to 650 million years with mice). Medaka shares similar features with zebrafish, including size, diet, organ system, gross anatomy, and living environment. However, while zebrafish regenerate almost every organ upon experimental injury, medaka shows uneven regenerative capacity. Their common and distinct biological features make them a unique platform for reciprocal analyses to understand the mechanisms of tissue regeneration. Here we summarize current knowledge about tissue regeneration in these fish models in terms of injured tissues, repairing mechanisms, available materials, and established technologies. We further highlight the concept of inter-species and inter-organ comparisons, which may reveal mechanistic insights and hint at therapeutic strategies for human diseases.

Keywords: zebrafish, medaka (*Oryzias latipes*), tissue regeneration, heart, retina, fin, evolution, comparative genomics

INTRODUCTION: TISSUE REGENERATION IN MODEL ORGANISMS

Reparative regeneration refers to replacing damaged or lost body parts with new tissue, an injury response that restores the tissue homeostasis and function in the optimal scenario (Iismaa et al., 2018). By studying regeneration, scientists can devise biological concepts for tissue repairing and apply them to traumatic injury and degenerative diseases in humans/patients. The studies encompass the strategy to stimulate the repair mechanism to replace the damaged tissues and organs, involve cross-discipline practices, and serves as a bridge between developmental biology and clinical study. A common way to study regeneration is to introduce experimental injury to the model animals and observe how they repair the tissue and recover from the injury.

In the Kingdom Animalia, the loss of regenerative ability coincides with the evolution of new and complex cell and tissue types (Brockes et al., 2001; Maginnis, 2006; Bely and Nyberg, 2010; Elchaninov et al., 2021). Anatomically simple organisms, such as hydra and planarians, can regenerate their entire body when cut into multiple pieces (Reddien and Alvarado, 2004; Reddy et al., 2019). Considerable members of early branching vertebrate lineages (like bony fish and amphibians) can also regrow various organs upon experimental injuries (Yun, 2015; Khyeam et al., 2021). In striking contrast, mammals (like mice and humans), retain a limited regenerative capacity only in some tissues and organs (Iismaa et al., 2018; **Figure 1**). The differences in regeneration capacity solely rely on the cellular source for replenishing lost or damaged tissue, which may come from one of three mechanisms, including the *proliferation* of progenitor/stem cells, *dedifferentiation* of mature cells into progenitors, and *transdifferentiation* from one cell type to another (Jopling et al., 2011). Regenerative species usually possess the pool of progenitor cells or the potential of dedifferentiation and transdifferentiation upon activating the regenerative program within the injured tissue. Taking the heart for example, most cardiomyocytes stop proliferating soon after birth, and there is no stem-like or progenitor cell population identified in the adult hearts (Bely and Nyberg, 2010; Steinhauser and Lee, 2011; Mollova et al., 2013; Bergmann et al., 2015). Instead, mature cardiomyocytes were stimulated to dedifferentiate, proliferate, and re-differentiate to replenish the lost tissue upon injury (Eschenhagen et al., 2017). Over the years, investigations across the animal kingdom have led us to compile a list of masters in tissue regeneration who also have comparable organ systems to humans, including zebrafish (Marques et al., 2019), newts (Laube et al., 2006), and Axolotl (Cano-Martinez et al., 2010; Simon and Tanaka, 2013; **Figure 1**).

Since regenerative capacity exists unevenly among species and their respective organs, an exciting way to uncover the mechanisms of tissue regeneration is by comparing the repair processes in animals with differential regenerative capacities. Such comparisons have been carried out in two ways: "Inter-species" comparing the repair of the same tissue/organ that is regenerative in one species (could also be age or living condition) but non-regenerative in another; Or "inter-organ" comparing two regenerative tissues within the same species to identify a central regenerative program (Potts et al., 2021). However, the regenerative species are usually quite distant in phylogeny, anatomy, and physiology from those non-regenerative ones, such as zebrafish and mice. It is thus essential to find more comparable species to overcome these shortcomings. In search of such comparative systems that can justify the disadvantages of comparing fish with mammals, zebrafish and medaka represent a more simplistic and feasible platform for comparing tissue repair and regeneration.

Zebrafish and medaka are two commonly used vertebrate models in biomedical research, given the homology with mammals and the availability of a wide range of research tools (Furutani-Seiki and Wittbrodt, 2004). Despite diverged 115–200 Mya, zebrafish and medaka are similar in anatomy, physiology, and genetics, with many conserved gene regulato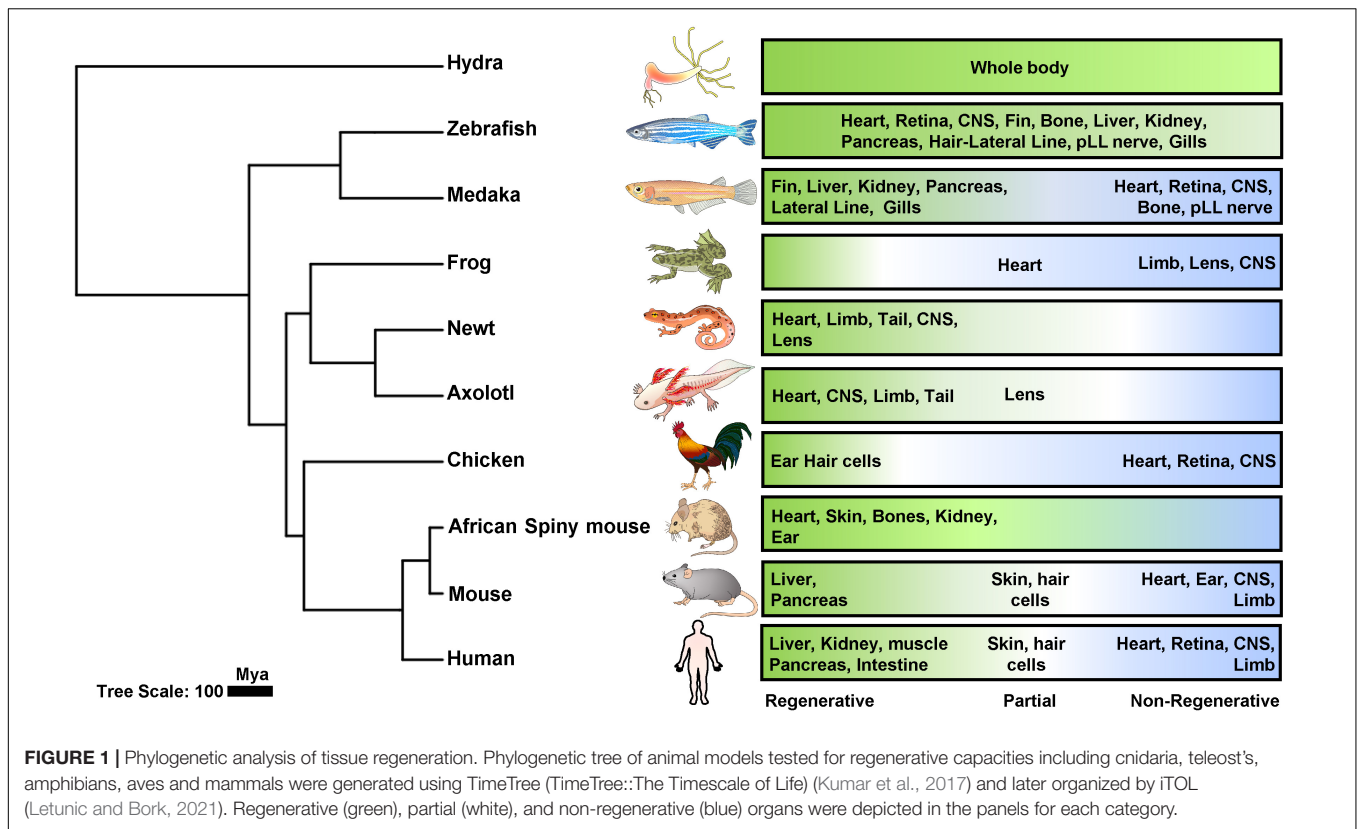ry elements. In addition, zebrafish shares more than 70% of homologous genes with humans, and conserved signaling pathways and metabolic networks, making it a valuable model for biomedical research (Howe et al., 2013). Interestingly, medaka possesses regenerative capacity in fin (Katogi et al., 2004), kidney (Watanabe et al., 2009), liver (Van Wettere et al., 2013), pancreas (Otsuka and Takeda, 2017), lateral line neuromasts (Seleit et al., 2017b), and gills (Stolper et al., 2019) but is impaired to regenerate the heart (Ito et al., 2014; Lai et al., 2017), retina (Lust and Wittbrodt, 2018), brain (Shimizu and Kawasaki, 2021), and posterior lateral line (pLL) nerve cells (Seleit et al., 2022). This uneven regenerative capacity across organs is in sharp contrast with zebrafish, which can regenerate almost all organs, including the heart (Poss et al., 2002), retina (Vihtelic and Hyde, 2000; Sherpa et al., 2008), brain (Kroehne et al., 2011; Marz et al., 2011; Kishimoto et al., 2012), spinal cord (Becker et al., 1997; Ghosh and Hui, 2018), notochord (Garcia et al., 2017; Lopez-Baez et al., 2018), fin (Poss et al., 2003), kidney (Diep et al., 2011), liver (Sadler et al., 2007), pancreas (Moss et al., 2009), gills (Mierzwa et al., 2020), and lateral line (Hair cells) (Lush and Piotrowski, 2014; Cruz et al., 2015). These features make them great models for studying tissue regeneration by inter-species comparisons. Even for the inter-organ comparisons, common vs. tissue-specific regenerative programs could be revealed in zebrafish, while tissue-specific injury responses relevant to regeneration may be explored in medaka, which will be further elaborated in this review.

Here, we highlight the potential of this comparative platform by summarizing the current knowledge from published work, available tools and techniques, and elaborate on current limitations and future outlooks. This platform may provide a new opportunity for investigating the intrinsic mechanisms of tissue regeneration at the organism level and in an unbiased manner. The constraints and triggers of tissue regeneration may further translate toward novel therapeutics for related human diseases.

EVOLUTION OF THE REGENERATIVE CAPACITY

Deciphering the underlying mechanisms of tissue regeneration across phylogeny requires the integrative knowledge of evolutionary biology since the trait (regeneration) changes over the course of evolution (Zattara et al., 2019). This phenomenon is due to the fact that maintaining regenerative capacities requires selective pressures, in terms of the frequency and severity of major damages in an extreme living environment (Morgan, 1901; Lin et al., 2017; Elchaninov et al., 2021). These damages may compromise the fitness of the organisms, but they are not always detrimental for survival and propagation as a selective pressure (Fox and McCoy, 2000; Bernardo and Agosta, 2005). As a result, a critical phylogenetic trend identified across the animal phyla reveals declined regenerative capacity instead of preservation (Bely, 2010; Bely and Nyberg, 2010).

Various theories have been proposed to explain the declined regenerative capacity, including low damage intensity over the evolution mentioned above and the changes in adaptive value

FIGURE 1 | Phylogenetic analysis of tissue regeneration. Phylogenetic tree of animal models tested for regenerative capacities including cnidaria, teleost's, amphibians, aves and mammals were generated using TimeTree (TimeTree::The Timescale of Life) (Kumar et al., 2017) and later organized by iTOL (Letunic and Bork, 2021). Regenerative (green), partial (white), and non-regenerative (blue) organs were depicted in the panels for each category.

of organs (Elchaninov et al., 2021). In addition, the loss of capacity in myocardial regeneration in adult mammals could be an evolutionary trade-off related to energy metabolism (Elhelaly et al., 2016). In a different context, the regenerative capacity of limbs in amphibians but lost in other tetrapods may result from the semiautonomous module of limb development, so their limb may regenerate as a separate organ in adults without the interactions with other transient structures during development (Galis et al., 2003). Another interesting observation is that the declined regenerative capacity seems to inversely correlate with complex immune systems during development and evolution (Mescher and Neff, 2005). For example, the development and maturation of the immune system strongly correlate with the decline of regenerative capacity during frog metamorphosis (Robert and Ohta, 2009; Godwin and Rosenthal, 2014) and mammalian cardiac maturation (Porrello et al., 2011; Vivien et al., 2016). Thus, the selection pressure of the immune system may have underlying influences on the regenerative capacity that reflect at the tissue or organismic levels. However, the immune system does not always obstruct regeneration. It even acts as a critical tissue regeneration component as a coordinated innate immune response is indispensable for regenerating the axolotl limb and neonatal mouse heart (Godwin et al., 2013; Aurora et al., 2014). Moreover, the current knowledge indicates the capacity to regenerate is not only confined to organ-specific or tissue-specific levels but a coordinated involvement of systemic responses (Aurora et al., 2014; Lai et al., 2017; Sanz-Morejon et al., 2019; Bevan et al., 2020).

It is known that the loss/gain of tissue regenerative ability has evolved independently several times over the course of evolutionary history (Zattara et al., 2019). Given this, it is of paramount importance to examine and compare regeneration in a lineage-specific context (Dwaraka and Voss, 2021). Despite the availability of systematic reviews on the evolutionary origin of regeneration, only a handful of studies have addressed the regenerative potential in a lineage-specific context and have reconstructed routes of the ancestral states with the organ of interests (Zattara et al., 2019; Dwaraka and Voss, 2021). Fortunately, growing research groups are proposing comparative analyses of tissue regeneration across animal phylogeny. Comparative phylogenetic studies investigating the regenerative capacity of diverse animal taxa bring invaluable insights into the origin and preservation of regeneration throughout evolution. Novel inferences may be drawn only by comparing a wide range of organisms covering major branches/lineages of interest.

Such a study was recently reported by Hirose et al. (2019) who used cardiomyocyte ploidy as an indicator of heart regeneration and assessed the ploidy of cardiomyocytes in 41 vertebrate species. They found that the diploid cardiomyocyte frequency inversely correlated with the energy metabolism process modulated by the thyroid signaling, an evolutionary trade-off for acquiring endothermy in mammals compared to fish (Hirose et al., 2019). Evolutionary trade-offs are the manifestation of loss or gain of a particular functional trait caused by opposing selections resulting from different environments at an apparent cost (Agrawal et al., 2010). More

examples of the trade-off between regenerative capacity and metabolism can be observed in Mexican cavefish (Stockdale et al., 2018). Stockdale et al. (2018) reported that the surface- and cavefish possessed similar levels of cardiomyocyte proliferative capacity, but the cave-fish showed differential upregulation of immune and scarring responses with downregulated metabolic genes compared to their surface-dwelling counterparts. These switch in metabolic regulation might play an essential role in the regenerative capacity of the cavefish when it fails to regenerate its heart and instead forms a fibrotic scar overtime. Furthermore, this intra-species comparative study nicely depicts that successful heart regeneration relies on the interplay of cardiomyocytes (CM) proliferation and scarring, which is absent in the cave-dwelling species (Stockdale et al., 2018). Moreover, the current evidence for heart regeneration further suggests that the loss of mammalian regenerative capacity is a one-trait evolutionary trade-off for higher energy metabolism in cardiac output and failure in cardiomyocyte proliferation as a capacity for heart regeneration (Elhelaly et al., 2016). The switch in metabolic reprogramming can be further correlated with cardiomyocyte proliferation observed during zebrafish heart regeneration switching from oxidative phosphorylation to glycolysis (Honkoop et al., 2019). These events, in turn, if activated in mouse hearts by ErbB2 signaling, can induce cardiomyocyte proliferation and improve functional recovery post-ischemic injury (Honkoop et al., 2019). Interestingly, medaka possesses the potential for testing these theories and makes people wonder the mechanisms underlying their uneven regenerative capacity amongst different organs, especially when compared to zebrafish.
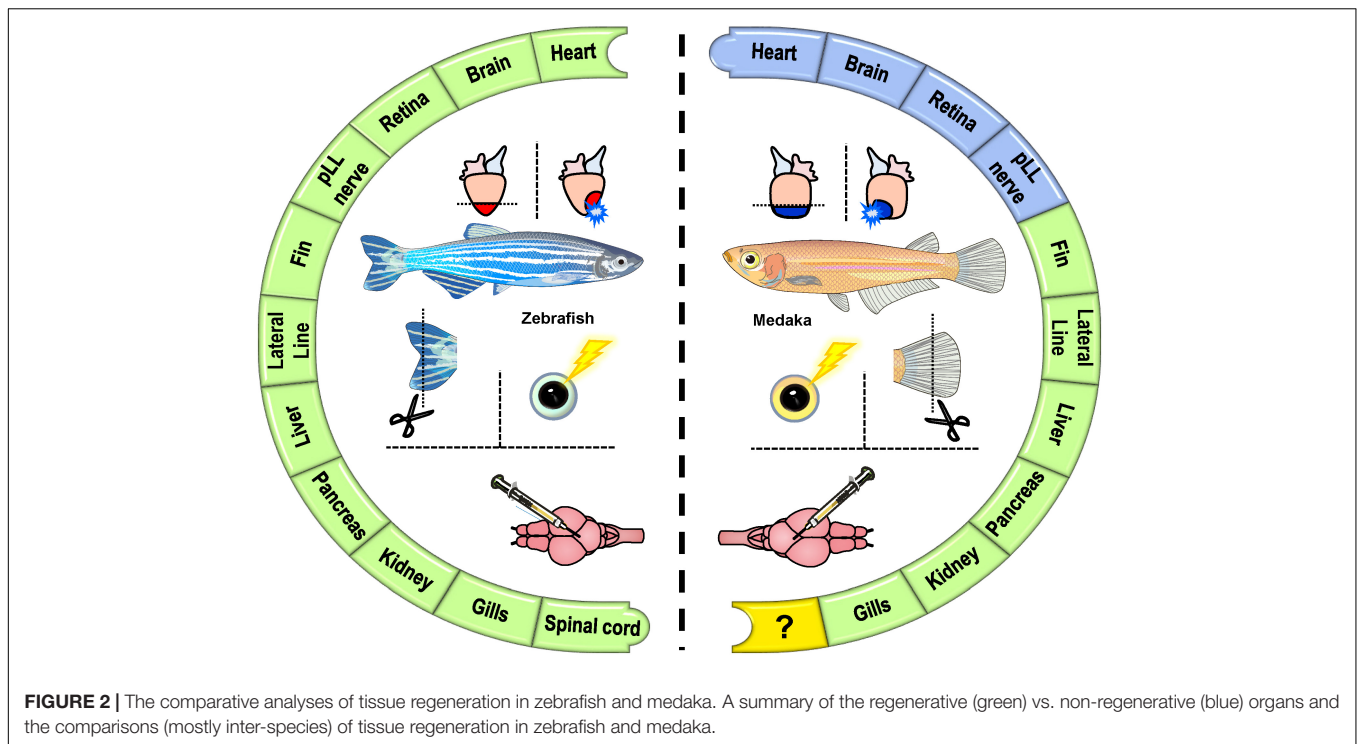
ZEBRAFISH AND MEDAKA: POWERFUL MODELS FOR COMPARATIVE STUDY

Among various model systems used to study regeneration, fish species are extensively investigated. Fish is a phylogenetically "inclusive" term that encompasses four major vertebrate lineages: Sarcopterygii (lobe-finned fish), Actinopterygii (ray-finned fish), Chondrichthyes (cartilaginous fish), and Agnatha (jawless fish). Interestingly, these primitive vertebrates exhibit uneven regenerative capacity among different organs, living conditions, and between phylogenetically close species, making them perfect models to reveal how regeneration works and how to preserve or rehabilitate it in other vertebrates that have lost the capacity. Among actinopterygian fish, zebrafish are natives of the river basins in India and a well-established animal model used extensively for scientific research since the 1980s (Streisinger et al., 1981, 1986). Over the decades, zebrafish has stood out as a powerful tool for studying developmental biology, evolution, human genetics, and diseases. The advantages of the zebrafish model include a small size for manipulation, short reproductive cycle, large clutches of embryos, rapid development, cheap maintenance, comparable organs to mammals, and fully sequenced genome with well-annotated genes (Gemberling et al., 2013; Howe et al., 2013; Beffagna, 2019). Most importantly, zebrafish regenerate almost all organs upon experimental injury

(Marques et al., 2019). On the other hand, medaka species are small egg-laying freshwater teleost fish home to Asia with native diversity from Japan, Korea, Taiwan, and China (Hilgers and Schwarzer, 2019). They live in rice paddy fields, rivers, and creeks in Japan, thus also named "Japanese Rice fish." As a resident of the temperate zone, medaka can tolerate a temperature range from 4 to 40°C for both embryos and adults in the wild. In particular, Japanese medaka (*Oryzias latipes*) is highly tolerant to inbreeding, ideal for laboratory conditions with 14 h light and 10 h dark circles for mating conditions, with simple dietary and habitat requirements (Kirchmaier et al., 2015). They were established as a genetic model as early as 1975 (Yamamoto, 1975) and were one of the first model organisms for genetic manipulations (Ozato et al., 1986). Additionally, medaka is an ideal model organism owning to short development (7–9 days) and reproduction cycle (2–3 months), fully sequenced genome (three strains), and a transparent body throughout the juvenile stage (Ishikawa, 2000; Wittbrodt et al., 2002; Kirchmaier et al., 2015). Although zebrafish and medaka are distant relatives that got separated around 110-200 million years ago during evolution (Wittbrodt et al., 2002), they are similar in size, anatomy, and physiology, allowing them to be raised in the same laboratory conditions in terms of feeding, light-dark cycle, water temperature/quality, and propagation (Furutani-Seiki and Wittbrodt, 2004). In addition to orthologous gene-sets for genome-wide profiling and reciprocal analyses, many materials and methods can be applied equally to both zebrafish and medaka, making them ideal for comparative studies than more distantly related species (**Figure 2**).

Inter-Species Comparisons: Cardiac Regeneration

As one of the most vital organs, mammalian hearts have a minimal capacity for regeneration upon disease or injury in the post-natal period, especially for replenishing cardiac muscle cells (cardiomyocytes, CMs). Instead, the infarcted hearts undergo fibrotic repair, which in turn deteriorates tissue contractility and function, eventually leading to heart failure and organismal death (Kong et al., 2014). In contrast to the limited regenerative capacity of adult mammals, certain fishes and amphibians, and even neonatal mice can regenerate their hearts after injury (Vivien et al., 2016). This is an excellent example of how the regenerative capacity of hearts exists unevenly across species and developmental stages, as mammals possess the regenerative capacity only for a short time window after birth (Porrello et al., 2011; Haubner et al., 2012, 2016). These mammalian and non-mammalian models provide unique opportunities to study the intrinsic capacity and mechanisms of heart regeneration. Amongst, extensive knowledge was gained from the zebrafish studies. Since the ground-breaking discovery of zebrafish heart regeneration by Poss et al. (2002), researchers have made in-depth investigations to understand the mechanisms of heart regeneration in zebrafish (Marques et al., 2019; Jaźwińska and Blanchoud, 2020; Potts et al., 2021). Briefly, zebrafish hearts mount a robust immune response in the recruitment of macrophages and neutrophils immediately after injury (Lai et al., 2017) and fast revascularization that expands

FIGURE 2 | The comparative analyses of tissue regeneration in zebrafish and medaka. A summary of the regenerative (green) vs. non-regenerative (blue) organs and the comparisons (mostly inter-species) of tissue regeneration in zebrafish and medaka.

superficially and intraventricularly and serve as the scaffold for CM repopulation (Marín-Juez et al., 2016, 2019). Almost concurrently, epicardium activates and expands by proliferation to cover the injured area and serve as a signaling hub to stimulate CM de-differentiation and proliferation in the border zone of the injured area (Kikuchi et al., 2010, 2011a,b; Jopling et al., 2011; González-Rosa et al., 2012; Cao and Poss, 2018). Newly formed CMs gradually replace scar tissue coincident with ECM remodeling (Sanchez-Iranzo et al., 2018) and scar resolution (Bevan et al., 2020; Simoes et al., 2020), eventually restoring the morphology and function of the heart. Conserved processes have been shown in neonatal mouse heart regeneration, particularly the source of regenerated CMs (Porrello et al., 2011; Vivien et al., 2016). Furthermore, hints gained from zebrafish studies have been applied to mice models to accelerate cardiac repair (Chen et al., 2016; Honkoop et al., 2019). A comparative study in zebrafish and mouse injured hearts even revealed microRNA dynamics that may regulate CM proliferation and cardiac repair (Crippa et al., 2016). However, considering the taxonomy distance between zebrafish and mice, a comparative approach may be more feasible for more closely related species with similar physiology and structure.

Unlike zebrafish, medaka showed impaired heart regeneration, indicated by a lack of revascularization, low CM proliferation, and a permanent fibrotic scar in the injured area after resection (Ito et al., 2014). To understand the differences in cardiac repair in zebrafish and medaka, Lai and colleagues performed a global transcriptomic analysis and revealed a robust immune response and angiogenic revascularization exist preferentially in zebrafish (Lai et al., 2017). Coincidently, they observed a reduced macrophage infiltration and prolonged

neutrophil recruitment/retention in medaka hearts compared to zebrafish. The blunted immune response in medaka encouraged the investigation of the acute immune response and timely macrophage recruitment in heart regeneration. Indeed, in a loss-of-function setting, delayed macrophage recruitment by clodronate liposome pre-depletion abolished the regenerative capacity in zebrafish (Lai et al., 2017), which correspond nicely with findings in neonatal mice (Aurora et al., 2014). These results support an essential role of macrophage function in heart regeneration across species and encore the requirement of the macrophage function in the regeneration of other organs, including fin, retina, optic tectum, brain, and spinal cord reviewed elsewhere (Var and Byrd-Jacobs, 2020). They further identified the immunostimulant poly I:C as one of the upstream candidates that may trigger the differential transcriptomic response found between zebrafish and medaka. Indeed, they further showed that stimulating immune response by poly I:C administration promotes heart regeneration in medaka in a gain-of-function setting (Lai et al., 2017). These results support the strength of comparative analysis using fish models to gain knowledge conserved across species and identify pro-regenerative factors. However, it remains unclear how poly I:C (or other immunostimulants) promote heart regeneration in medaka and whether the same principle may apply to mammals, awaiting further investigation.

Inter-Species Comparisons: Retina Regeneration

The capacity to regenerate retinal neurons after injury also varies drastically among vertebrate species. While mammalian Müller

glia (MG) do not spontaneously regenerate lost retinal neurons, zebrafish MG cells possess a robust capacity to regenerate all retinal cell types and recover their visual ability (Vihtelic and Hyde, 2000; Sherpa et al., 2008; Goldman, 2014; Gorsuch and Hyde, 2014; Lenkowski and Raymond, 2014). Several pluripotent factors, including *ascl1a, lin-28,* and *sox2,* regulate the dedifferentiation, reprogramming, and proliferation of MG cells into various retinal cell types during retina regeneration in zebrafish (Ramachandran et al., 2010a; Gorsuch et al., 2017). Sox2 is also one of the four Yamanaka factors that induced pluripotent stem cell status (Takahashi et al., 2007). In addition to retina, retinal pigment epithelium (RPE) regeneration was also recently described in zebrafish (Leach et al., 2021). Similar to heart regeneration, the immune response, particularly the macrophages and microglia cells, responds to injury and plays a critical role in retina and RPE regeneration, potentially associated with phagocytotic debris clearance and cytokine secretion (Mitchell et al., 2019; Leach et al., 2021).

During retina development, medaka neural stem cells behave similarly to those in zebrafish (Martinez-Morales et al., 2009; Centanin et al., 2011, 2014). However, Lust and Wittbrodt discovered that medaka showed limited regenerative capacity in the retina. The MG cells proliferate but fail to self-renew and reprogram, eventually giving rise to only photoreceptor cells (Lust and Wittbrodt, 2018). Moreover, by comparing medaka with zebrafish, they identified that medaka MG cells fail to maintain *sox2* expression after injury and demonstrated that sustained *sox2* expression in medaka MGs confers regenerative response (Lust and Wittbrodt, 2018). Similar to the above-mentioned reciprocal analyses in heart regeneration, Lust and Wittbrodt were able to identify the critical factor and demonstrated the functional relevance of *sox2* expression in promoting retina regeneration.

More recently, Hoang et al. (2020) identified the evolutionarily conserved and species-specific gene regulatory networks that control the quiescent, reactive, and proliferative MG transition after retinal injury in another cross-species comparison between mice, chick, and zebrafish. They further demonstrated that deleting the factors maintaining the quiescent state may promote MG reprogramming into regeneration-competent cells in adult mice (Hoang et al., 2020).

Inter-Species Comparisons: Central Nervous System Regeneration

Unlike mammals, zebrafish respond to injury or degeneration by inducing specific neurogenic programs and constitutive neurogenesis for tissue regeneration (Diotel et al., 2020). Learning the regenerative mechanisms occurring in zebrafish will be invaluable for developing therapeutics for brain injury and degenerative diseases. In contrast to target-oriented studies, new knowledge may come from side-by-side and unbiased comparisons of animal models with divergent regenerative capacities. Unfortunately, mice brains and zebrafish brains show distinct features other than regenerative capacity, including the overall anatomy and neurogenic niches, thus preventing direct comparisons (Diotel et al., 2020; Labusch et al., 2020). Therefore,

it is relevant to explore the mechanisms of brain regeneration in more closely related models.

The regenerative capacity of zebrafish central nervous system (CNS) has been investigated in the optic tectum (Ito et al., 2010; Shimizu et al., 2018; Lindsey et al., 2019) and telencephalon (Kroehne et al., 2011; Marz et al., 2011; Kishimoto et al., 2012). In the adult zebrafish CNS, both MG and the radial glia (RG) cells are activated to proliferate and differentiate into new neuronal cells following injury (Raymond et al., 2006; Ito et al., 2010; Shimizu et al., 2018). These regenerative responses seem to be induced and facilitated by immune responses (Kyritsis et al., 2012; Caldwell et al., 2019), while a specific inflammatory signaling cascade is stimulated by microglia during zebrafish brain repair (Kanagaraj et al., 2020).

A comparative study of brain regeneration in medaka and zebrafish has also been reported very recently (Shimizu and Kawasaki, 2021). Medaka shares a similar brain structure with zebrafish and neural stem cells (NSCs) niche for brain development and growth (Adolf et al., 2006; Grandel et al., 2006; Alunni et al., 2010; Kuroyanagi et al., 2010). Main NSCs exist in the optic tectum of both zebrafish and medaka, including the proliferative neuroepithelial-like stem (NE) cells and the quiescent RG cells (Alunni et al., 2010; Ito et al., 2010; Takeuchi and Okubo, 2013; Dambroise et al., 2017). However, medaka could not regenerate their optic tectum after stab injury and thus leaving a permanent scar (Shimizu and Kawasaki, 2021). In medaka, RG cells were similarly activated for proliferation upon tectum injury, but they failed to differentiate into neuron cells. Unlike the scenario in the retina, *sox2* is substantially expressed in both zebrafish and medaka optic tectum and does not associate with the differential regenerative ability. Instead, the expression of pro-regenerative transcriptional factors *ascl1a* and *oct4* were missing in the medaka. As a result, glial scar-like structures composed of GFAP+ radial fibers filled the injured area of the medaka optical tectum. Follow-up studies might be required to test the functional relevance of the ectopic expression of *ascl1a* and *oct4* in promoting RG differentiation and optic tectum regeneration in medaka.

Inter-Species Comparisons: Fin Regeneration

Among various tissues and organs, appendage regeneration draws major attention early on in the field as teleost fish, urodeles, and amphibians all can regenerate their fins, arms, and legs following amputation (Daponte et al., 2021). Compared to limbs of urodeles and amphibians, fish fin structure is simpler and consists of bony fin rays covered by thin epidermal cells (Grandel and Schulte-Merker, 1998). Nevertheless, limb and fin are homologous tissue across vertebrate species (Yano and Tamura, 2013). A forward-genetic screen done in zebrafish identified a novel and conserved regulator of appendage patterning. When mutated, zebrafish formed limb-like bones in fins, suggesting the conservation in skeleton development and the potential of fin-to-limb transition (Hawkins et al., 2021). The regenerative capacity of the fish fin was examined as early as the 1700s to understand appendage regeneration with

the first reports by French naturalist Broussonet (Broussonet, 1786; Broussonet, 1789). Like the limb regeneration in urodeles and amphibians, zebrafish repair their caudal fin by blastema-mediated epimorphic regeneration (Poss et al., 2003). In this context, blastema originates from dedifferentiated mesenchymal cells and is the primary source for growing new tissues, including bone, nerve, and vessel (Poss et al., 2003; Straube and Tanaka, 2006; Pfefferli and Jazwinska, 2015). Conserved pathways, including the Wnt/β-catenin pathway, were shown to regulate appendage regeneration across different vertebrate species, including zebrafish, Xenopus, and axolotl (Kawakami et al., 2006; Yokoyama et al., 2007).

Like zebrafish, medaka also regenerates their fin after amputation via blastema-mediated epimorphic regeneration (Katogi et al., 2004; Nakatani et al., 2007). It will be interesting to learn if medaka fin regeneration shares a conserved regenerative program with zebrafish in a cross-species study. In addition, inflammation and macrophages play a central role in both heart and fin regeneration in zebrafish but seem deficient/blunt in medaka hearts upon injury (Petrie et al., 2014; Lai et al., 2017). One may wonder whether systemic inflammation and immune response contribute differently upon fin and heart injury in medaka, which will be further discussed and await future investigation.

Overall, all these studies highlight the strength of inter-species comparisons between zebrafish (regenerative) and medaka (non-regenerative) organs to identify (and in some cases also to validate) the potential triggers of tissue regeneration. It is worth mentioning that other comparisons of organisms/conditions exhibiting diverse regenerative capacity have also been reported. For example, Stockdale and colleagues identified genes fundamental to heart regeneration by comparing the injury response of regenerative Astyanax mexicanus surface fish with their non-regenerative counterparts Pachón cave-dwelling fish (Stockdale et al., 2018). Following such regenerative traits among other species, researchers have also explored the evolutionary concept of regeneration amongst other teleost species (**Table 1**). In addition, comparing the transcriptomes and open chromatin landscapes of the cardiac cells isolated from the regenerative neonatal vs. non-regenerative adult mice hearts, Wang Z. et al. (2020) revealed the gene regulatory networks in diverse cardiac cell types and extracellular mediators for cardiomyocyte proliferation, angiogenesis, and fibroblast activation. Furthermore, mammals like the African spiny mouse (Acomys) can regenerate their ear, skin, heart, and bones in contrast to the house mouse (Mus musculus), providing more opportunities for cross-species analyses (Seifert et al., 2012; Matias Santos et al., 2016; Simkin et al., 2017; Qi et al., 2021).

Comparing organisms with similar regenerative properties may also identify the conserved regenerative programs. For example, from an inter-species comparison of zebrafish and African killifish (Nothobranchius furzeri) following fin amputation, Wang and colleagues identified the evolutionary conserved regenerative response elements (RRE) (Wang W. et al., 2020). Activation of inhba, a gene downstream of the RRE, is essential for both fin and heart regeneration and requires

TABLE 1 | Fish models and organs for regeneration research.

Species	Organs
Zebrafish (*Danio rerio*)	Heart (Poss et al., 2002)
	Retina (Vihtelic and Hyde, 2000; Sherpa et al., 2008)
	Brain (Kroehne et al., 2011; Marz et al., 2011; Kishimoto et al., 2012)
	Fin (Poss et al., 2003)
	Kidney (Diep et al., 2011)
	Liver (Sadler et al., 2007)
	Pancreas (Moss et al., 2009)
	Notochord (Garcia et al., 2017; Lopez-Baez et al., 2018)
	Lateral line (Hair cells) (Lush and Piotrowski, 2014; Cruz et al., 2015)
	Gills (Mierzwa et al., 2020)
	Intestine (Schall et al., 2015)
	Spinal cord (Becker et al., 1997; Ghosh and Hui, 2018)
Giant Danio (*Devario aequipinnatus*)	Heart (Lafontant et al., 2012)
	Lateral Line (Mekdara et al., 2018)
Goldfish (*Carassius auratus*)	Heart (Grivas et al., 2014)
	Retina (Raymond et al., 1988)
	Fin (Jh, 1947; Darnet et al., 2019)
	Spinal cord (Bernstein, 1964)
Grass carp (*Ctenopharyngodon idella*)	Heart (Long et al., 2019)
	Gonads (Underwood et al., 1986)
Medaka (*Oryzias latipes*)	Heart (Ito et al., 2014; Lai et al., 2017)
	Retina (Lust and Wittbrodt, 2018)
	Brain (optic tectum) (Shimizu and Kawasaki, 2021)
	Caudal Fin (Katogi et al., 2004)
	Kidney (Watanabe et al., 2009)
	Liver (Van Wettere et al., 2013)
	Pancreas (Otsuka and Takeda, 2017)
	Notochord (Seleit et al., 2020)
	Lateral Line (Seleit et al., 2017b)
	Posterior lateral line (pLL) nerve (Seleit et al., 2022)
	Gill (Stolper et al., 2019)
African Killifish (*Nothobranchius furzeri*)	Fin (Wendler et al., 2015)
	Heart and fin (Wang W. et al., 2020)
	Brain (Van Houcke et al., 2021)
Platyfish (*Xiphophorus maculatus*)	Fin (Offen et al., 2008)
Atlantic Salmon (*Salmo salar L.*)	Heart (Ferguson et al., 2005)
	Skin (Sveen et al., 2019)
Mexican cave/surface fish (*Astyanax mexicanus*)	Heart and Fin (Stockdale et al., 2018)
Senegal bichir (*Polypterus senegalus*)	Heart (Kikuchi et al., 2011b)
	Pectoral Fin (Cuervo et al., 2012)

the binding motifs of activator protein 1 (AP-1) complex. Such enhancer is also present in mammals, shares Ap-1 binding motifs, and responds to injury, although it cannot promote regeneration. These results suggest that RREs might have been repurposed in regeneration-incompetent animals during evolution and only promote tissue repair but not regeneration (Yang and Kang, 2019; Wang W. et al., 2020). Of note, killifish possess the regenerative capacity in multiple organs, including the heart (Wang W. et al., 2020), fin (Wendler et al., 2015), and brain (Van Houcke et al., 2021) while being phylogenetically

TABLE 2 | Injury models developed in zebrafish and medaka.

Tissue type	Injury Type	Zebrafish references	Medaka references
Heart	Resection	Poss et al., 2002	Ito et al., 2014
	Cryoinjury	Chablais et al., 2011; Gonzalez-Rosa et al., 2011; Schnabel et al., 2011	Lai et al., 2017
	Genetic ablation	Cardiomyocytes (Wang J. et al., 2011)	Not available
Fin	Resection	Géraudie et al., 1994; Poleo et al., 2001	Katogi et al., 2004
	Cryoinjury	Chassot et al., 2016	Not available
Retina	Light, Laser	Vihtelic and Hyde, 2000; DiCicco et al., 2014	Lust and Wittbrodt, 2018
	Stabbing	Senut et al., 2004	
	Chemical	Fimbel et al., 2007; Powell et al., 2016	Not available
Brain	Stabbing	Kroehne et al., 2011; Marz et al., 2011	Shimizu and Kawasaki, 2021
	Traumatic Brain Injury	Maheras et al., 2018	Not available
	Genetic ablation	Hypocretin Neurons (Elbaz et al., 2012); Radial glial specific (Shimizu et al., 2015); dopaminergic neuron-specific (Godoy et al., 2015)	Not available
Spinal Cord	Transection	Becker et al., 1997	Not available
Bone	Genetic ablation	Osteoblasts (Singh et al., 2012)	Osteoblasts (Willems et al., 2012)
Notochord	Laser	Goldstein and Fishman, 1998	Seleit et al., 2020
	Stabbing	Lopez-Baez et al., 2018	Not available
	Genetic ablation	Vacuolated cells (Garcia et al., 2017)	Not available
Lateral Line	Chemical	Harris et al., 2003	Not available
	Laser Ablation	Schuck and Smith, 2009; Cruz et al., 2015	Seleit et al., 2017b, 2022
Kidney	Chemical	Reimschuessel and Williams, 1995	Watanabe et al., 2009
Liver	Chemical	Cox et al., 2014	Van Wettere et al., 2013
	Resection	Sadler et al., 2007	Not available
	Genetic ablation	Hepatocytes (Curado et al., 2007)	Not available
Gills	Resection	Mierzwa et al., 2020	Stolper et al., 2019
	Cryoinjury	Ramel et al., 2021	Not available
Pancreas	Genetic ablation	Beta cells (Pisharath et al., 2007)	Beta cells (Otsuka and Takeda, 2017)
Intestine	Resection	Schall et al., 2015	Not available

closer to medaka (Terzibasi et al., 2007), represent an alternative model for inter-species comparison.

Inter-Organ Comparisons in Medaka and Zebrafish (Regenerative Programs, Regulatory Elements, and Systemic Immune Responses)

In addition to the availability of progenitor/stem cell populations in each tissue/organ, we wonder how systemic responses, including immune response, neural innervation, hormonal regulation, metabolic shift, contribute differently to the respective injured tissues/organs of the same organism and lead to uneven regenerative capacity. The problem is especially apparent when one teleost zebrafish can regenerate organs such as the heart, retina, and brain, while another teleost medaka cannot. Taking the heart for example, the blunt immune response seems to be the major obstacle for medaka to initiate regenerative programs, but how does the same systemic (immune) response sustain the regeneration of other organs, for example, the fin? Are there tissue-specific contributions/responses, for example, residential immune cells, tissue-specific injury response elements, or even changes in the epigenomic landscape? These questions may be best addressed in medaka where the organ-specific regenerative capacities are uneven and well studied, including the regenerative

fin (Katogi et al., 2004), kidney (Watanabe et al., 2009), liver (Van Wettere et al., 2013), and pancreas (Otsuka and Takeda, 2017), and non-regenerative heart (Ito et al., 2014; Lai et al., 2017), retina (Lust and Wittbrodt, 2018), and brain (Shimizu and Kawasaki, 2021). The potential findings can be cross-species compared and further validated in zebrafish loss-of-function and medaka gain-of-function experiments. A similar concept could also apply to other species. Differential regenerative capacity can be observed in lower vertebrates where some lizards can replace their tail but not their limb (Alibardi and Toni, 2005). Even in mice, the uneven regenerative capacity exists ranging from active (intestine and skin), partial (liver, pancreas, muscle), to none (CNS, heart, and most other internal organs) (Iismaa et al., 2018; **Figure 1**).

Even between two regenerative organs, researchers have identified common and tissue-specific regeneration responsive elements/enhancers by inter-organ comparisons. For example, Kang et al. (2016) have performed such a comparative study identifying a tissue regeneration enhancer element (TREE) from zebrafish heart and fin, which locates upstream of *lepb* gene and activates following injury. This element could also be activated in neonatal mouse tissues upon injury and may be engineered to modulate the regenerative potential of vertebrate organs. Another study by Pfefferli and Jaźwińska (2017) identified a 3.18 kb regulatory element upstream of *ctgfa* gene, named as *careg* element that drives the regenerative response in both zebrafish

TABLE 3 | Visualization tools developed in zebrafish and medaka.

Tissue type	Cell-type	Zebrafish transgenic lines (References)	Medaka transgenic lines (References)
Blood vessels	Pan-endothelial cells	*Tg(tie2:EGFP)* (Motoike et al., 2000) *Tg(fli1a:EGFP)^y1* (Lawson and Weinstein, 2002)	*Tg(tie2:GFP)* (Nakatani et al., 2008) *Tg(fli1:GFP)* (Moriyama et al., 2010)
	Arterial- endothelial cells	*Tg(kdrl:mCherry)^is5* (Wang et al., 2010)	*Tg(kdrl:DsRed2)* (TG1252, NBRP)
Lymphatic vessels	Pan-lymphatic cells	*Tg(lyve1:DsRed2)^nz101* (Okuda et al., 2012) *TgBAC(flt4:Citrine)^hu7135* (Gordon et al., 2013) *Tg(mrc1a:egfp)^y251* (Jung et al., 2017)	*Tg(flt4-EGFP)* (Deguchi et al., 2012)
Heart cells	Pan- cardiomyocytes	*Tg(cmlc2:DsRed2-Nuc)* (Rottbauer et al., 2002) *Tg(myl7:EGFP)^twu26* (Huang et al., 2003)	*Cab-Tg(zfmlc2-5.1k:DsRed2-nuc)* (Taneda et al., 2010); Anti-MyHC (MF20) (Ito et al., 2014)
	Dedifferentiating-cardiomyocytes	*Tg(gata4:EGFP)^ae1* (Kikuchi et al., 2010) *TgBAC(nppa:mCitrine)* (Honkoop et al., 2019)	Not available
	Epicardium	*Tg(wt1b:GFP)* (Perner et al., 2007) *Tg(tcf21:nucEGFP)^pd41* (Wang J. et al., 2011)	Not available
	Endocardium	*Tg(flt1:YFP)^hu4624* (Hogan et al., 2009) Anti-Raldh2 (Kikuchi et al., 2011b)	*Tg(raldh2-GFP)* (Ito et al., 2014)
Muscles and whole body	Skeletal muscles	*Tg(mylz2:gfp)* (Ju et al., 2003)	*Tg(mylz2:gfp)* (Zeng et al., 2005)
	Ubiquitous	*Tg(actc1b:GFP)* (Higashijima et al., 1997) *Tg(bactin2:switch)* (Bertrand et al., 2010) *Tg(-3.5ubi:EGFP)* (Mosimann et al., 2011)	*Tg(pOBA-GFP)* (Hamada et al., 1998) *Tg(EF-1α-A-GFP)* (Kinoshita et al., 2000) *Tg(CMV-EGFP-ITR)* (Chou et al., 2001) *Tg(β-actin-EGFP-ITR)* (Chou et al., 2001) *Wimbledon* (Centanin et al., 2011) Gaudi Toolkit (Centanin et al., 2014)
Skin	Epithelial cells	*Tg(krt4:nlsEGFP)^cy34* (Chen et al., 2011)	*Tg(krt8:rfp)* (Zeng et al., 2005) *Tg(K15:H2B-EGFP)* (Seleit et al., 2017a,b) *Tg(K15:H2B-EGFP)* and *Tg(K15:LifeAct-tRFP)* (Seleit et al., 2022)
Fibroblasts	Activated fibroblasts	*Tg(postnb:citrine)^cn6* (Sanchez-Iranzo et al., 2018)	Not available
	Collagen producing fibroblasts	*Tg(col1a2:loxP-mCherry-NTR)^cn11* (Sanchez-Iranzo et al., 2018)	Not available
	Fibroblasts	*Tg1(-6.8wt1a:EGFP)^li7Tg* (Bollig et al., 2009)	Not available
Immune cells	Macrophages	*Tg(mpeg1:EGFP)^gl22* (Ellett et al., 2011) *Tg(mpeg1.4:mCherry-F)^ump2* (Bernut et al., 2014) *Tg(mfap4:tdTomato-CAAX)^xt6* (Walton et al., 2015)	*Tg(mpeg1:mCherry)* (Phan et al., 2020) Isolectin B4 (Lai et al., 2017)
	Mononuclear phagocyte system	*Tg(ptprc:DsRed)^sd3* (Bertrand et al., 2008) *Tg(mhc2dab:GFP)^sd6* (Wittamer et al., 2011)	*Tg(Cxcr3a:GFP)* (Aghaallaei et al., 2010)
	Pro-inflammatory cells	*Tg(tnfa:EGFP-F)^ump5Tg* (Nguyen-Chi et al., 2015) *Tg(irg1:EGFP)* (Sanderson et al., 2015)	Not available
	Neutrophils	*TgBAC(mpx:GFP)^i114* (Renshaw et al., 2006)	*Tg(FmpoP::EB3-EGFP/FmpoP::RFP-Lifeact)* (Crespo et al., 2014) *Tg(FmpoP::mCherry)* (TG1044, NBRP)
	T-cells	*Tg(lck:lck-EGFP)^cz2* (Langenau et al., 2004) *Tg(ikzf1:GFP)^fr24* (Bajoghli et al., 2009)	*Tg(lck:gfp)* (Bajoghli et al., 2015)
	T-regulatory cells	*TgBAC(foxp3a:EGFP)* (Hui et al., 2017)	Not available
	Progenitors and thymocytes	*Tg(rag1:GFP)* (Jessen et al., 1999) *Tg(rag2:GFP)* (Jessen et al., 2001)	*Tg(rag1-egfp)* (Li et al., 2007) *Tg(ccr9a:gfp)* and *Tg(rag2:gfp-pest)* (Bajoghli et al., 2015)
	B-cells	*Tg(Cau.Ighv-ighm:EGFP)^sd19* (Page et al., 2013) *Tg(cd79a:GFP)* and *Tg(cd79b:GFP)* (Liu et al., 2017)	Not available
Blood	Erythrocyte	*Tg(gata1:DsRed)^sd2* (Traver et al., 2003) *Tg(runx1P1:EGFP)* and *Tg(runx1P2:EGFP)* (Yi Ni Lam et al., 2009)	*Tg(fli::GFP;gata1::GFP)* (Schaafhausen et al., 2013)
	Thrombocytes	*Tg(CD41:GFP)* (Lin et al., 2005)	Not available
Eyes	Rod cells	*Tg(XlRho:EGFP)^fl1* (Fadool, 2003)	Not available
	Müller glia cells	*Tg(gfap:EGFP)^nt11* (Thummel et al., 2008)	*Tg(rx2:H2B-RFP)* (Inoue and Wittbrodt, 2011) *Tg(rx2:lifeact-EGFP)* and *Tg(rx2:H2B-EGFP)* (Lust and Wittbrodt, 2018)
	Photoreceptor	*Tg(-5.5opn1sw1:EGFP)^kj9* (Takechi et al., 2003)	
	Retinal pigment epithelium (RPE)	*Tg(rpe65a:EGFP)* (Collery et al., 2016)	

(Continued)

TABLE 3 | (Continued)

Tissue type	Cell-type	Zebrafish transgenic lines (References)	Medaka transgenic lines (References)
CNS	Pan-neurons	*Tg(huC:GFP)* (Park et al., 2000)	*Tg(kif5a:gfp)* (Kawasaki et al., 2012)
	Radial glial cells	*Tg(gfap:GFP)$^{mi200-1}$* (Raymond et al., 2006) *Tg(cyp19a1b:cyp19a1b-GFP)* (Tong et al., 2009)	Anti-Gfap immunostaining, *Tg(cyp19a1b-GFP)* (Takeuchi and Okubo, 2013)
	Neural stem cells	*Tg(-1.7Cau.Tuba1:GFP)* (Goldman et al., 2001)	*Tg(rx2::H2B-RFP)* (Inoue and Wittbrodt, 2011; Reinhardt et al., 2015) *Tg(wdr12:GFP)* (Dambroise et al., 2017) *Tg(cndp::eGFP-caax)* (Becker et al., 2021)
	Oligodendrocyte	*Tg(olig2:DsRed2)* and *Tg(sox10:mRFP)* (Kucenas et al., 2008)	Not available
Notochord	Sheath cells	*Tg(col9a2:GFPCaaX)^{pd1151}* (Garcia et al., 2017)	*Tg(desmogon:EGFP)* (Seleit et al., 2020)
	Vacuolated cells	*Tg(col8a1a:GFPCaaX)* (Garcia et al., 2017)	
	Intervertebral disk	*Tg(twhh:gfp)* (Du and Dienhart, 2001)	Not available
Lateral Line	Neuromast	*Tg(brn3c:GAP43-GFP)^{s356t}* (Xiao et al., 2005)	*Tg(eya1:EGFP), Tg(eya1:mECFP), Tg(K15:H2B-EGFP),* and *Tg(K15:H2B-RFP)* (Seleit et al., 2017a,b) *Tg(K15:LifeAct-tRFP)* (Seleit et al., 2022)
Fin and Bone	Osteoblasts and precursors	*Tg(sp7:EGFP)^{b1212}* (DeLaurier et al., 2010)	*Tg(osx-mCherry)* (Renn and Winkler, 2009) *Tg(col10a1:nlGFP)* (Renn et al., 2013)
	Osteoclasts	*TgBAC(ctsk:Citrine)* (Bussmann and Schulte-Merker, 2011)	*Tg(ctsk:mEGFP)* (To et al., 2012) *Tg(TRAP:GFP)* (Chatani et al., 2011)
Pancreas	Pancreatic endocrine cells	*Tg(-6.5pdx1:GFP)* (Huang et al., 2001) *Tg(-8.5nkx2.2a:GFP)* (Zecchin et al., 2007) *Tg(-4.0ins:GFP)* (Huang et al., 2001)	*Tg(pdx1-EGFP)* (Otsuka et al., 2015) *Tg(insulin-EGFP-NTR)* (Otsuka et al., 2015)
	Pancreatic exocrine cells	*Tg(elaA:gfp)* (Wan et al., 2006)	*Tg(ptf1a-mCherry)* (Otsuka et al., 2015)
Liver	Hepatocytes	*Tg(-2.8fabp10a:EGFP)* (Her et al., 2003) *Tg(-1.7apoa2:GFP)* (Wang R. et al., 2011)	*Tg(chg-L1.5 kb/GFP-emgb/RFP)* (Ueno et al., 2004)

fin and heart via TGFβ/Activin-β signaling pathway. This type of study paved the way for identifying evolutionarily conserved RREs, which can also be analyzed in medaka to decipher how these RREs exist and regulate the regenerative programs in a tissue-specific manner.

MATERIALS AND METHODS AVAILABLE FOR COMPARATIVE STUDY IN ZEBRAFISH AND MEDAKA

Here, we highlight the materials and methods selected from published studies to accelerate comparative studies in tissue regeneration using zebrafish and medaka, including the injury methods, visualization of gene expression and specific cell types, and functional assays by drug delivery and genetic modifications. Online resources and new experimental models will also be summarized in this section.

Injury Models

Various injury models have been established in fish models to introduce tissue injury and investigate the reparative process. In addition to the feasibility and reproducibility, these methods were often established based on the similarity to the human diseases or trauma conditions to gain translational value (**Table 2**). The resection or amputation model is one of the most commonly used injury models, involving surgical removal of a part of the tissue for observing the restoration of size, morphology/structure, and function of the injured tissue. Resection is straightforward,

cheap, and reproducible and has been widely adopted to fin (Poss et al., 2003; Nakatani et al., 2007) and heart (Poss et al., 2002; Ito et al., 2014) regeneration studies in both zebrafish and medaka. However, resection is often accompanied by excessive bleeding and open wounds, which leads to infection and high mortality. Also, resection is sometimes infeasible for internal organs or tissues those unexposed or too small. Similar models include stabbing and transection, which works by surgically disrupting the integrity without removing any tissue and are well established in the retina, brain, and spinal cord regeneration in both zebrafish (Becker et al., 1997; Marz et al., 2011; Shimizu et al., 2018) and medaka (Shimizu and Kawasaki, 2021).

Slightly different from resection, researchers adapted the cauterization method in fish models to mimic the fibrotic repair in mammalian organs, which is highly associated with the inflammatory response (Strungs et al., 2013; Polizzotti et al., 2016). The cauterization technique involves burning or freezing the target tissue with electric or metal probes and introducing necrotic and apoptotic cell death. Cryoinjury is popular in heart regeneration studies in both zebrafish (Gonzalez-Rosa et al., 2011; Schnabel et al., 2011; Dyck et al., 2020) and medaka (Lai et al., 2017) as it mimics the myocardial infarction in mammals better than resection model (Chablais et al., 2011; Darehzereshki et al., 2015). This technique can also be applied to external organs, such as the fin (Chassot et al., 2016) and gills (Ramel et al., 2021). However, cauterization is technically challenging and less reproducible compared to resection. Also, the wound usually takes a longer time to recover as the cell debris needs to be cleared before regeneration occurs (Schnabel et al., 2011). To increase the

accuracy and reproducibility, cauterization can also be performed by using high-powered lasers in fish tissues, including the retina (Conedera et al., 2017; Lust and Wittbrodt, 2018) and skin (Richardson et al., 2013). The target tissue has to be exposed or transparent for laser penetration in this case. Overall, most physical injuries are invasive to cause high mortality and take practice to be consistent.

Apart from physical injury models, genetic cell ablation models in fish were established by expressing enzymes that catabolize cytotoxic products added to the system or induce cell death directly (**Table 2**). The former method was developed by expressing the bacterial enzyme Nitroreductase (NTR), which alone is not toxic but can catabolize the prodrug metronidazole (Mtz) to induce cytotoxicity (Lindmark and Müller, 1976). This system can achieve spatial (tissue-specific expression of NTR) and temporal control (the timing of adding Mtz), and labeling the target cells (co-expression with reporter system) at the same time. NTR/Mtz system has been used to tease out the functions of specific cell types in a complex process of organ regeneration in zebrafish, including the heart (Curado et al., 2007; Wang et al., 2013; Zhang et al., 2013), fin (Petrie et al., 2014), pancreatic β-cells (Pisharath et al., 2007), bone (Willems et al., 2012) and RPE regeneration (Hanovice et al., 2019). This system is also applicable to medaka, demonstrated by accessing regeneration capacity using NTR/Mtz mediated genetic ablation of the pancreatic β-cell population (Otsuka and Takeda, 2017), osteoblasts (Willems et al., 2012), and bone progenitor cells (Dasyani et al., 2019) in fin regeneration.

The latter genetic ablation tool to study zebrafish development and regeneration involves diphtheria toxin A (DTA) expression under a tissue-specific promoter, exampled by *crystallin* promoter-driven DTA expression in lens (Kurita et al., 2003), *elastase A* promoter-driven DTA expression in exocrine pancreas (Wan et al., 2006), and *myl7* promoter-driven DTA expression in cardiomyocytes (Wang J. et al., 2011). Though the DTA approach lacks temporal control for activation, it is highly toxic for killing the target cells efficiently. In a modified method, the temporal control can be achieved by expressing the human diphtheria toxin receptor (DTR) and further activate cytotoxicity by diphtheria toxin injection (Jimenez et al., 2021). The genetic ablation models are technically simpler with faster recovery. These models can be used combined with physical injury to tease the role of a specific cell type during complex organ regeneration. For example, Sanchez-Iranzo et al. (2018) depleted fibroblast cells after cardiac cryoinjury and demonstrated how fibroblasts contribute to heart regeneration. Overall, most of these injury models developed in zebrafish may also apply to medaka in comparative studies of tissue regeneration.

Visualization Tools

One of the best attributes of using zebrafish and medaka as research models is the tools and techniques available for visualizing specific cell types and biological processes *in vivo*. Here, we summarize the visualization tools that have been established in fish models, especially in zebrafish and correspondingly in medaka, with a focus on the transgenic reporter lines (**Table 3**) and alternative approaches.

Since fluorescence reporter driven by tissue-specific gene promoter is applicable and efficient in zebrafish and medaka, many transgenic lines have been generated to study specific tissues/organs in development and diseases. Here we summarize tissue-specific reporters described in major tissue regeneration studies previously mentioned in **Table 3**. In addition to tissue-specific reporter lines, researchers can also use antibodies against cell-specific transcription factors or cytosolic proteins to assess cellular dynamics in growth, development, and regeneration. For example, Mef-2 (sc-313), nkx2.5 (GTX128357) or MF20 (Fischman, D.A., DSHB) antibody can be used in combination with proliferation/cell cycle markers PCNA (GTX124496), Anti-phospho-Histone H3 (Ser10) (06-670, Merck), and BrdU/EdU (C10086, ThermoFisher, Eugene, OR, United States) to label the proliferating CMs (Chablais et al., 2011; Chablais and Jaźwińska, 2012a). Similarly, transgenic medaka lines have also been generated to facilitate cardiac research using zebrafish *cmlc2* regulatory elements for myocardial expression (Taneda et al., 2010). In addition to labeling cardiac tissues, researchers have successfully developed medaka reporters utilizing zebrafish skeletal specific *mylz2* promoter to label skeletal muscles (Zeng et al., 2005). Vice versa, medaka *mylz2* promoter can also recapitulate GFP expression in zebrafish (Zeng et al., 2005). On the same note, medaka β-*actin* promoter can drive ubiquitous gene expression in both medaka and zebrafish (Yoshinari et al., 2012), while zebrafish *krt8* promoter can label both skin and intestinal epithelium in medaka, as almost identical to zebrafish (Zeng et al., 2005). These examples showed that the transcriptional regulation of many genes is highly conserved in both species, with many tissue-specific transgenes developed to facilitate research, as summarized in **Table 3**.

Restoring vasculature and circulation is one of the first steps during tissue regeneration (Jung and Kleinheinz, 2013). Both these blood vessels and lymphatic vessels that regulate tissue homeostasis and immune cell trafficking can be visualized by reporters and have been used extensively for regenerative studies in zebrafish (**Table 3**). To name a few of the most commonly used reporter lines, *tie2* reporter for pan-endothelial cells (Motoike et al., 2000), *fli1a* reporter for endothelial and endocardial cells (Lawson and Weinstein, 2002), *kdrl* reporter for arterial vessels (Wang et al., 2010), and *lyve1* (Okuda et al., 2012) reporter for lymphatic vessels in zebrafish. Correspondingly, a wide range of transgenic reporter strains has been generated in medaka based on orthologous gene promoters (**Table 3**). Moreover, one can also use staining methods to label the vasculature when transgenic animals are inaccessible. One of the widely adopted vasculature staining methods involves alkaline phosphatase (AP) staining, which relies on the endogenous AP activity to convert NBT/BCIP into purple precipitates in endothelial cells for rapid visualization in larvae (Childs et al., 2002) and heart (Lai et al., 2017). In addition, the Fli1 antibody (ab133485) can be used to mark endothelial cell nuclei in zebrafish by immunostaining (Bensimon-Brito et al., 2020). Aside from post-fixation staining, angiography can be achieved by fluorescent dextran injection into the circulation of larval (Hoeppner et al., 2015; Takanezawa et al., 2021) and adult fish (Pugach et al., 2009).

Immune response, especially inflammatory cell infiltration and resolution, is a critical component of tissue regeneration to prevent infection, clear damaged tissue, maintain tissue integrity, and sometimes even is associated with the fibrotic response and cell proliferation (Julier et al., 2017). On top of the tremendous capacity in regeneration, zebrafish possess both innate and adaptive immunity comparable to mammals (Trede et al., 2004), making it a powerful model to study the role of immune response in tissue repair and regeneration (Var and Byrd-Jacobs, 2020). Inflammatory cells, including neutrophils and macrophages, are among the first responders recruited to the injured tissue by chemokines and damage-associated molecular patterns (DAMPs) (McDonald et al., 2010; Soehnlein and Lindbom, 2010). Some of the zebrafish reporter lines have been used to visualize these innate immune cells, including fluorescent genes expression driven by neutrophil-specific *mpx* promoter (Renshaw et al., 2006) and macrophages specific *mpeg1.1/mpeg1.4* (Ellett et al., 2011) and *mfap4* (Walton et al., 2015) promoters. Taking advantage of the transparent tissue at the larval stage, zebrafish have been extensively used for studying the dynamic and function of these inflammatory cells in tissue repair/regeneration (Li et al., 2012). Apart from the innate immune system, some adaptive immune cell reporters were also established in zebrafish (**Table 3**). Materials for zebrafish immune research have also been previously reviewed (Martins et al., 2019). The immune system in medaka is less studied compared to zebrafish. Still, some immune cell reporters have been generated in medaka based on zebrafish orthologous genes (**Table 3**), including neutrophil-specific *mpo* reporter (alias to *mpx*) (Grabher et al., 2007; Crespo et al., 2014), macrophages specific *mpeg1.1* reporter (Phan et al., 2020), and pan mononuclear phagocytes *cxcr3.2* reporter (Aghaallaei et al., 2010). For the adaptive immune cells, medaka gained interest for studying T-cell development where Tg lines were developed respectively (Bajoghli et al., 2019). Given the importance of immune response in tissue repair/regeneration and the amount of knowledge gained in zebrafish, it is pretty evident that corresponding transgenic reporter lines in medaka await future development for comparative studies. Specifically, it would be interesting to learn more about the critical roles of immune cells that plays similarly or differently in these two model systems.

Due to the limited resource of antibodies against fish proteins and reporters for labeling immune cells, other approaches can be applied to label and even isolate immune cells. For example, isolectin B4 (IB4) and liposome-uptake may label macrophage and other phagocytes in both zebrafish and medaka. In a comparative study, IB4 labels mainly macrophages in zebrafish and medaka and show colocalized signals with zebrafish mpeg1 reporter signals (Lai et al., 2017). On the other hand, DiI liposomes can label the phagocytes efficiently in both zebrafish and medaka based on their properties of macrophage ablation when loaded with clodronate (Lai et al., 2017). Despite in limited numbers, some antibodies work in both fish models in labeling the immune cells, including Lcp1 (GTX124420) (Redd et al., 2006), Lyz (GTX132379) for leukocytes, Spi/Pu.1 for myeloid cells (GTX128266), Mpx (GTX128379) for neutrophils (Lai et al., 2017), Mpeg1 (GTX54246) for macrophages (Simoes et al., 2020), and anti-4C4 for microglia (Becker and Becker, 2001).

Here, we have tabulated the most widely used fish reporter and transgenic lines in **Table 3**. More transgenic lines that label different tissues can be easily looked up in the Zebrafish Information Network (ZFIN[1]) and accessed from the Zebrafish International Resource Center (ZIRC[2]) and the European Zebrafish Resource Center (EZRC[3]), or the NBRP Medaka website[4]. Overall, common regulatory elements between zebrafish and medaka support that the activation of zebrafish-specific factors can be well recapitulated in the medaka and vice-versa. This evidence further highlights the conserved gene-regulatory networks between zebrafish and medaka, making them excellent models to perform comparative studies in tissue regeneration.

Genetic Manipulations in Zebrafish and Medaka

Taking advantage of being model organisms and a broad research community, zebrafish and medaka are well-equipped with tools for genetic manipulations for generating animal models for specific cell ablations, visualization, and functional manipulations introduced previously. Here, we summarize these toolsets established in zebrafish and medaka (**Table 4**) to investigate the cellular and molecular mechanisms of tissue regeneration.

Genetic manipulation in forward genetic screening has been established in fish models early on (Driever et al., 1996; Wienholds et al., 2003). As a standard method, ENU (ethylnitrosourea) treatment introduced point mutations via base alkylation that give rise to single base mutations (often called ENU mutants) in zebrafish (Driever et al., 1996) and medaka (Loosli et al., 2000; Furutani-Seiki et al., 2004). Lacking efficient methods for targeted gene mutagenesis used to be a weak spot of zebrafish reverse genetics, but was recently overcome by the invention of zinc-finger nucleases (ZFN) (Doyon et al., 2008), transcription activator-like effector nucleases (TALENs) (Huang et al., 2011; Bedell et al., 2012), and the Clustered, Regularly Interspaced, Short Palindromic Repeat (CRISPR)/CRISPR-associated 9 (Cas9) technology (Hruscha et al., 2013; Hwang et al., 2013). CRISPR became the favorable genetic manipulation strategy given its ease to generate and assemble, and application in almost all eukaryotic cells. In addition to gene knockout/mutagenesis, CRISPR technology was further modified for generating knock-in/transgenic zebrafish carrying reporter/functional genes under endogenous gene regulation (Kimura et al., 2014). Like zebrafish, genome editing using TALEN (Ansai et al., 2013, 2014) and CRISPR/Cas9 (Ansai and Kinoshita, 2014) have been established in medaka. CRISPR/Cas9 mediated gene knock-in via NHEJ was used to generate transgenic and mutant medaka with a high germline transmission rate (Watakabe et al., 2018). In addition, the knock-in method using CRISPR was also applied to generate conditional knockout zebrafish by targeted insertion of loxP sites

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[1]https://zfin.org/

[2]https://zebrafish.org/home/guide.php

[3]https://www.ezrc.kit.edu/

[4]https://shigen.nig.ac.jp/medaka/

TABLE 4 | Genetic manipulation tools in zebrafish and medaka.

Tools	Zebrafish (References)	Medaka (References)
ENU (ethylnitrosourea) mutagenesis	Driever et al., 1996	Loosli et al., 2000; Furutani-Seiki et al., 2004
ENU tiling	Moens et al., 2008	Taniguchi et al., 2006
ENU screens	Kettleborough et al., 2013	Furutani-Seiki et al., 2004
ZFN (zinc-finger nucleases)	Meng et al., 2008	Ansai et al., 2012
TALENs (transcription activator-like effector nucleases)	Huang et al., 2011; Sander et al., 2011	Ansai et al., 2013, 2014
CRISPR/Cas9: NHEJ	Hruscha et al., 2013; Hwang et al., 2013	Ansai and Kinoshita, 2014
CRISPR/Cas9: HDR	Kimura et al., 2014	Murakami et al., 2017
Tol2 transposon system	Kawakami and Shima, 1999	Koga et al., 2002; Kawakami, 2007
TgBAC cloning	Suster et al., 2011	Nakamura et al., 2008
I-SceI meganuclease	Grabher et al., 2004	Thermes et al., 2002; Grabher and Wittbrodt, 2007
Frog Prince	Miskey et al., 2003	Sano et al., 2009
Ac/Ds system	Ng and Gong, 2011; Froschauer et al., 2012	Emelyanov et al., 2006
Sleeping Beauty	Davidson et al., 2003	Grabher et al., 2003
PhiC31	Mosimann et al., 2013	Kirchmaier et al., 2013
Morpholinos	Nasevicius and Ekker, 2000	Carl et al., 2002
Toolkits for transactivation	GENEWELD toolbox (Wierson et al., 2020)	Gaudi toolbox (Centanin et al., 2014)
Cre/loxP system	Thummel et al., 2005; Le et al., 2007	Okuyama et al., 2013
Gal4/UAS	Asakawa and Kawakami, 2008	Grabher and Wittbrodt, 2004
Tet system	Knopf et al., 2010	Hosoya et al., 2021
Mtz/NTR ablation	Curado et al., 2007	Willems et al., 2012
DTA ablation	Kurita et al., 2003	Not available
siRNA mediated transient knockdown	Xiao et al., 2018	Not available
Viral mediated transduction	Gulías et al., 2019	Suehiro et al., 2010

(Burg et al., 2018). Instead of NHEJ mediated knock-in which is error-prone, Wierson et al. (2020) have further developed knock-in method based on homology mediated end joining (HMEJ) repair for a more efficient and precise genome editing in zebrafish known as the GENEWELD method. Likewise, homology-directed repair (HDR) mediated knock-in strategies were also feasible in medaka (Murakami et al., 2017).

This concurrent development of technologies in zebrafish and medaka highlights the reciprocal nature of exchanging tools and methods between these model systems, facilitating the advancement of scientific research. Besides mutagenesis, genetic manipulation via stable transgenesis was first demonstrated in medaka (Ozato et al., 1986). Later, Kawakami and Shima (1999) identified the *Tol2* transposon system in Medaka and adapted

this system in zebrafish for transgenesis which revolutionized the field. To better recapitulate the endogenous gene expression patterns, insertion of BAC constructs by *Tol2* transposase has been widely used in generating zebrafish reporter lines (Suster et al., 2011). Despite the fact that *Tol2* was originally identified in medaka, it is more efficient in zebrafish (Kawakami, 2007). Therefore, another method for insertional transgenesis was developed in fish models using I-SceI meganuclease and greatly facilitated transgenesis in medaka (Thermes et al., 2002; Grabher and Wittbrodt, 2008).

As applications, spatial (e.g., specific tissue) and temporal regulation of ectopic gene expression can be achieved by combining transgenic lines generated by the above-mentioned methods (**Tables 4**, **5**). For example, the Cre/lox system is widely used to perform reverse genetics, ectopic gene expression, and lineage tracing experiments in multicellular organisms, including zebrafish (Felker and Mosimann, 2016). To achieve spatial-temporal control, the Cre recombinase gene is fused with a human estrogen receptor (ER) domain and expressed under tissue-specific promoter, resulting in recombination of lox sequences in specific tissue upon estrogen stimulation (Metzger et al., 1995; Feil et al., 1996). Since then, there have been growing numbers of tissue-specific Cre lines generated in zebrafish (Jungke et al., 2013, 2015). Within the scope of tissue repair and regeneration, we have summarized a list of Cre driver and switch lines applied in previously described studies (**Table 5**). Additionally, robust co-expression of multiple genes following switch cassette can be accomplished by placing polycistronic ORFs separated by short viral 2A peptides (Provost et al., 2007). In contrast to zebrafish, there is way fewer medaka Cre/lox transgenic lines that we found and summarized with respect to the comprehensive list in zebrafish with available databases like CreZoo (Jungke et al., 2013, 2015). Fortunately, the advances of CRISPR technology allow genetic manipulation in both fish models and generate powerful tools for fate mapping and functional experiments (Liu et al., 2019). Overall, our review encompasses a portion of tools and strategies commonly used in zebrafish and medaka, which were extensively reviewed elsewhere for medaka (Kirchmaier et al., 2015) and zebrafish (Sassen and Köster, 2015), respectively.

Delivery of Pharmaceutical Reagents

Since zebrafish and medaka are routinely used for drug screening and validations, developing various routes of pharmaceutic administration is essential (**Table 6**). As these fish are tiny compared to mice, the development of administration methods requires further optimization to mimic the delivery route in mice.

Intraperitoneal (IP) injection was one of the first delivery methods introduced to deliver reagents in adult zebrafish and is adapted from veterinary practice in bigger fishes (Kinkel et al., 2010). The injection is performed using a 31G needle with a small injection volume (usually $< 10-15$ µl) into the abdominal cavity posterior to the pelvic girdle and midline to the pelvic fins in zebrafish (Kinkel et al., 2010). The reagents administered by IP injection will distribute majorly to the spleen and liver within 72 h and later into the circulation, making it a favorable method for studying biochemical modulation in

TABLE 5 | The Cre drivers and switch lines for studying tissue regeneration.

Tissue type	Zebrafish transgenic lines (References)	Medaka transgenic lines (References)
Cardiomyocytes	*Tg(myl7:creERT2)* (Kikuchi et al., 2010) *Tg(gata4:creERT2)* (Kikuchi et al., 2011a)	Not available
Skeletal muscles	*Tg(cry:mCherry;-1.9mylz2:CreERT2)* (Mukherjee and Liao, 2018)	*Tg(myl2::nlsCreCherry)* (TG938, NBRP)
Endothelial cells	*Tg(fli1a:CreERT2)[cn9]* (Sanchez-Iranzo et al., 2018)	Not available
Epicardial cells	*Tg(tcf21:CreERT2)[pd42Tg]* (Kikuchi et al., 2011a)	Not available
Neuronal cells	*Tg(Cau.tuba1a:CreERT2, Cau.tuba1a:CFP)[mi19/+]* (Ramachandran et al., 2010b)	*Tg(rx2::CreERT2)* (Reinhardt et al., 2015) *Tg(K15:Ert2-Cre)* (Seleit et al., 2017b) *Tg(cndp::CreERT2)* (Becker et al., 2021)
Macrophages	*Tg(mpeg:Cre)[fh506]* (Roh-Johnson et al., 2017) *Tg(mfap4:iCre:p2A-tdTomato)[xt8]* (Walton et al., 2015)	Not available
Fibroblast and collagen producing cells	*Tg(periostin:CreERT2)[cn7] and Tg(wt1a:CreERT2)[cn10]* (Sanchez-Iranzo et al., 2018)	Not available
Bone	*Tg(Ola.Sp7:CreERT2-P2A-mCherry)[tud8]* (Knopf et al., 2011)	Not available
Heat-shock (temporal)	*Tg(hsp70l:mCherry, Cre-ERT2)[tud104]* (Hans et al., 2011)	Gaudi[HspCRE.A] (Centanin et al., 2014)
Pan-cells switch type	*(ubi:Switch) and Tg(-3.5ubb:CreErT2, myl7:EGFP)[cz1702]* (Mosimann et al., 2011) *Tg(bactin2:loxp-DsRed-STOP-loxp-EGFP)* (Kikuchi et al., 2010)	*GaudiRSG toolkit* (Centanin et al., 2014) *Tg(Olactb:loxP-dsR2-loxP-EGFP)* (Yoshinari et al., 2012)
Switch ablation line	*Tg(bactin2:loxP-mCherry-STOP-loxP-DTA176)[pd36]* (Wang J. et al., 2011)	Not available

zebrafish over multiple injections or an extended period (Ruyra et al., 2014). IP is widely used for systemic administration of drugs, small-molecule inhibitors, nanoparticles, reagents in regeneration studies, including clodronate liposomes for ablating macrophages (de Preux Charles et al., 2016), poly I:C for immune-stimulation in medaka (Lai et al., 2017), mTOR-inhibitor rapamycin for autophagy inhibition (Chavez et al., 2020), IWR-1-endo for Wnt inhibition (Chen et al., 2009; Zhao et al., 2019), and tamoxifen for Cre-mediated recombination (Hans et al., 2009).

On the other hand, intravenous (IV) injection is effective for drug delivery in mice but has been technically challenging for zebrafish, due to the small vessel diameter and poor vasculature visibility. To improve vessel visibility, transparent

casper fishes can be injected intravenously through their cardinal vein described in cancer research in zebrafish (Benjamin and Hynes, 2017). As alternative methods for direct access to the circulation, the intra-cardiac injection has been tested but showed high mortality (White et al., 2008), while the retro-orbital (RO) injection is suitable for delivering both reagents and cells into the blood circulation (Pugach et al., 2009; Simoes et al., 2020).

For more tissue/organ-localized delivery methods, intra-tissue injections may be applied. For example, intrathoracic (IT) injections were developed in zebrafish to test the effects of exogenous factors on adult heart regeneration, including nanoparticles encapsulated siRNAs (Xiao et al., 2018; Bise and Jazwinska, 2019). Cerebroventricular microinjection (CVMI) was also developed to deliver reagents to the adult zebrafish brain (Kizil and Brand, 2011). Intravitreal injections for the targeted delivery to the vitreous space of the retina (Fimbel et al., 2007) and intraspinal injection to the spinal cord were also developed in zebrafish (Wehner et al., 2018).

In contrast to invasive methods, which sometimes lead to tissue damage and mortality, a straightforward and convenient way for pharmaceutic delivery is immersion/incubation. Although immersion/incubation can be applied to both larvae and adults, it is more costly for incubating adults due to a large amount of reagent needed to reach the same dose. The biodistribution from immersion varies among reagents and different stages. In adults, the reagent is mainly intake through gills and ingestion, then absorbed/digested in the intestine and liver, which resembles oral uptake in the mice model (Ruyra et al., 2014). Examples of incubation experiments include tamoxifen treatment for Cre activation and Erbb2 inhibitor AG1478 in heart regeneration of both zebrafish larvae and adults (de Koning et al., 2015; Gemberling et al., 2015). Incubation of Alk5/4 inhibitor SB431542 has also been used in adult fin (Jaźwińska et al., 2007) and heart (Chablais and Jaźwińska, 2012b) to understand the dynamics of fibrosis in tissue regeneration.

Overall, based on the size and anatomic similarities between zebrafish and medaka, most of these delivery methods (**Table 6**) can be adapted in medaka and are regularly used in our laboratory as well as in other studies (Maekawa et al., 2016; Lai et al., 2017; Marín-Juez et al., 2019).

Genomics Resources for Zebrafish and Medaka

Due to the interest in exploring cellular and molecular mechanisms throughout the last few decades, both zebrafish (~1,412 Mb) (Howe et al., 2013) and medaka genome (~800 Mb) (Kasahara et al., 2007; Kobayashi and Takeda, 2008) have been sequenced and are publicly available in the databases, including Ensembl for zebrafish[5] (see footnote 1) and medaka[6] (**Table 7**). Like zebrafish, medaka has emerged as one of the most popular and influential animal models to investigate development and disease. At the genomic level, the regenerative capacity of zebrafish might rely on gene regulatory networks, which might be repressed in other non-regenerative

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[5]http://asia.ensembl.org/Danio_rerio/Info/Index

[6]https://asia.ensembl.org/Oryzias_latipes/Info/Annotation

TABLE 6 | Tutorials/protocols for injury and drug delivery for zebrafish and medaka.

Description	Website	References
Dissection of different organs from the Adult Zebrafish	Dissection of Organs from the Adult Zebrafish | Protocol (jove.com)	Gupta and Mullins, 2010
Dissection of the Adult Zebrafish Kidney	Dissection of the Adult Zebrafish Kidney | Protocol (jove.com)	Gerlach et al., 2011
Induction of myocardial infarction in adult zebrafish using cryoinjury	Induction of Myocardial Infarction in Adult Zebrafish Using Cryoinjury | Protocol (jove.com)	Chablais and Jaźwińska, 2012a
Brain injury model by stabbing in Adult Zebrafish	Stab Wound Injury of the Zebrafish Adult Telencephalon: A Method to Investigate Vertebrate Brain Neurogenesis and Regeneration | Protocol (jove.com)	Schmidt et al., 2014
Spinal cord injury by transection in larval zebrafish	Spinal Cord Transection in the Larval Zebrafish | Protocol (jove.com) Zebrafish In Situ Spinal Cord Preparation for Electrophysiological Recordings from Spinal Sensory and Motor Neurons | Protocol (jove.com)	Briona and Dorsky, 2014; Moreno et al., 2017
Laser-induced retinal injury model in zebrafish	Müller Glia Cell Activation in a Laser-induced Retinal Degeneration and Regeneration Model in Zebrafish | Protocol (jove.com)	Conedera et al., 2017
Examining muscle regeneration in zebrafish models of muscle disease	Examining Muscle Regeneration in Zebrafish Models of Muscle Disease | Protocol (jove.com)	Au - Montandon et al., 2021
Hepatocyte-specific ablation in zebrafish to study biliary-driven liver regeneration	Hepatocyte-specific Ablation in Zebrafish to Study Biliary-driven Liver Regeneration | Protocol (jove.com)	Choi et al., 2015
Intraperitoneal injection in zebrafish	Intraperitoneal Injection: A Method of Solution Delivery into the Abdominal Cavity of an Adult Zebrafish | Protocol (jove.com)	Kinkel et al., 2010
Intrathoracic injection for the study of adult zebrafish heart	Intrathoracic Injection for the Study of Adult Zebrafish Heart | Protocol (jove.com)	Bise and Jazwinska, 2019
Retro-orbital injection in adult zebrafish	Retro-orbital Injection in Adult Zebrafish | Protocol (jove.com)	Pugach et al., 2009
Nanoparticle-mediated siRNA gene-silencing in adult zebrafish heart	Nanoparticle-mediated siRNA Gene-silencing in Adult Zebrafish Heart | Protocol (jove.com)	Xiao et al., 2018
CRISPR/Cas9-generated gene knockouts in zebrafish	Efficient Production and Identification of CRISPR/Cas9-generated Gene Knockouts in the Model System Danio rerio | Protocol (jove.com)	Sorlien et al., 2018
Imaging blood vessels and lymphatic vessels in the zebrafish	Methods in Cell Biology | The Zebrafish - Cellular and Developmental Biology, Part A Cellular Biology | ScienceDirect.com by Elsevier	Jung et al., 2016
Microinjection of medaka embryos for use as a model genetic organism	Microinjection of Medaka Embryos for use as a Model Genetic Organism | Protocol (jove.com)	Porazinski et al., 2010b
Dechorionation of medaka embryos and cell transplantation for the generation of chimeras	Dechorionation of Medaka Embryos and Cell Transplantation for the Generation of Chimeras | Protocol (jove.com)	Porazinski et al., 2010a
Medaka: Biology, Management, and Experimental protocols	Volume 1 and 2 (https://onlinelibrary.wiley.com/doi/book/10.1002/9781119575399#)	Kinoshita et al., 2009; Murata et al., 2019

animal models (Yang and Kang, 2019). Early findings in zebrafish suggest epigenetic modifications ranging from histone modifications to initiation of enhancer-induced activation of regenerative programs (Kang et al., 2016; Pfefferli and Jaźwińska, 2017). Growing evidence support the compatibility of zebrafish and medaka for comparative transcriptomic analyses (Tena et al., 2014; Lai et al., 2017). Moreover, with the advances of epigenetic profiling, medaka has also been explored for epigenetic changes associated with embryogenesis, development, and evolution (Nakamura et al., 2014; Tena et al., 2014; Ichikawa et al., 2017; Marletaz et al., 2018; Uesaka et al., 2019; Li et al., 2020). These properties may bring medaka as a new teleost model in epigenetics for comparative studies in tissue regeneration.

Hybrid/Chimera Fish and Cell Transplantations

Among various teleost fishes that come in different shapes and sizes, zebrafish and medaka have a similar developmental process overall. However, medaka shows a slower pace and hatch at 9 days compared to 3 days in zebrafish. Considering the similarities and differences between zebrafish and medaka, inter-species blastula transplantation was explored to study the genetic developmental timing during organogenesis (Hong et al., 2012; Fuhrmann et al., 2020). Generating chimeric organisms named "Zebraka" or "Medrafish" involves cell transplantation at the blastula stage and ectopic formation of chimeric organs like retina from zebrafish donor cells in the medaka host. This approach helps researchers determine the transcriptional dynamics of retinal organogenesis and further state the existence of organ-intrinsic mechanisms independent of the development pace of the host (Fuhrmann et al., 2020). It will be intriguing to consider the differential regenerative capacity of each organ in these hybrid animals. For example, if the heart was contributed by zebrafish donor cells and grows in medaka, would it still be regenerative (and why)? Hybrid animals may help researchers dissect the intrinsic and extrinsic properties of tissue regeneration, and zebrafish and medaka chimeras may provide a unique opportunity for such study.

TABLE 7 | Resources for zebrafish and medaka research.

Fish	Resource	Description	Website and references
Zebrafish	The Zebrafish Information Network (ZFIN)	Central database of zebrafish resources, studies and protocols	http://zfin.org/ (Ruzicka et al., 2019)
	Ensembl: *Danio rerio*	Genome assembly, GRCz11	http://asia.ensembl.org/Danio_rerio/Info/Index
	zfRegeneration	Dataset for zebrafish associated regeneration studies	http://www.zfregeneration.org/ (Nieto-Arellano and Sanchez-Iranzo, 2019)
	CreZoo	Database of Zebrafish Cre driver lines	Zebrafish CreZoo (Jungke et al., 2013)
	Zebrafish International Resource Center	Zebrafish stock center, United States	https://zebrafish.org/home/guide.php
	European Zebrafish Resource Center (EZRC)	Zebrafish stock center, KIT-Europe	https://www.ezrc.kit.edu/index.php
	The Taiwan Zebrafish Core Facility (TZCF)	Core facility for Zebrafish stock	http://www.tzcf-tzenh.org/ (You et al., 2016)
	NBRP-Zebrafish	Japan stock center for zebrafish resource	https://shigen.nig.ac.jp/zebra/index_en.html
	China Zebrafish Resource Center (CZRC)	Zebrafish resources, developing new lines and technology	http://en.zfish.cn/
Medaka	NBRP medaka	Central repository and achieve for medaka resources	https://shigen.nig.ac.jp/medaka/\penalty-\@M (Sasado et al., 2010)
	NBRP strains	Repository for strains and transgenics	https://shigen.nig.ac.jp/medaka/strain/strainTop.jsp
	Ensembl: Japanese medaka HdrR	Gene assembly and gene annotation (ASM223467v1)	http://asia.ensembl.org/Oryzias_latipes/Info/Index
	NBRP genome tools	Genome Mapping	http://viewer.shigen.info/medakavw/mapview/
	MEPD	Gene expression data by *in situ* hybridization	http://mepd.cos.uni-heidelberg.de/mepd/ (Alonso-Barba et al., 2016)
	mODP	OMICs data and epigenetic modification database	http://tulab.genetics.ac.cn/modp/#/Browser?species=medaka (Li et al., 2020)
Both Models	CCTop	CRISPR/Cas9 design tool	https://cctop.cos.uni-heidelberg.de:8043/index.html (Stemmer et al., 2015)
	CRISPRscan	CRISPR/Cas9 design tool	https://www.crisprscan.org/ (Moreno-Mateos et al., 2015)

Similar ideas have been exploited in the intra-species blastula transplantation in embryonic and adoptive transfer in adult zebrafish to determine the cellular contribution of specific biological processes (cell-autonomous vs. non-cell-autonomous actions). The concept was recently adopted in a heart regeneration study where macrophages were isolated from zebrafish larvae donors and adoptively transferred into adult hosts. Larval macrophages were found to infiltrate the injured hearts and contribute to scar formation by directly secreting collagens in adults (Simoes et al., 2020). Similar strategies may pave the way for future research, in which zebrafish donor cells might be transferred in medaka host or vice-versa and determine the cellular contributions in tissue regeneration.

LIMITATIONS, FUTURE DIRECTIONS, AND CONCLUDING REMARKS

In this review, we illustrated the concept of comparative study in tissue regeneration and highlighted the examples in zebrafish and medaka models. Zebrafish and medaka are phylogenetically close model organisms compared to animals from different phyla across the animal kingdom yet possess a distinct tissue regeneration capacity. Various tools and techniques commonly used in zebrafish and medaka were summarized here, supporting the unique strength of conducting comparative tissue regeneration research. Nevertheless, we cannot ignore some technical challenges and conceptual oversight that must be addressed or overcome.

On a technical aspect, orthologous gene annotation and identification are critical for inter-species comparisons. The Zebrafish genome has been well annotated and referenced due to a broad research interest with orthologous genes identified and translatable to the mammalian system (Howe et al., 2013). However, the medaka genome is less annotated than zebrafish. The limitation may sometimes be overcome by mapping the medaka genome against zebrafish to identify the orthologous genes. Though this might not be the optimal approach for genome annotation, it is currently the most feasible method to translate genetic information to the zebrafish and the mammalian context. Using such a method, Lai et al. (2017) have identified more than 15,000 orthologous genes across zebrafish and medaka in a comparative transcriptomic analysis.

On a conceptual aspect, it is still unclear how the trait of regeneration evolved along with all the other physiological and anatomical differences among species under the pressure of natural selection. Following the same logic, the similarities and differences between zebrafish and medaka might not necessarily associate with their regenerative capacity, which

confounds the causal relationship between candidate factors and tissue regeneration. In addition, the concept of zebrafish and medaka comparison is based on the existence of conserved mechanisms underly tissue regeneration between these organisms, which might not be accurate, and the same blindside also exists for other inter-species comparisons. In light of this, potential factors identified from the comparative analyses must be further examined in both gain-of-function and loss-of-function experiments to determine their exact role in tissue regeneration. Comparative studies in the heart and retina provide nice examples of such practice (Lai et al., 2017; Lust and Wittbrodt, 2018). To gain translational opportunities, candidate factors (biological processes/signaling pathways) should be further tested to regulate regenerative capacity in mammals. Overall, the comparative approach in different models may gain basic knowledge in tissue regeneration and hint at new therapeutic strategies.

Since the pioneer studies in zebrafish tissue regeneration, broad interests have been invested in the regenerative program and other mechanistic insights underlying various tissue regeneration, hoping that the knowledge will hint or translate into therapeutics in regenerative medicine. Although the medaka has only begun to enter the stage of regenerative biology, their similar characteristics to zebrafish and abundant resources as a model animal draw more and more attention for inter-species and inter-organ comparisons in tissue regeneration and await further exploration.

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KC, SL, and S-LL contributed to the conception, writing and revision of the manuscript. KC drafted the manuscript and prepared the tables and figures. S-LL reviewed, edited, and oversaw the manuscript preparation. All the authors read and approved the submitted version.

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