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EXPLOITING THE DIFFERENCES BETWEEN ZEBRAFISH AND MEDAKA IN BIOLOGICAL RESEARCH: A COMPLEMENTARY APPROACH

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ABSTRACT

Comparing two complementary species is a promising approach to broadening our understanding of disease simulation. Zebrafish and medaka are the top two fish models in biomedical research and their soaring profiles in the last three decades are compelling. Although there are far more studies using the zebrafish model than medaka in the literature, the two systems are comparable and complementary to each other. Despite the similarities, there are few anatomic and transcriptomic differences between the two species. The successful genome sequencing of medaka and zebrafish has shown that fishes and higher animals are identical in terms of genetic composition. Approximately 20,000 genes in medaka are nearly the same as that of humans with an 80% ortholog correlation while the zebrafish has a total of 26,000 genes with 71.4% of human genes. Zebrafish and medaka offer several advantages as models for investigating human disorders. Firstly, the cost-effectiveness of maintaining a lab that is borne out of its small size, short generation time, and short life span is comparably better than higher animal models. Other qualities of zebrafish and medaka are high fecundity and transparent embryos which enhances visualization at different stages of embryogenesis. The purpose of this review is to highlight the anatomic and transcriptomic differences between the two species and the successes recorded so far using these teleost fishes complementarily in research, for instance in genetic manipulation. These differences which are due to evolutionary distance are the reasons why the two systems have been found complimentary.

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Introduction

The last three decade has seen the mouse becoming the preferred lab animal in mimicking human diseases in preclinical studies [1]. Notwithstanding the strength of the murine model, it has some experimental limitations that are difficult to succumb to in simulating human disorder. For instance, it is technically demanding to conduct large-scale studies, particularly in chemical and genetic screening [2]. As alternative models, zebrafish (Danio rerio) and medaka (Oryzias sp.) are comparably better when it comes to managing animals in a study requiring a large number of samples regularly within a limited time [3]. Aside from the fact that they can be raised in a small tank, hundreds of embryos can be produced weekly by a pair of fish. In addition, while embryos can grow to adulthood after fertilization-independent of the parent, the inner tissues are seen clearly and fishes can be subjected to experimental manipulation [2]. The high point of the zebrafish genome-sequencing project is the discovery of 70% similarity between the human protein-coding genes and the zebrafish, including genes involved in diseases which suggests that zebrafish can be an appropriate model for human physiological and pathological studies [1, 4-6]. Zebrafish

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modeling has witnessed rapid development in recent times with the availability of technologies for manipulating genes and analysis at cellular and molecular levels. Innovations in in-vivo live imaging, high-throughput DNA and RNA sequencing, and genome editing with successes in developing a fish version of most mouse techniques are a pointer to the fact that the zebrafish model will remain a foremost model in the 21st century [2].

Unfortunately, despite medaka being a small freshwater fish commonly used as a model for an aquatic toxicology study, it has not been considered for human behavioral research especially interspecific behavioral diversities [7]. This observation is not peculiar to behavioral research, medaka patronage in modeling human disease is still very low despite all the genetic and physiological properties conserved between the two teleost species. Research has shown that medaka is an important model for developmental biology and large-scale genomics [8, 9]. In as much as zebrafish have attained an enviable position among the fish models for human diseases, complementing zebrafish with medaka will ensure the development of more efficient human disease models [10].

The main aim of this review is to highlight the achievement so far in deploying both zebrafish and medaka in biological research. Additionally, this work is focused on reviewing the anatomic and transcriptomic differences between the two species and how to maximize the two systems by adopting a complementary approach to research as has been demonstrated in genetic manipulation. Besides, either zebrafish or medaka could be favored for a particular study based on its strengths or weaknesses.

The History of Zebrafish and Medaka in Biomedical Research

Fish has a long history as a research tool in the biological sciences to investigate and elucidate complicated physiological processes and pathological disorders found in higher vertebrates especially humans [11]. Studies with fish models are an excellent approach to understanding fundamental biological systems shared by both humans and fish thereby providing insights into normal human biological processes and human pathological disorders [12].

The two most popular fish models in biomedical research are zebrafish and medaka [13]. However, it should be noted that zebrafish and medaka do not belong to the same family. While zebrafish belong to the Cyprinidae family with a freshwater origin (order Cypriniforms), medaka belongs to the Adrianichthyidae family (order Beloniformes) and its ancestors lived in a seawater habitat [14].

Medaka has so many mutants that have been found relevant in genetic research, developmental biology, and later medicine. The successful genome sequencing of medaka and zebrafish has shown that fishes and higher animals are identical in terms of genetic composition. For instance, approximately 20,000 genes in medaka are nearly the same as that of humans with an 80% ortholog correlation with humans [15]. Nevertheless, the zebrafish has a total of 26,000 genes with 71.4% of human genes having one or more zebrafish orthologues [16].

Medaka came into the limelight in 1913 as a tool to prove Mendelian inheritance theory and 8 years later it became the first vertebrate used to show how the crossing over between X and Y chromosomes and Y-linked inheritance occurs [17]. Subsequent studies in pigmentation, toxicology, sex determination, and biological development were reportedly successful using the medaka model. Stable stem-like cells and stable transgenesis established in medaka happened to be the first of its kind in any fish species [18].

The year 1930 marked the historical year in which zebrafish was used as an experimental model to unravel environmental stress-associated disorders ranging from anatomical, developmental and behavioral through manipulation of the fish's external environment [19]. Again in 1965, zebrafish was found ahead of all other fish species as the appropriate model for simulating chemical carcinogenesis, after it developed hepatic neoplasia upon exposure to diethylnitrosamine. Zebrafish later emerged as a model for the genetics and developmental research in the 1970s and the 1980s [20].

Despite various identical features between these two species, it is quite obvious that zebrafish are more favored in studies involving genetics, developmental biology, and medicine. To highlight the gap between the two fishes in human medical research, a search was conducted on PubMed. Medaka and human medicine were searched from the year 2000 to the year 2020. The same was done for zebrafish and human medicine as shown in **Figure 1** below.

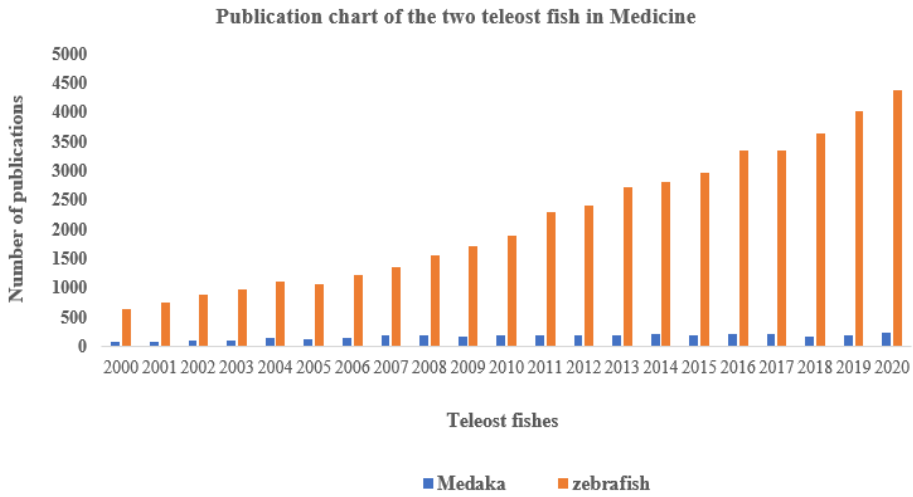

Figure 1. The number of publications related to medaka and zebrafish in Medicine between the year 2000 and year 2020 (searched in PubMed only). The number of articles in which zebrafish was mentioned totaled 45,273 while that of medaka was 3,658 during the period. Within twenty years, publications that featured zebrafish increased from 657 to 4,396 (669%) but for medaka, a paltry increase from 80 to 244 was recorded (305%).

Distinguishing Features between Zebrafish and Medaka

Despite the two teleost fishes having similar anatomical features, there are minor differences due to the huge phylogenetic distance between these two species. As biological research progresses using both medaka and zebrafish, more revelations in terms of distinguishing features between the two species will be of utmost relevance to the concept of complementarity which has not been fully tapped into. Some of the differences are the skeleton, dentition, pattern of pigment cells, thymus, glomerulus, eyes, heart asymmetry, and Parapineal organ.

Skeleton

The major difference between the vertebral bones of the two teleost fishes is the richness of the osteocytic network in zebrafish **(Figure 2)**, a phenomenon that is completely absent in medaka. Medaka belongs to the more evolutionarily advanced teleost having anosteocytic bones [21]. This critical difference is likely pointing to the probability of the bony elements of their skeleton being distinct in structural and mechanical aspects or both, most especially the vertebrae which are heavily loaded bones. Differences such as these can be associated with the contrasting mechanism of osteogenesis presently believed to occur between anosteocytic and osteocytic bone [22].

Characteristically, the formation of osteocytic bone by the osteoblast which becomes entrapped in the osteoid they secrete is followed by the osteoblast undergoing many morphological and physiological changes, thereby culminating in the development of a sophisticated network of living osteocytes within the bone matrix. Nonetheless, the prevailing paradigm for the formation of anosteocytic bone suggests that osteoblasts remain perpetually on the external surface of the newly formed bone, and do not become entangled in the osteoid. A process such as this requires the osteoblast to function in a characteristically different way in osteocytic and anosteocytic skeletons. Analysis of the spatial variation of mineral density distribution and x-ray attenuation along the longitudinal axis of vertebrae from both medaka and zebrafish showed a differential distribution, with the bone material in the vertebra cones having a lesser mineral density in comparison to the middle region, with a steady decrease in mineral density toward the edges of vertebrae [22].

Although, both medaka and zebrafish exhibit this differential pattern, it was observed that the mineral density at the edges of the cones is lower in the medaka compared with the same location in zebrafish. Interestingly, a previous study has reported a similar pattern of mineral distribution. It was discovered that in the entire length of the centrum, the mineral density of medaka vertebrae is significantly higher than the mineral density of zebrafish vertebrae [23, 24].

Figure 2. Image of zebrafish skeleton [25]

Dentition

One of the benefits of studying the dentition of the teleost is the fact that they can replace their dentition from the embryo stage through adulthood. This unique feature could benefit humans and other mammals that are not capable of replacing their dentition in adulthood. Due to their evolutionary distance, medaka and zebrafish have dentitions that differ in various ways. The differences reflect some extent the diversity that is found in teleost dentitions. Medaka has an inconstant and a high number of teeth in contrast to zebrafish which have a small and constant number of teeth. While zebrafish have only pharyngeal teeth and lack oral teeth, medaka has both oral and pharyngeal teeth Click or tap here to enter text. Regarding shape and type, there are no differences in medaka and zebrafish as both teleosts have mild heterodonty [25, 26]. Meanwhile, the development of replacement teeth in the two species includes the budding of epithelium and reciprocal interaction of the mesenchyme. In medaka, the development of replacement teeth arises from the epithelial budding of oral epithelium. However, in zebrafish, the budding of epithelium is initiated from the outer dental epithelium of the predecessor and a distinct successional dental lamina in embryonic zebrafish and adult zebrafish, respectively [27].

Thymus

Similar to mammals, adult teleost has a thymus with a distinctive medullary and cortical organization which ranges from one to multiple lobules. Both medaka and zebrafish have just one thymic lobule on each side of their body. It has been shown that medaka experiences spatial organization of thymocytes into apparent thymic microenvironment much earlier and is already identifiable at the larval stage. Compartmentalization of the thymic in zebrafish occurs later in juveniles between the ages of 2- and 3 weeks post-fertilization (wpf) [28].

Furthermore, optical transparency which is seen as a critical advantage of using zebrafish and medaka for research involving the tracking of molecules and lymphoid progenitors from hematopoietic tissue is premised on the closeness of the thymus to the skin [27]. Zebrafish larvae have between 20 and 50 thymocytes, while freshly hatched medaka have more than 1000 thymocytes [29].

In both medaka and zebrafish, the thymus grows to reach the peak of output during adolescence before it undergoes regression due to aging. Nevertheless, the shrinking time point of the thymus among the teleosts varies. The thymic structure in some teleosts remains intact for their whole life. Medaka belongs to this group of teleosts in which there is no difference between the histological analysis of the thymus of a 3-year-old medaka and that of a 3-month-old. Contrarily, zebrafish start to regress as early as 15 wpf. Taking into consideration that the rapid decline of the thymus is a detrimental process, an analytical comparison between zebrafish and medaka can go a long way in enriching our understanding of the molecular mechanisms of age-related thymic involution [30].

Eye

Another organ in which there are minor differences between medaka and zebrafish is the eye. In contrast to medaka where there are no gross changes to the lens in the young and the old, abundance and aggregation of lens crystallins are quite obvious as the zebrafish ages [13]. Some of the other differences in the retina are the formation of the optic primordium which is completed 12 hpf in zebrafish in contrast to 26 hpf in medaka. Similarly, retinotectal projection is differentiated within 48 hpf in zebrafish while the same developmental phase takes 4 to 6 dpf in medaka. Besides, the concurrent appearance of rod opsin and Zpr-1 (prominent photoreceptor markers) in the cell layer of a photoreceptor is peculiar to zebrafish but their expression in medaka is approximately 24 hours apart [31].

The Pattern of Pigment Cells

The elegant stripes of the zebrafish are a result of the autonomous pattern formation of the skin pigment cells. The formation of the stripes is associated with a mutation in 7 loci. However, medaka adults lack an ordered body pigmentation but they exhibit a relatively simpler pattern of evenly distributed pigment cellsClick or tap here to enter text. Detecting at the molecular level what is responsible for these overwhelming differences in appearance will boost our insight into pigment formation patterns, a poorly understood phenomenon in vertebrates [32].

Heart Asymmetry

Left-sided laterality of heart asymmetry is well-conserved among vertebrates but it is not unusual to see several species showing spontaneous reversal of this asymmetry. A decline in heart reversals has been reported during the evolution of vertebrates [33]. Approximately 5% decline in heart reversals in fish, which came down to 1-2% in amphibians and birds, and a mere 0.1% in mammals indicate a canalization of heart laterality during vertebrate evolution. Research has shown that while medaka deviated from a teleost pattern by showing 0% heart laterality, zebrafish displayed a teleost pattern of 5% laterality [33].

It is being suggested that the inbreeding nature of the medaka strains decreases the normal fluctuation of individual laterality indicating the possibility of a more robust symmetry-breaking mechanism and resistance to genetic and environmental perturbation in medaka than in other analyzed teleosts including zebrafish [8]. However, the determination of vertebrate laterality is based on a major mechanism that involves the generation of a leftward flow of extracellular fluid within the kupffer's vesicle (KV) of teleosts and the ventral node of mice. Interestingly, a recent study has shown that the KV of medaka is closer in semblance to the mammalian node than to the zebrafish KV when considering the robustness of the nodal flow and

cytoarchitectonic organization of ciliated cells [33].

Parapineal Organ

Research has revealed that left-sided positioning of the Parapineal organ is an evolutionarily conserved feature of asymmetric brain morphogenesis among teleosts. Click or tap here to enter text. However, there are significant differences between zebrafish and medaka in terms of the size of the Parapineal organ in relation to the pineal organ and the pattern of efferent connectivity. While the Parapineal organ is approximately 10% of the pineal in zebrafish and the efferent connectivity pattern is evenly distributed in the left habenula, the Parapineal organ in medaka is 60% of the pineal and the efferent connectivity forms a big and clearly defined Antero-dorsomedial neuropil domain within the left habenular [33].

Glomerulus

Unlike zebrafish, the pronephros of the glomerular primordium of medaka has an epithelial with a C-shape. In addition, the C-shaped primordium consists of a distinct balloon-like capillary which later split into several smaller capillaries. In zebrafish, the glomerulus is formed by the fusion of two pronephric glomeruli at the midline but in medaka, the pronephric glomeruli do not fuse because the interglomerular mesangium is interposed between them. the pronephric development in medaka is also characterized by interglomerular mesangial cells (IGMCs) which consist of several cytoplasmic granules. There is a likelihood that the cytoplasmic granules contain renin protein [34].

There are lots of gains in studying the glomerular development in the medaka pronephric glomerulus side-by-side zebrafish. For instance, podocyte differentiation in medaka which is a morphological process is more identical to mammals than zebrafish. Most especially, in the medaka, the pronephros of the glomerular primordium exhibits a C-shaped epithelial layer common with primitive podocytes which are similar to a mammalian S-shaped body. It is safe to speculate that the morphological processes involved in podocyte development between mammals and medaka will show substantial parallels. Click or tap here to enter text. Furthermore, these findings provide the basis for future pronephric analyses of medaka mutants with defective pronephric glomerulus which can give an insight into all aspects of glomerulus function and possibly enhance our understanding of human glomerular disease **(Table 1)** [35].

Table 1. Different features in zebrafish and medaka

Features	Zebrafish	Medaka	Reference
Skeleton	Osteocytic skeleton type	anosteocytic skeleton type	[22]
Dentition	pharyngeal teeth No oral teeth Variable number Large number	pharyngeal teeth Oral teeth present Constant number Few numbers	[25-27]
Thymus **a. Thymic lobe** **b. Compartmentalization** **c. Number of thymocytes** **d. Aging**	One thymic lobe on each side of the body. Compartmentalization of the thymic occurs at the embryo stage 20-50 thymocytes Regression starts from age 15 weeks	One thymic lobe on each side of the body Compartmentalization of the thymic occur at the juvenile stage More than 1000 thymocytes No sign of regression is observed in the thymus until adulthood	[27-30]
Glomerulus	The pronephric glomeruli fuse	The pronephric glomeruli don't fuse	[34, 35]
Eye **a. Lens** **b. Retina**	Lens shows an obvious aggregation of crystallin in old zebrafish There are apparent changes in the retina as the zebrafish ages.	Aggregation of crystallin in the lens is not seen in old medaka No apparent changes in the retina as the medaka ages	[13]
Pigment cells	Has elegant stripes and ordered body pigmentation	Has neither stripes nor ordered body pigmentation	[32]
Heart asymmetry	Display teleost pattern of 5% laterality	Display 0% laterality	[33]
Parapineal organ	Approx. 10% of the pineal	Approx. 60% of the pineal	[33]

Comparing Gene Expression Patterns in Selected Organs of Zebrafish and Medaka

To complement transcriptomic and epigenomic data sets that have been previously reported in zebrafish, RNA-seq and genomics tracks were generated for major histone modifications (H3k4me3 and H3k27ac) from 1 day 20 hours medaka embryos which were found to be of anatomic correspondence with 24-hpf zebrafish embryos in the phylotypic period.

Comparative analysis of fish transcriptomes reveals that expression levels of tissue-specific genes correspond with similarities in anatomy and heterochrony between zebrafish and medaka [36].

Moreover, comparative epigenomic analysis of putative active regulatory regions (PARRs) shows 64% sequence level dissimilarity between the two teleosts **(Figure 3)**. Among the conserved regions, just 14% fall within the shared putative active regulatory regions (SPARRs) (the region where the two species are simultaneously active through the phylotypic stage). However, genes linked with this small group of co-acetylated regions display a more complex and broader regulatory landscape. This collection of genes is highly endowed in transcription factors and signaling molecules that play major roles in the control circuits associated with the specification of tissues and organs [37].

Nonetheless, there is major conservation between zebrafish and medaka in terms of the relative timing of ontogenetic events in mid-embryogenesis. The conservation between these two species has been reported in the development of the lens vesicle, optic cup, general brain morphology as well as the onset of a heart beating. Despite the observed similarities, a small number of heterochrony (a few exceptions to major developmental sequence) were also evidently proven. For instance, at a stage where somitogenesis is just 50% through in medaka, it is already completed in zebrafish. There are two major differences between the two species during somitogenesis. Firstly, in contrast to static medaka embryos, zebrafish display instantaneous vibrations of the trunk and the tail at 24 hpf [37]. A second major heterochrony is the ability of zebrafish to form its fin bud as early as 22 hpf while the formation is delayed until 2 days 10 hours in medaka embryos. On the other hand, differences in anatomical traits between the two species during organogenesis are limited to the development of pancreatic and hepatic buds in which the events progress faster in medaka than in zebrafish [37].

For interspecies comparisons, levels of expression of a group of 9178 orthologs were analyzed, except for those with low RNA expression (less than 1 read). It was discovered that there is a strong correlation between the total transcriptomes of zebrafish and medaka (Pearson correlation of 0.71). This is in concordance with a study in which vertebrate transcriptomes that give the highest correlation coefficient were compared for the duration of the pharyngula stage.

Based on the ZFIN expression database, a comparative genetic profile for different structures in zebrafish and medaka was done by making a selection of tissue-specific genes [38]. The level of expression of genes in the eye, an organ with no anatomical differences between zebrafish and medaka was compared with the expression in the muscles for which anatomical differences were obvious. It was discovered that 30% of the expressed genes in the muscles were upregulated by more than 4-fold in zebrafish compared with the upregulation in medaka. This is quite consistent with morphological data. Intriguingly, only 11.3% of the genes in the eyes show a similar level of expression in the two species [37].

When the analysis was extended to the nervous system-specific genes, significantly higher RNA levels were observed in zebrafish in comparison with medaka. This indicates a premature nervous system development which may be connected with the capacity of zebrafish embryos to actively twitch tail musculature 24 hpf having formed the neuromuscular junctions. However, there are no significant differences between zebrafish and medaka for other tissue-specific genes analyzed except in the epidermis, where little but significant difference in gene expression was observed [36].

A critical look at tissues that develop faster in zebrafish than in medaka (the nervous system and the muscles) suggest that this phenomenon may be due to ecological adaptations which vary from one specie to the other **(Table 2)**. For instance, zebrafish are known for producing large clutches of eggs (up to 300) and the crucial part is that an approximate 2-day development culminates in eggs being hatched as free-swimming larvae. Contrastingly, medaka produces between 10 and 30 embryos which grow at a slower rate than in zebrafish. This indicates that, although anatomical similarities are optimal at the phylotypic stage, adaptive requirements and ecological strategies are crucial determinants of the developmental timing of individual tissues [39].

In furtherance of the independent comparison of the transcriptome of zebrafish and medaka by a team of researchers, the edgeR package was used to compute differentially expressed genes [40]. When a false discover threshold (FDR) is less than 5% and a fold change higher than fourfold was selected, a total number of 1085 genes (an equivalent of 15.2% of the gene on the ortholog list) were identified as having high expression in zebrafish and 600 genes (an equivalent of 8.4% of the genes on the ortholog list) were up-regulated in medaka [36].

However, it is interesting to note that when the DAVID gene ontology (GO) analysis of differentially expressed genes was used to obtain the functional categories of biological process, significant upregulation was confirmed in zebrafish for genes related to neurological system process and muscle tissue development. Similarly, differences between the two species were found in biological processes that were not discovered via direct morphological observation such as cardiac muscle tissue development, protein localization, and signaling cascade. In the case of upregulated transcripts in medaka, the overrepresentation of genes linked to oxidation-reduction and cofactor metabolic process were discovered with respect to zebrafish [36].

Furthermore, a bioinformatics tool, PANTHER was used for the comparison of enrichment GO terms in genes upregulated in zebrafish and medaka. It was discovered that there were significantly enriched GO terms associated with muscle development and synaptic transmission (e.g., synaptic transmission, neurological system process, mesoderm development, the transmission of nerve impulse, and muscle organ development) in genes upregulated in zebrafish. In the case of medaka upregulated transcripts, less significantly enriched GO terms were found which were child terms linked to metabolic processes such as lipid metabolic process, carbohydrate metabolic process, and cellular amino acid metabolic process. This is a corroboration of analysis previously done using DAVID [37].

Lastly, in situ hybridization was used to investigate the differences in zebrafish and medaka brains based on 14 genes. It was discovered that up-regulation of some of these genes in the telencephalic region in medaka embryos differs to a certain extent

from those reported in zebrafish at comparable stages (48-54hpf for medaka and 24-28hpf for zebrafish) Click or tap here to enter text.. One of the genes is pax6 which is expressed in the dorsal region of the telencephalon in medaka embryos while the same pax6 and another gene, pax6.1 were found to be expressed in the caudal region of the telencephalon in zebrafish embryos 24hpf [41]. Similarly, there are differences between zebrafish and medaka in terms of the expressions of otx1 and emx2 24 hpf. On the contrary, the differences observed in the expression patterns of bf1 and dlx2 in the telencephalon of the two species were insignificant. Aside from telencephalon, the gene expression patterns in other regions of the brain are similar between the two species [42].

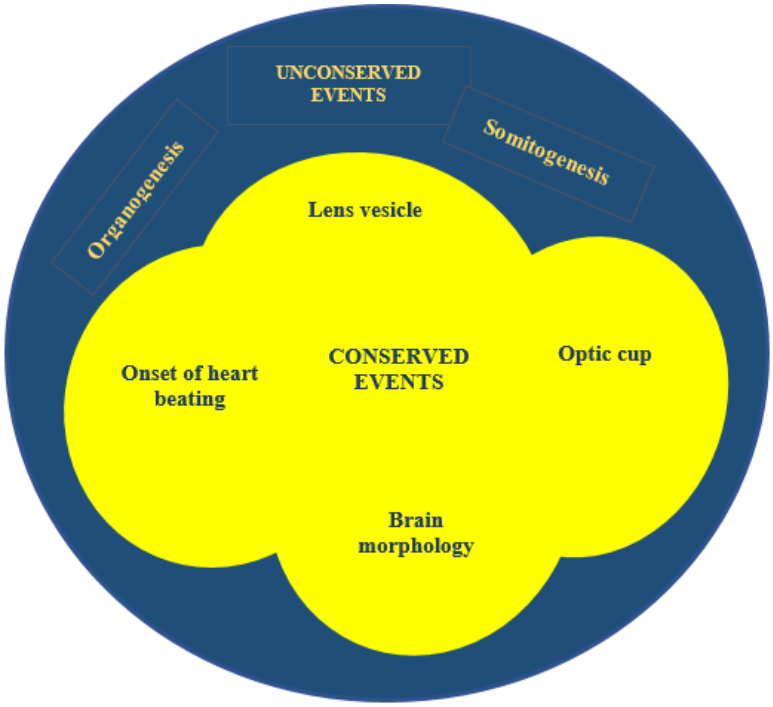

Figure 3. The conserved and unconserved events between zebrafish and medaka during embryogenesis

Table 2. A summary of comparative transcriptomic and epigenetic data between zebrafish and medaka

Events/Analytical packages	Zebrafish	Medaka	References
RNA-seq and genomics tracks			
a. Somitogenesis	Instantaneous vibration of the trunk and tail	Immobile at 24hpf	[37]
b. Organogenesis	Formation of hepatic and pancreatic bud is slow	Formation of the bud is faster	
Analysis using edgeR analysis	1085 genes were identified as having high expression	600 genes were up-regulated	[37, 40]
Analysis using DAVID Gene ontology analysis of differentially expressed genes	Upregulation of genes related to neurological system process and muscle tissue development	Genes related to oxidation-reduction and cofactor metabolic process are overrepresented with respect to zebrafish	[37]
Analysis using PANTHER	Enrichment in GO terms linked to muscle development and synaptic transmission	Enriched GO terms linked to lipid metabolic process, carbohydrate, and cellular metabolic process	[37]
In situ hybridization using 14 gene probes in the brain	Pax 6 and Pax 6.1 are expressed in the caudal region of the telencephalon	Pax is expressed in the dorsal region of the telencephalon	[38]

Results and Discussion

Complementing zebrafish with medaka has been a huge success in research fields. For instance, large-scale mutagenesis was promoted by the biological features of zebrafish that are shared by medaka. Some of these features are fecundity, short generation time, rapid development, and easy husbandry [32]. Both teleost fish have embryos that are well suited for the

analysis of development at the cellular levels because of externally fertilized, transparent, and rapidly developing embryos [43]. Although, as it has been highlighted, there are minor differences between zebrafish and medaka in terms of the timing of development of a few organs during embryogenesis.

Interestingly, there are some exclusive qualities found in medaka making it the appropriate complementary system to the zebrafish model. Firstly, medaka has been found very valuable in the development of low temperatures for recognizing temperature-sensitive alleles [32]. It is also considered the suitable model for studying inbred strains which provide low phenotypic variation and enable cell transplantation analysis in adults, for example, validation of carcinoma cells. Further, the maintenance of mutant strains in medaka was one of the first fish specie to be successful because frozen sperms can be reliably stored [44].

Zebrafish are no doubt an extremely valuable system for developmental biology, but the recent event of large-scale genomics has proven that zebrafish do not display the extent of synteny present in medaka [45]. Without any doubt, the impact of the zebrafish model in scientific research cannot be overemphasized, but additional data from complementary models like medaka will allow vetting the findings in zebrafish as well as providing added information for a comprehensive understanding of human diseases [46].

Exploring the evolutionary distance between biomedical models to strengthen the comparative approach is a win-win situation for the scientific community. When an experimental outcome from side-by-side analyses using two or more models agrees, the findings are strengthened. But if the models do not agree, it provides insight into alternative mechanisms, thereby aiding our understanding. Therefore, scientists stand to gain enormously from using two models to study identical variables [8, 32]. Such comparison provides researchers with an extremely potent comparative experimental tandem that can be used to solve complex problems such as the etiology and progression of human disease [46].

One of the areas where these two models have been used to complement and improve human disease models is genetic manipulation. The development of concurrent technologies in medaka and zebrafish underlines the reciprocal nature of exchanging methods and tools between these two systems thereby advancing scientific research. The very first genetic manipulation was demonstrated through stable transgenesis in medaka [47]. Thereafter, a team of researchers identified the Tol2 transposon system in medaka which was later adapted in zebrafish for transgenesis [48]. This feat revolutionized the field of genetic manipulation in model systems. To effectively recapitulate the endogenous gene expression patterns, the insertion of BAC constructs by Tol2 transposase has been used extensively in producing zebrafish reporter lines. Despite medaka being the model through which Tol2 was originally identified, the efficiency of the Tol2 system is higher in zebrafish than in medaka. Transgenesis in medaka has been facilitated by the development of insertional transgenesis in fish models using I-SceI meganuclease [49].

Importantly, there is evidence that medaka may soon be considered the preferred model for mimicking diabetic nephropathy in humans. According to the criteria given by the Animal Model of Diabetic Complication Consortium (AMDCC), no rodent animal is deemed appropriate for simulating diabetic nephropathy. Nevertheless, research has proven that medaka could serve as a good translational model for the disease. In the process of developing this model, both medaka and zebrafish were put on a high-fat diet but only medaka developed diabetic nephropathy which was characterized by enlarged glomeruli, high blood glucose, and glomerular capillary dilation [10]. Other studies in which medaka may be preferred over zebrafish are chronic mycobacteriosis, xenobiotic stimulated hepatic fibrosis, hypohidrotic ectodermal dysplasia, osteoporosis, alcohol research, and human neurotoxicology [10, 50].

Conclusion

In summary, despite the minor differences between zebrafish and medaka, the similarities between them are huge. The importance of a comparison of these two phylogenetically related fish models cannot be overemphasized. Zebrafish is by far the most sought-after fish model, comparison such as this will enrich the knowledge of the research community on alternatives like medaka and the fact that the housing and the cost of raising the two species are similar. In addition to this, this work will guide researchers on how best to put the teleost fish to use and which of the specie should be chosen for a particular study, and the possibility of even combining the two models to compare and contrast pathways, mechanisms, genes, and proteins involved. Essentially, the physiological differences between medaka and zebrafish can help us understand similar pathways in humans thereby expanding our horizon on the best approach to treating human disorders.

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