Developmental Genetics of Adaptation in Fishes: The Case for Novelty

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color pattern, development, evolution, gender, jaws, teeth

Abstract

During the past decade of study in evolutionary developmental biology, we have seen the focus shift away from the stunning conservation of form and function between distantly related taxa toward the causal explanation of differences between closely related species. A number of fish models have emerged at the forefront of this effort to dissect the developmental genetic and molecular basis of evolutionary novelty and adaptation. We review the highlights of this research, concentrating our attention on skeletal morphology (cranial and postcranial), pigmentation patterning, and sex determination. Thus far, the genes involved in adaptation among fishes belong to well-characterized molecular pathways. We synthesize the current state of knowledge to evaluate theories about the interplay between development and evolution. General rules of evolutionary change have not materialized; however, the field is wide open, and fishes will likely continue to contribute insights to this central biological question.

INTRODUCTION

Fishes, Novelty, and How Development Works

Melanophore: melanin-containing pigment cell of ectothermic vertebrates that is derived from the neural crest

Forward genetics: approach that starts with a phenotype of interest and then tries to identify genetic variants that are associated with the phenotypic differences

Reverse genetics: approach that starts by creating or identifying mutations in a gene of interest and then assays the phenotype of individuals carrying the mutation

The publication in December 1996 of an entire issue of *Development* dedicated to the zebrafish embryo and its embryogenesis changed the way evolutionary biologists think about fishes. The description of mutants in pathways affecting most aspects of vertebrate morphology (brains, eyes, jaws, fins, pigment) provided resounding evidence of the interplay between genes and development on a comprehensive scale. The simple figures used to document phenotypes (e.g., cleared and stained embryos lacking jaw bones or with duplicated cartilages, fishes without melanophores) provided visual compendia of developmental diversity. Students with favorite traits now had favorite mutants. The landmark issue of *Development* was particularly inspirational to those interested in evolution. The zebrafish mutants, first the domain of biomedicine, contributed to an undercurrent of discovery that adaptation (when development works) was just the flip side of disease (when development fails). Comparative biologists recognized that understanding the key to complex phenotypes and evolutionary novelty, encoded in the genome and unveiled through the developing embryo, was a tractable research objective.

This mindset was accompanied by major challenges. Conceptually, mutant screens are an imperfect metaphor for the identification of genotype-phenotype associations in nature. First, the classical experimental paradigm of forward genetics has sought to minimize complexity by isolating the effects of single mutations. Second, most zebrafish mutants were embryonic lethals; they never developed to function as adults. Subsequently, biologists have inferred how development works by studying how development fails. This approach has advanced our knowledge of gene function, but has also underscored the notion that genes do not operate in a vacuum, that environmental and genomic context matters. As such, a major and complementary objective of current research is to understand the molecular basis of natural diversity. Notably, understanding the origin of biological diversity was named one of the "25 Hard Questions" by *Science* magazine in July 2005, and "Evolution in Action" was *Science*'s 2005 Breakthrough of the Year.

Teleost fishes represent a unique assemblage in which to study the genetics of adaptation and evolutionary novelty, or how development works. First, the group contains bona fide model organisms (*Danio*, *Takifugu*, *Tetraodon*, *Oryzias*), with research programs in forward and reverse genetics, molecular biology, and genomics providing information, hypotheses, and technical insight. Second, the species richness and diversity of fishes are unrivaled among vertebrates. Closely related species differ in a wide range of traits, many of which we explore below. Numerous natural lineages are amenable to genetic and developmental analysis because barriers to hybridization are minimal or absent and embryos are easy to manipulate (e.g., danios, sticklebacks, cichlids). Understanding the genetics of development in natural lineages would provide theoretically novel insights into gene function because (*a*) new genes, not identified in mutant screens, might be involved and (*b*) new mutations, compatible with adult viability, would likely play a role.

Here, we review recent advances in the developmental genetics of adaptation in teleost fishes. We focus on three types of traits: skeletons (including craniofacial and postcranial elements), pigmentation, and sex (gender) determination. These traits have received considerable attention from researchers and fit together conceptually. Skeletal elements and pigment patterns have their cellular origin in the vertebrate cell type called the neural crest (Gans & Northcutt 1983, Hall 1999). Pigment patterns and skeletal variants are sometimes linked to sex chromosomes, and theoretical population genetic models of adaptive speciation predict linkage among these trait types (reviewed in Bolnick & Fitzpatrick 2007). Some of the evolutionary lineages and the traits we highlight have been reviewed elsewhere in the past few years (Cresko et al. 2007, Kazianis 2006). Our goal is to describe and summarize this vast primary literature to examine if diverse adaptations in different fish lineages share common developmental pathways or common gene regulatory logic. We integrate these data to address hypotheses that codify the rules of evolutionary development among closely related organisms.

Neural crest: a pluripotent population of embryonic precursor cells that contributes to numerous vertebrate traits

SKELETONS

Traveling Light: Adaptation via Loss

Recent work has yielded considerable insight into the developmental genetics of trait loss in fishes. Assorted lineages have lost features of the craniofacial (i.e., teeth) and postcranial skeletons (i.e., ribs and fins), as well as body armor, scales, eyes, and pigmentation (see below) (**Table 1**; **Figure 1**). Research to date suggests that trait loss is controlled by a small number of genes of large effect and high penetrance; further study is required to determine if this is a general rule.

Table 1 Summary of genes involved in adaptation among different fish lineages

Trait	Lineage	Gene	Data[a]	Gene type[b]
Pelvic fin loss	Pufferfishes	*hoxd9a*	T	I/O
Pelvic fin loss	Stickleback	*pitx1*	Both	I/O
Eye loss	Cavefish	*shh*, *twhh*	T	Plug-in
Pigment loss	Cavefish	*oca2*	Both	DGB
Armor loss	Stickleback	*eda*	G	Plug-in
Tooth loss	Cypriniforms	FGF, *dlx2*	T	Plug-in
Jaw function	Cichlid	*bmp4*	Both	Plug-in
Sex determination	Medaka	*dmy*	G	I/O

[a]Data column specifies the type of data [genetic (G), transcriptional (T), or both] used to demonstrate the relationship between genotype and phenotype. Genetic data is an association between genotype and phenotype found by genetic linkage or genetic association analysis. Transcriptional data is an association between genotype and phenotype found by showing a correlation between a phenotypic difference and a difference in a gene's expression pattern.

[b]Gene type column assigns genes according to Davidson & Erwin's (2006) terminology. DGB, differentiation gene battery; I/O, input/output.

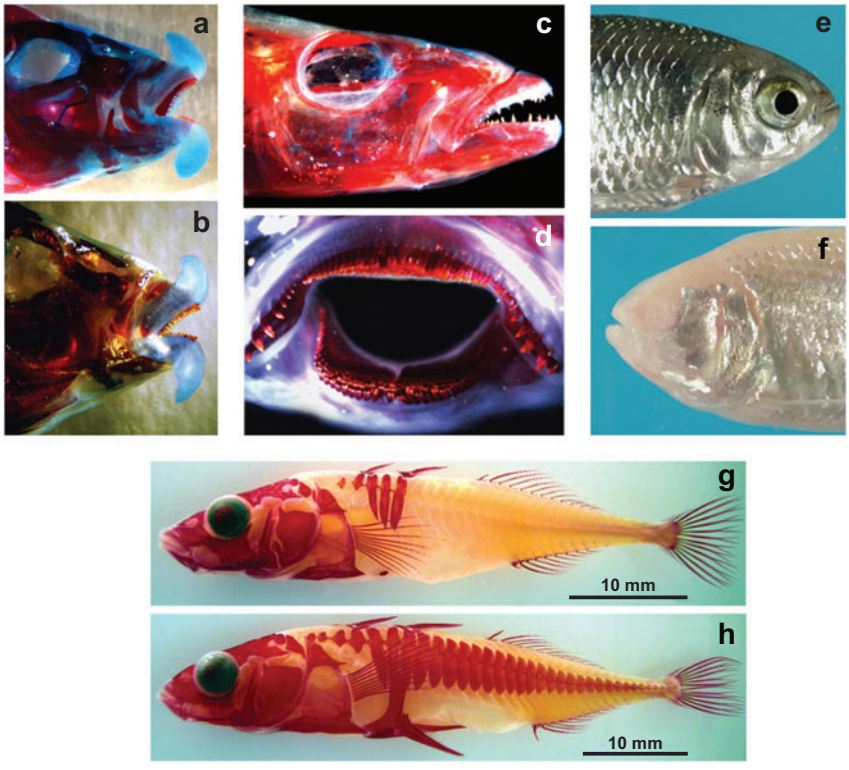

Figure 1

Variation in skeletal morphology and anatomy among model teleosts. (*a*) *Placidochromis milomo* (Lake Malawi) and (*b*) *Lobochilotes labiatus* (Lake Tanganyika), demonstrating parallel evolution of cartilaginous fleshy lips, function unknown. (*c*) *Rhamphochromis esox*, a piscivore from Lake Malawi with a highly kinematic jaw and unicuspid teeth. (*d*) An oral view of *Pseudotropheus elongatus*, an algae eater from Lake Malawi with multiple rows of multicuspid teeth. (*e*) Eyed and pigmented versus (*f*) eyeless and albino tetras, *Astyanax*. (*g*, *h*) Variation in body armor and pelvic spines among Alaskan sticklebacks. Photos of tetras and sticklebacks are courtesy of Yoshiyuki Yamamoto and William Cresko, respectively.

Quantitative trait locus (QTL): a genomic region that has been shown by linkage mapping studies to harbor genetic variation that contributes to segregating phenotypic variation

Understanding the developmental genetic basis of adaptation builds on decades of natural history, field ecology, and evolutionary biology. For instance, Northern Hemisphere stickleback fish have independently colonized freshwater habitats from marine ancestors soon after the last glacial maximum (~10,000 years ago). Riverine, lacustrine, and stream populations have evolved numerous adaptations, including changes in body size, habitat use, gill raker number, and the reduction of body armor [i.e., scales that are modified to form bony plates, as well as pelvic and dorsal spines (Bell & Foster 1994)] (**Figure 1**). Peichel et al. (2001) mapped the genetic basis of pelvic and armor reduction in backcross progeny of lacustrine benthic versus limnetic threespine sticklebacks from Priest Lake, British Columbia. A single quantitative trait locus (QTL) for pelvic spine length was located on chromosome 8, and QTL

for body armor (plates) were located on chromosomes 13 and 26. Each of these genomic regions explained a substantial portion of phenotypic variation in the focal trait [percent variance explained (PVE) = ~25%].

Percent variance explained (PVE): the amount of segregating phenotypic variation explained by a particular QTL

Subsequent to this study, numerous reports have refined the story for each trait. Colosimo et al. (2004) used F_2 fishes from an intercross of marine versus Paxton Lake, British Columbia, parents to document a QTL of major effect (PVE > 75%) for body armor on chromosome 4, with four additional minor effect loci on separate chromosomes. The major locus for armored plates on chromosome 4 also segregated in a California stream population. This locus was later identified as *ectodysplasin* (*eda*) by positional cloning, linkage disequilibrium mapping, and transgenesis (Colosimo et al. 2005). Notably, *eda* low-plate alleles segregate at low frequency in marine high-plated ancestral populations, explaining the parallel loss of armor in most freshwater lineages (Colosimo et al. 2005).

Shapiro et al. (2004) used a similar cross-design to identify a major QTL for pelvic reduction on stickleback chromosome 7, with four additional minor effect loci on different chromosomes. Mapping of candidate genes and in situ hybridization strongly suggest that regulatory mutations in *pitx1* (paired-like homeodomain transcription factor 1) are responsible for this phenotype. Similarly, genetic complementation analysis implicated *pitx1* in the pelvic reduction of other freshwater threespine stickleback populations (Shapiro et al. 2004) and distantly related (common ancestor at least 10 mya) ninespine stickleback populations (Shapiro et al. 2006). Cresko et al. (2004) studied the genetics of bony armor loss among Alaskan freshwater threespine stickleback populations and demonstrated parallel Mendelian control of both pelvic and armor phenotypes. Alaskan sticklebacks segregated for a pelvic reduction gene on chromosome 7 (likely *pitx1*), and armor phenotypes mapped to the *eda* locus on chromosome 4 (Miller et al. 2007).

Other fish lineages show analogous loss of scale or pelvic structures; strikingly, these phenotypes result from alterations in the same developmental pathways identified in stickleback. Kondo et al. (2001) reported that the spontaneous medaka mutant *rs-3*, which lacks scales, is encoded by the receptor for *ectodysplasin* (*edar*). Pelvic fin loss in pufferfishes is accompanied by altered expression of the limb-positioning marker *hoxd9a*, which is upstream of *pitx1* (Tanaka et al. 2005). Finally, additional fish groups are characterized by the loss of morphological features, from eyes to oral jaw teeth. Blind cavefishes (*Astyanax*) possess eyes that degenerate during development (**Figure 1**). Cave populations are characterized by expanded sonic hedgehog (*shh*) and tiggy-winkle hedgehog (*twhh*) expression at the embryonic midline when compared to their surface-dwelling eyed ancestors (Yamamoto et al. 2004). Zebrafish and other cypriniform fishes lack teeth on their oral jaws. This may result from altered fibroblast growth factor (FGF) signaling through *dlx2* in oral epithelium (Stock et al. 2006).

Fish Jaws and Dentitions: Elaboration and Complexity

Detailed study of trait loss in fishes provided some of the first evidence that genetic mapping and assays of gene expression could be used to understand the molecular

control of natural adaptations. Of course, trait loss may be a special case of adaptation: what about the more complex morphologies in which individuals differ in the subtler aspects of shape, size, and function? The natural history of fish feeding ecology, functional morphology, and diversity provided a place to begin. Notable features of the fish craniofacial skeleton include (*a*) two sets of toothed jaws (oral and pharyngeal) elaborated to (sometimes) bizarre extremes (**Figure 1**), (*b*) dentitions on jaws and numerous other bony elements replaced continuously through development, and (*c*) a long and perhaps dubious history of these traits as markers of evolutionary relationships.

Cichlid fishes have figured prominently in studies attempting to identify the developmental genetic basis of craniofacial adaptation, largely because they represent closely related species with a wide range of trophic and dental morphologies (Albertson & Kocher 2006). Albertson et al. (2003) mapped QTL for craniofacial morphology in the F_2 of a cross between two Lake Malawi cichlids with divergent feeding strategies. Genes of large effect (10%–25% PVE) for multiple craniofacial phenotypes mapped to common intervals of chromosomes 1, 2, and 16 [reassigned to chromosomes 7, 15, and 19 after comparison to the more extensive tilapia cichlid map (Lee et al. 2005, Streelman & Albertson 2006)], leading to speculation that trait linkage on chromosomes might facilitate the rapid and replicative evolution of jaw design among rift lake cichlids (**Figure 1**). Using a test that compares the direction of QTL effects to a neutral expectation, the authors documented strong directional selection on the oral jaw apparatus and the dentition (Albertson et al. 2003). In 2005, Albertson and colleagues focused on the functional aspects of lower jaw shape that represent a trade-off between the speed and force of jaw opening and closing (Albertson et al. 2005, Hulsey et al. 2005). Importantly, they showed that opening and closing lever systems were genetically decoupled with QTL localized to different chromosomes. They observed that the gene *bmp4* mapped to the closing lever system QTL interval (on chromosome 19) and subsequently demonstrated greater *bmp4* expression in the parental species with more robust jaws [similar to results in Darwin's finches (Abzhanov et al. 2004)]. Finally, they showed that *bmp4* injection into zebrafish embryos was sufficient to recapitulate the lower jaw–shape phenotype observed in cichlids. This study provided a possible explanation for the observation that *bmp4* evolves rapidly and non-neutrally among East African cichlids (Terai et al. 2002b). Given the avid interest in modeling fish jaws as simple versus complex biomechanical systems (Alfaro et al. 2004, Hulsey et al. 2005, Wainwright 2007), the cichlid system is ideal for further exploration in this context.

Recent work in fishes has demonstrated the complexity of dental patterning in vertebrates. Fraser et al. (2004) showed that first-generation teeth on the oral jaw of rainbow trout express *pitx2*, *shh*, and *bmp4* in similar spatiotemporal patterns to the mouse, suggesting the conservation of these molecules in the initiation of odontogenesis since the common ancestor of fish and mammals (~450 mya). However, not all is conserved between mammals and fishes, or even between the oral and pharyngeal jaws of fishes. Notably, Fraser et al. (2004) described differences in *pitx2* expression during continued morphogenesis of trout teeth, with *pitx2* expression present in oral jaw teeth but absent from pharyngeal teeth. Working with zebrafish, Laurenti et al.

(2004) similarly demonstrated differences between pharyngeal first-generation teeth and the oral teeth of mammals (zebrafish lack teeth on the oral jaw so no direct comparison is possible). Specifically, the gene *eve1*, a member of the homeobox-containing evx gene family, not expressed during tooth development in mammals, is expressed during tooth initiation and morphogenesis of the first pharyngeal tooth. Jackman et al. (2004) used chemical knockdown of FGF signaling to show that FGFs are required for zebrafish first-generation tooth development. Furthermore, *fgf8* and *pax9* were not expressed under normal conditions in zebrafish tooth germs (unlike in mouse), and both *Dlx* and *Lhx* genes were expressed in dental mesenchyme (as in mouse molars).

In 2003, Streelman and colleagues demonstrated that tooth number was correlated with tooth cusp number in natural populations of cichlid fish from Lake Malawi, East Africa (Streelman et al. 2003b). Given simple genetic control of tooth shape in this system (Albertson et al. 2003) and the iterative role of certain genes in the stages of tooth development (Peters & Balling 1999), these authors suggested that variation in the expression of a single activating or inhibitory molecule might integrate tooth and cusp number (Streelman et al. 2003b; also Plikus et al. 2005). Streelman & Albertson (2006) subsequently identified a QTL of major effect for tooth shape on cichlid chromosome 5, near genes for orange blotch (OB) color and sex (Streelman et al. 2003a) (see below). Furthermore, they demonstrated, using *bmp4* as a marker of tooth initiation, that tooth number and spacing are specified earlier than tooth shape.

Much is left to learn about fish dentitions. For instance, first-generation teeth are morphologically unlike replacement teeth (Sire et al. 2002), do not show species-specific adult shapes, and exhibit unique gene-expression programs (Fraser et al. 2006). There is great interest in tooth replacement and its molecular mechanisms because subsequent tooth generations may arise from stemlike cells (Huysseune & Thesleff 2004), yet only one study to date has examined gene-expression programs in replacement dentitions (Fraser et al. 2006). No study has investigated the molecular choreography of tooth replacement in species with adult teeth shaped differently than first-generation teeth, and no study has examined how lingual rows of teeth are initiated and patterned (e.g., cichlid species can have more than 15 rows of teeth on the oral jaws). Understanding the molecules involved in the complexity of fish odontogenesis will shed light on the general mechanisms of periodic patterning applicable not only to dentitions (Salazar-Ciudad & Jernvall 2002), but also to other organs such as hair and feathers (Houghton et al. 2005).

PIGMENTATION

Pigment patterns represent one of the most extraordinary illustrations of teleost adaptation (**Figure 2**). Famous examples include coral reef fishes, cichlids of East Africa, and aquarium favorites such as guppies and loaches. The myriad pigment patterns of teleosts serve in a variety of roles, including warning coloration, camouflage, schooling, mate recognition, and mate choice (Couldridge & Alexander 2002, Endler 1988, Engeszer et al. 2004, Jordan et al. 2003, McMillan et al. 1999, Millar et al. 2006, Rosenthal & Ryan 2005).

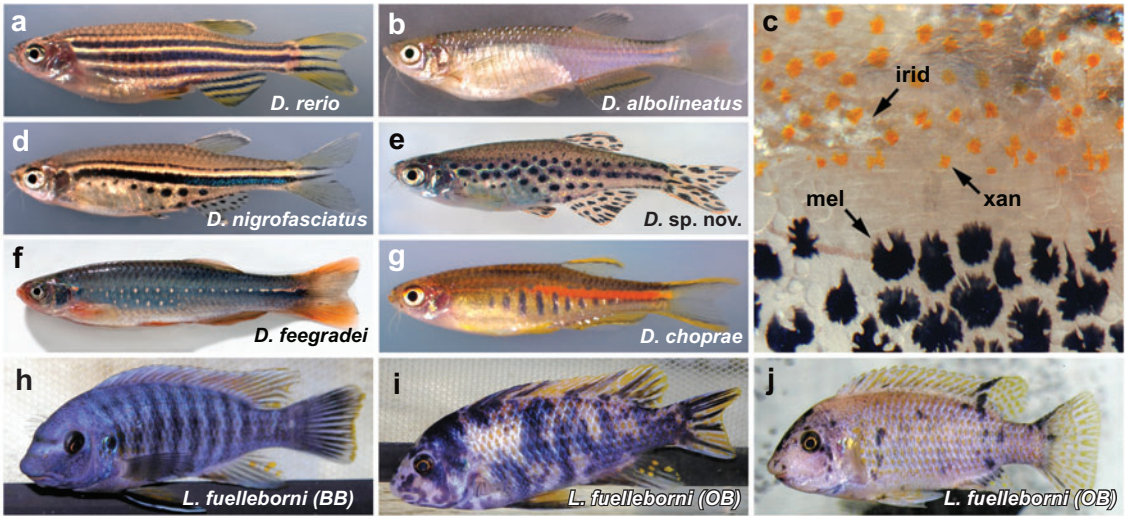

Figure 2

Pigment pattern variation and pigment cells of teleosts. Shown are several species within *Danio* (*a–g*), as well as the cichlid *Labeotropheus fuelleborni* (*h–j*), illustrating differing color patterns associated with the absence and presence of the orange blotch polymorphism [blue-black (BB) and orange blotch (OB), respectively). Panel *c* shows melanophores (mel), xanthophores (xan), and iridophores (irid) in the *D. rerio* adult pigment pattern. Iridescent iridophores are present throughout but can be seen here only where they catch the light.

Pigment Patterns Through Development

Vertebrate skin pigment cells are derived embryologically from neural crest cells, which also contribute to craniofacial bone, cartilage, and teeth and produce most of the peripheral nervous system (Hall 1999, Le Douarin 1999). Neural crest cells have long been recognized as a key vertebrate innovation (Gans & Northcutt 1983), and pigment patterns, in addition to skeletons (see above), have provided a valuable opportunity to study the developmental and genetic factors responsible for evolutionary changes in the patterning of neural crest–derived traits. In contrast to studies of skeletal diversification, which have focused largely on particular genes and tissues, studies of pigmentation have emphasized the cellular mechanisms of pigment pattern development. The different emphasis reflects the notion that evolutionary changes in gene activity are only interpretable in a cellular context (e.g., Parichy 2005) and this cellular context has thus far been less explored for pigment patterning as compared to skeletogenesis.

Pigment patterns reflect the numbers and arrangements of several classes of pigment cells, or chromatophores. These include black melanophores, yellow or orange xanthophores, red erythrophores, blue cyanophores, white leucophores, and iridescent iridophores (Bagnara & Matsumoto 2006, Parichy et al. 2006). The color of each class of cell results from the particular pigments contained within specialized organelles. By combining different classes of cells, different spatial arrangements of

cells, and different pigment concentrations within individual cells, a seemingly infinite range of patterns and colors can be produced.

Most fishes exhibit different pigment patterns during different life-cycle phases. The first pattern to develop arises as embryonic neural crest cells disperse from above the neural tube, differentiating chromatophores during or even prior to their migration and subsequently colonizing specific locations to generate an embryonic/early larval pigment pattern (Kelsh 2004, Raible & Eisen 1994). Commonly this consists of stripes of melanophores dorsally, laterally, and ventrally, with xanthophores broadly scattered over the flank (Lamoreux et al. 2005, Quigley et al. 2004), although a variety of other patterns also occur. The functional significance of these pigment patterns remains unexplored.

The diversity of teleost pigmentation consists mostly of patterns expressed in the adult. In some species, the adult pigment patterns develop during metamorphosis, when the larval form is transformed into a juvenile by remodeling or the initial appearance of a variety of traits [e.g., fins, skin, scales, skeleton, gut, kidney, and sensory systems (Webb 1999)]. Pigment pattern metamorphosis has been most studied in the zebrafish, *Danio rerio* (**Figure 2**). In this species, metamorphic melanophores differentiate scattered over the flank, and then melanophores coalesce at sites of adult stripe formation, with additional metamorphic melanophores differentiating already within the stripes; most embryonic/early larval melanophores die (Parichy & Turner 2003b).

Developmental changes in pigment pattern also can occur during later development, particularly with the onset of sexual maturation, and these may be either permanent or transient, as is the case for nuptial coloration (Beeching et al. 2002, Dickman et al. 1988, Maan et al. 2006, Mabee 1995). To date, virtually nothing is known about the molecular and cellular bases of pigment pattern changes within the adult phases of the life cycle.

Genes Underlying Changes in Pigmentation

One way that teleost pigment patterns evolve is by modifying the quantity or quality of the pigments carried by chromatophores. Two recent studies provide nice examples of how genetic approaches can provide insights into the evolution of pigmentation in fishes and beyond.

In Mexican tetras, *Astyanax*, several cave-dwelling populations exhibit a suite of derived traits including albinism, reduced eyes, and enhancements of other sensory systems (Jeffery 2001, Yamamoto et al. 2004) (**Figure 1**). The phylogeography of these populations is complex, although cave forms have clearly evolved repeatedly (Strecker et al. 2004). Despite their albinism, cavefish retain melanophores (McCauley et al. 2004), and genetic mapping identified a major effect QTL for melanin loss (Protas et al. 2006). By mapping candidate genes associated with mammalian albinism, researchers found a correspondence between the cavefish QTL and *oculocutaneous albinism-2* (*oca2*). Complementation tests showed that albinism in a second cavefish population is associated with the same locus, and molecular analyses revealed that each population harbors different small genomic deletions within *oca2*. The deletions

are functionally significant as *oca2* complementary DNA from melanized, surface-dwelling *Astyanax* allows the melanization of murine *oca2*-deficient melanocytes, whereas the two cavefish deletion complementary DNAs do not. This study nicely shows how pigmentation loss can result independently from changes at the same locus and suggests that such parallelism may reflect both an absence of pleiotropic effects and the large size of *oca2*, making it a high-frequency target for selection. These results are reminiscent of recent studies of *MC1R* in mammalian pigmentation (Hoekstra et al. 2006). The cavefish example also illustrates how knowledge of pigment cell genes and development in mammals can be applied to understanding pigment evolution in teleosts.

Knowledge of pigment development in teleosts also can inform us about the evolution of pigment in mammals, including humans. A striking example is the *D. rerio golden* mutant, which has reduced melanin but otherwise normal melanophores. Positional cloning identified *golden* as *slc24a5*, which encodes a sodium/calcium transporter localized to pigment granules within melanophores (Lamason et al. 2005). Mutations in *aim1*, also a transporter involved in melanin synthesis, explain a similar orange-red medaka variant called b (Fukamachi et al. 2001). Remarkably, a polymorphism within human *SLC24A5* is associated with different pigmentation between European and African populations, and significantly reduced heterozygosity indicates past selection at this locus. Whether variation at *slc24a5* or *aim1* has contributed to pigment evolution in teleosts and other taxa remains to be determined.

Mechanistic Bases for Cellular Pattern Diversification

Beyond changes in pigment content, a major factor in teleost pigment pattern diversification has been changes to the numbers and arrangements of chromatophore classes. Such variation has received extensive theoretical attention (Asai et al. 1999, Miguez & Munuzuri 2006, Painter et al. 1999), and recent studies have started to elucidate the underlying mechanisms, primarily using *D. rerio* and its relatives.

One recent insight concerns the origins of chromatophores responsible for pattern diversification. Unlike embryonic/early larval melanophores that differentiate directly from neural crest cells, metamorphic melanophores in *D. rerio* differentiate from latent precursors of presumptive neural crest origin (Johnson et al. 1995, Parichy & Turner 2003b, Parichy et al. 2003). Mounting evidence suggests these precursors are stem cells, able to generate differentiated progeny while themselves remaining undifferentiated (Parichy & Turner 2003a, Yang & Johnson 2006). A sister species, *D. nigrofasciatus*, exhibits superficially similar adult stripes to *D. rerio*, yet cell lineage analyses reveal these stripes are formed largely by reorganizing embryonic/early larval neural crest–derived melanophores rather than by differentiating stem cell–derived metamorphic melanophores (Quigley et al. 2004). Thus, danios exhibit at least two different modes of pigment pattern metamorphosis.

Analyses of danios show that cryptic but genetically distinct populations of metamorphic melanophores differentially contribute to pigment pattern evolution (Johnson et al. 1995; Parichy et al. 1999, 2000a,b). In *D. rerio*, early metamorphic melanophores that are initially dispersed and then migrate into stripes depend on

the kit receptor tyrosine kinase, as they are ablated in *kit* mutants. By contrast, late metamorphic melanophores that develop already within stripes do so independently of *kit*; i.e., they persist—in stripes—in *kit* mutants. As distinct populations of *kit*-dependent and *kit*-independent melanocytes have not been found in mammals, these cell populations might be unique to *D. rerio*. To test this idea, a recent study isolated a *kit* mutant in *D. albolineatus*, which normally exhibits uniformly dispersed melanophores. The mutant retained a population of *kit*-independent melanophores, showing conservation of these cellular populations in at least one other danio. Strikingly, and in contrast to the uniform wild-type *D. albolineatus* pattern (**Figure 2**), the *kit*-independent melanophores occurred in stripes. These and other data showed that *D. albolineatus* has latent stripe-forming potential, and that stripe loss in this species occurred in part by a failure of *kit*-dependent melanophores to migrate into stripes, thereby obscuring the stripes formed by *kit*-independent melanophores (Mills et al. 2007, Quigley et al. 2005). These studies show how a manipulative, genetic approach can be used to deconstruct the evolution of an adult phenotype.

Studies of danios also suggest that an important factor in pigment pattern diversification depends on chromatophore interactions. In *D. rerio*, stripes arise through interactions between melanophores and xanthophores, and between cells within each of these classes (Maderspacher & Nusslein-Volhard 2003, Parichy & Turner 2003a, Watanabe et al. 2006). Genetic analyses indicate that variation in danio pigment patterns likely reflect evolutionary modifications to the strength and timing of these interactions, which appear to serve as a pattern-generating mechanism that can be deployed at different times and in different places (Parichy & Turner 2003a, Quigley et al. 2005). Interspecific complementation testing of candidate genes identified as *D. rerio* mutants further revealed that such interactions are likely to be perturbed in *D. albolineatus*—contributing to the uniform pigment pattern—owing to changes in *colony stimulating factor 1 receptor* (*csf1r*, *fms*), which encodes a receptor tyrosine kinase expressed by cells of the xanthophore lineage (Parichy & Johnson 2001, Quigley et al. 2005).

Although danios are an especially tractable system for analyzing pigment pattern development and evolution, these species represent only a small fraction of teleost pigment pattern diversity. In this regard two additional groups are especially interesting—guppies and cichlids—both because of color pattern variation and because of the deep foundation of ecological and behavioral observations regarding these patterns (Genner & Turner 2005, Lindholm et al. 2004, Seehausen et al. 1999). For cichlids, a particularly exciting recent advance is the ability to map factors genetically using closely related species. For instance, a QTL associated with alternative barred and OB postmetamorphic color patterns in *Metraclima zebra* maps to the vicinity of c-*ski1* on chromosome 5 (Streelman et al. 2003a) (**Figure 2**). As representative cichlid genome sequences become available (**Table 2**), identification of this locus and other inferred genetic factors (Barson et al. 2007, Maan et al. 2006) will provide new and important insights into pigment pattern diversification. Moreover, mechanistic studies of danios and other model organisms should provide inroads to understanding the cellular bases for pattern diversification in these other species.

Table 2 Genomic resources for model teleosts

Resource	Species	Web site
Cichlid Genome Consortium	Cichlids	**http://www.cichlidgenome.org**
Ensembl	Zebrafish, stickleback pufferfish, medaka	**http://www.ensembl.org**
JGI	Pufferfish (*Takifugu*)	**http://genome.jgi-psf.org/Takru4/Takru4.home.html**
Medaka home page	Medaka	**http://biol1.bio.nagoya-u.ac.jp:8000**
Genoscope	Pufferfish (*Tetraodon*)	**http://www.genoscope.cns.fr/externe/tetranew/**
Sanger Institute	Zebrafish	**http://www.sanger.ac.uk/Projects/D_rerio/**
Stanford Genome Evolution Center	Zebrafish, stickleback	**http://cegs.stanford.edu/index.jsp**
Xiphophorus home page	*Xiphophorus*	**http://xiphophorus.org**
Zebrafish Information Network	Zebrafish	**http://zfin.org**

Pigmentation Genes Evolve Rapidly in Teleosts

A problem complementary to the evolution of pigment patterns is the evolution of pigment pattern genes, and several recent studies have assessed naturally occurring variation at such loci. For example, surveys of several cichlid species with diverse color patterns found differential rates of evolution among loci and between recently duplicated paralogous copies, including *csf1r*, which is mentioned above (Braasch et al. 2006, Sugie et al. 2004). An especially intriguing example is *hagoromo*, which encodes an F-box/WD-40 repeat protein that is required for metamorphic melanophore development in *D. rerio* (Kawakami et al. 2000). Analyses of more than a dozen cichlid species reveal accelerated rates of amino acid evolution in specific domains and an extraordinary increase in the complexity of alternatively spliced *hagoromo* transcripts (Terai et al. 2002a, 2003). It will be fascinating to learn how *hagoromo* functions in pigment pattern development and to test its causal involvement in generating species-specific pigment patterns.

SEX (GENDER) DETERMINATION

Sex Determination Mechanisms in Fish Are Diverse

Most developmental pathways, such as those discussed above, are well conserved across disparate taxa. By contrast, the developmental pathways that determine sex are strikingly variable and can even differ between closely related species. Teleost fishes present attractive models to understand the evolution of sex determination pathways, as the entire range of environmental and genetic sex-determining mechanisms is represented across lineages (Devlin & Nagahama 2002). For example, many fishes have environmentally determined sex, which can depend on factors such as temperature or social interactions. Genetic mechanisms of sex determination in fishes may be polygenic or simple and associated either with no cytogenetically visible sex chromosomes or with heteromorphic sex chromosomes in either males (XY systems) or females (ZW systems). This wide diversity of sex determination mechanisms can be found even in closely related fish species (Devlin & Nagahama 2002, Mank et al. 2006).

Cytogenetically visible sex chromosome: in this context heteromorphic chromosomes belonging to one sex that can be observed by examining chromosome squashes under a light microscope

Particularly apposite examples of this diversity are found within poeciliid fishes [guppies, mollies, swordtails, and platyfish (Volff & Schartl 2001)], salmonid fishes (Phillips et al. 2001, Woram et al. 2003), the stickleback family Gastesteidae (Chen & Reisman 1970), and the tilapia genus *Oreochromis* (Lee et al. 2003, 2004). Diversity of sex determination mechanisms in closely related fish species supports the hypothesis that this developmental pathway is evolutionarily plastic and that sex determination mechanisms and sex chromosomes can evolve rapidly.

The plasticity of sex determination mechanisms in fish is highlighted by recent work in medaka (*Oryzias latipes*). With the identification of a duplicated copy of the *dmrt1* gene called *dmrt1bY* or *DMY* as the medaka master sex determination locus (Matsuda et al. 2002, Nanda et al. 2002), there was speculation that this gene would serve a similar role in all fish, just as *Sry* is the master sex determination switch in nearly all mammals (Marshall Graves 2002). Although the *Dmrt* gene family is widely present in fish (Volff et al. 2003b), the *dmrt1bY/DMY* gene is absent from other fish species (Kondo et al. 2003, Veith et al. 2003). In fact, although *dmrt1bY/DMY* is present in a second species, *Oryzias curvinotus* (Kondo et al. 2004, Matsuda et al. 2003), other species within the *Oryzias* genus do not have this gene (Kondo et al. 2003, 2004), suggesting that *dmrt1bY/DMY* has arisen within the *Oryzias* lineage in the past 10 million years (Kondo et al. 2004).

The enormous variation in sex determination pathways in fish presents an opportunity to understand the mechanisms by which sex determination genes arise and sex determination pathways evolve. Remarkably, the mechanisms of sex determination remain unknown for *D. rerio*, although multiple loci and environmental influences are likely to be involved. Currently, efforts are underway to identify the master sex determination genes in platyfish, tilapia, salmonids, and stickleback. This work should identify whether there are common themes that connect the types of genes used as master sex determination loci, as well as provide insights into the evolution of sex determination pathways.

Sex Chromosome Evolution in Teleosts

In addition to the diversity of sex determination mechanisms in fish, there is also great diversity in the presence of sex chromosomes. Approximately 10% of fish species have cytogenetically visible sex chromosomes (Devlin & Nagahama 2002). However, this is likely an underestimate of the number of fish species that have sex chromosome systems because young sex chromosome systems that are in early stages of differentiation are unlikely to be observed by traditional cytogenetic analysis. Many closely related species of fish differ in sex chromosome complement, suggesting that sex chromosomes can arise rapidly in fish. Many fish sex chromosomes are therefore likely to be younger than the stable XX-XY sex chromosome system in mammals, which is over 300 million years old (Graves 2006). Therefore, studying sex chromosomes in fish provides a unique opportunity to investigate the genetic and molecular events that accompany the earliest stages of sex chromosome evolution.

After the acquisition of a sex determination locus, one of the first steps in the evolution of a sex chromosome is the suppression of recombination around a sex

determination locus, which has been hypothesized to occur to reduce recombination between the sex determination locus and linked genes with sex-specific fitness effects (Bull 1983, Fisher 1931, Rice 1987a). This suppression of recombination leaves the heterogametic sex with one chromosome in a consistently heterozygous state, which ultimately results in the degeneration of sex-linked loci in the heterogametic sex (Bull 1983, Charlesworth 1991, Rice 1987b). Based on these models, it is predicted that a sex chromosome would show reduction of recombination near the sex determination region, resulting in the loss of homology between the X and the Y chromosome, particularly owing to the accumulation of deleterious mutations, including an increase in transposable elements on the Y chromosome. Chromosome rearrangements may or may not accompany these early stages of sex chromosome evolution. Recent studies of the sex chromosomes of a number of different fish species have begun to illuminate these processes on a molecular level and have also begun to provide insight into the timing of events in sex chromosome evolution.

In particular, recent work in medaka fish (Kondo et al. 2006) has provided a detailed molecular view of the events that accompany the early stages of sex chromosome evolution, just after the evolution of a new sex determination gene. As described above, the sex determination gene in *O. latipes* was recently identified as the *dmrt1bY/DMY* gene, a duplicate copy of the *dmrt1* gene (Matsuda et al. 2002, Nanda et al. 2002). Kondo et al. (2006) cloned and sequenced the regions flanking *dmrt1bY* on both the X and the Y chromosome, as well as the *dmrt1* region. They found a completely Y-specific region that resulted from a duplication of a 43-kb region of chromosome 9 that includes the *dmrt1* gene. A number of repetitive elements have accumulated within the Y-specific region, accounting for an increase in its size to 258 kb. Thus, in this relatively young (less than 10 million years old) sex chromosome system (Kondo et al. 2004), there is evidence for both degeneration of Y-linked sequences and accumulation of repetitive DNA (Kondo et al. 2006).

It may be that the *dmrt1bY/DMY* locus in medaka represents a unique mechanism of sex chromosome evolution. To gain insights into the general mechanisms that underlie the evolution of sex chromosomes, it is important to analyze other sex chromosome systems of differing ages. In fishes, there are a number of other sex chromosome systems in species with the requisite genetic and genomic tools for this analysis. To date, the most well-studied systems have been poeciliid fishes (guppies and platyfish), salmonid species, threespine stickleback (*Gasterosteus aculeatus*), and tilapiine cichlids (*Oreochromis* spp.). In most of these systems, genetic analysis has revealed a genetic basis for sex determination even in the absence of cytogenetically visible sex chromosomes.

There must be some differentiation between sex chromosomes in most of these sex chromosome systems, as researchers have observed reduction in recombination between the X and the Y chromosomes near the sex determination region in threespine stickleback (Peichel et al. 2004), blue tilapia (Lee et al. 2004), and platyfish (Gutbrod & Schartl 1999, Morizot et al. 1991). Given the loss of recombination near sex determination regions of these fish, it is not surprising that there is also evidence that many of these systems have accumulated repetitive DNA. In tilapia, there are subtle differences in the amount of heterochromatin, which consists of repetitive DNA

elements that have accumulated on the Y chromosome relative to the X (Griffin et al. 2002, Harvey et al. 2002). Similarly, the sex determination region of lake trout, brown trout, and Atlantic salmon is next to a large heterochromatic block (Artieri et al. 2006, Phillips & Ihssen 1985, Phillips et al. 2002). Sequencing of X- and Y-specific bacterial artificial chromosome clones in threespine stickleback (*G. aculeatus*) and platyfish (*X. maculatus*) revealed that the Y chromosomes in both species had significantly more repetitive and transposable elements than the X chromosomes (Froschauer et al. 2002, Peichel et al. 2004, Schultheis et al. 2006).

Beyond examining the accumulation of transposable elements, investigators have done relatively little to explore the effects of loss of recombination at the sequence level. That viable and fertile YY salmonid (Chevassus 1988), tilapia (Penman & McAndrew 2000), and platyfish (Kallman 1984) males can be generated suggests that genes required for viability and fertility on the Y chromosome have not been rendered nonfunctional. Some sex-linked genes in platyfish appear to be pseudogenes; however, there are a number of duplicate copies of these genes, such that at least one functional copy might remain (Volff et al. 2003a). There are a number of sequence differences between the X and the Y chromosome in the threespine stickleback (Peichel et al. 2004); however, it is not known whether genes on the stickleback Y have become nonfunctional or whether YY individuals can be generated in stickleback. In the future, it will be important to compare the levels of cytogenetic differentiation with levels of sequence divergence and to explore in more detail the molecular changes that have occurred in the regions around a sex determination locus.

Sexually antagonistic gene: a gene with a differential fitness effect in the sexes, so expression in one sex is beneficial but expression in the other sex is detrimental

Pigmentation and Skeletal Traits Are Linked on Sex Chromosomes

Reduction of recombination around a sex determination locus appears to be a general phenomenon in sex chromosome evolution. Theoretical work suggests that this may result from linkage of a sexually antagonistic gene to the sex determination locus, which would select for the loss of recombination to prevent detrimental alleles from being expressed in the wrong sex (Bull 1983, Fisher 1931, Rice 1987a). Thus, we might expect that there would be an excess of sexually antagonistic genes linked to the sex chromosomes. In particular, male display traits, such as color, can be considered sexually antagonistic traits because expression in males is beneficial, but expression in females would be deleterious, as it might expose females to predation and incur production costs (Bull 1983, Endler 1980, Fisher 1931). This model does not exclude species with female display traits; in this case we might simply expect to see linkage of female display traits to a female determining locus. In support of this model, there is good evidence for linkage of (fe)male display traits to sex chromosomes in a number of fish species (Lindholm & Breden 2002).

The poeciliid fish provide some of the most spectacular examples of sex linkage of male display traits (Lindholm & Breden 2002). In guppies (which have an XY sex determination system), pigmentation, fin size and shape, courtship behavior, and male attractiveness are linked to the Y chromosome (Brooks 2000, Brooks & Endler 2001). The Y-linked color patterns are extremely polymorphic in natural populations and differ in their attractiveness to females (Lindholm et al. 2004). Different Y-linked color

alleles are associated with increased predation (Endler 1983) and mortality (Brooks 2000), suggesting that a balance between natural and sexual selection contributes to the maintenance of color polymorphisms in guppy populations (Endler 1980).

In another poeciliid fish genus, *Xiphophorus*, a number of traits involved in male attractiveness are closely linked to the sex determination locus on the Y chromosome (Basolo 2006, Cummings et al. 2006, Rosenthal & García de León 2006). As in guppies, pigmentation loci are tightly linked to the sex determination locus and are highly polymorphic within and between *Xiphophorus* populations (Kallman 1975). In addition, the puberty or pituitary locus is tightly linked to the sex determination locus and determines both the onset of sexual maturity (Kallman & Borkoski 1978, Kallman et al. 1973) and reproductive tactics (Zimmerer & Kallman 1989). This locus is also highly polymorphic, leading to alternative mating strategies within populations. Males that mature later are robust and ornamented and have elaborate courtship behaviors, whereas the males that mature early are small, have little ornamentation, and perform sneaker copulations. As for color, this polymorphism is likely to be maintained within populations owing to a balance of natural and sexual selection (Ryan et al. 1992). Although large males are favored by sexual selection and are preferred by females (Ryan et al. 1990), they are not favored by natural selection and are more heavily preyed upon (Rosenthal et al. 2001), providing an advantage for smaller and less conspicuous males.

Traits important for adaptation have been found linked to sex chromosomes in several other fishes. Among Malawi cichlids of the genus *Metriaclima*, sex is determined by a locus on chromosome 7, unless the OB trait is segregating in the family, in which case sex is under the control of a dominant female determiner linked to OB on chromosome 5 (Streelman et al. 2003a; T.D. Kocher, personal communication). Notably, genes for jaw shape and function map to cichlid chromosome 7 (Albertson et al. 2003, 2005; see above), and a QTL of major effect for tooth shape maps to chromosome 5 and is linked to the sex determination locus, as well as to genes for coloration (OB locus) and putative color preference (opsin gene cluster) (Carleton & Kocher 2001, Streelman & Albertson 2006). In tilapiine cichlids, a red color mutant maps close to the sex-determining locus of female heterogametic species on chromosome 3 (Lee et al. 2005). Finally, at least one skeletal trait, the size of the opercle bone, has been mapped to the stickleback sex chromosome (Kimmel et al. 2005). These latter data provide empirical evidence for quantitative genetic models of adaptive speciation that predict gametic association between ecological, marker, and preference traits (Dieckmann & Doebeli 1999, Kondrashov & Kondrashov 1999) on incipient sex chromosomes with reduced recombination.

SYNTHESIS AND PERSPECTIVE

The studies reviewed above have engendered novel insights into the developmental genetic basis of adaptation. Conceptually, this has shifted focus toward studying how development works in diverse and highly complex natural systems. Much has been learned about how genes with manifold pleiotropic functions (e.g., *pitx1*, *bmp4*, *shh*) can be employed specifically in an organ- or tissue-specific manner (Albertson et al.

2005, Shapiro et al. 2004, Yamamoto et al. 2004). Less satisfying, however, is that new genes or new gene functions have not been discovered; the genes involved in the traits we highlight might have been predicted in the context of traditional developmental genetics research. This is either because forward and reverse genetic screens are so thorough that they are redundant or because investigators have thus far studied a biased set of natural mutations [i.e., genes of large effect (Orr 1998)]. The next 5–10 years of research will address this question as new techniques (e.g., Miller et al. 2007) and improved genomic resources (**Table 2**) are used to investigate new traits in more teleost lineages. In summation, we consider a major question in evolutionary biology addressed by the studies reviewed here.

Gene regulatory networks (GRNs): the sum total of genes and their connections that influence a biological output, often depicted or modeled as wiring diagrams or logic circuits

Modularity: generally, the evolutionary or developmental decoupling of components involved in form and/or function

How Does Evolution Happen?

Many authors have discussed whether there are general rules governing evolutionary developmental biology (Carroll 2005, Gerhart & Kirschner 1997, Wilkins 2001). Davidson & Erwin (2006) have codified such rules in terms of gene regulatory networks (GRNs) and the evolutionary scale of change among the components of such networks. At one extreme are kernels, or sets of genes at the core of GRNs, that may be conserved over long periods of evolutionary time. At the other extreme are differentiation gene batteries (DGBs), genes involved in terminal differentiation of tissues or structures; DGBs reside at the periphery of GRNs and might be employed to distinguish among closely related species. In fact, Davidson & Erwin (2006) propose a "relation between the network-component class in which changes might occur and the taxonomic level of morphogenetic effects." According to Davidson & Erwin's (2006; their figure 3) hierarchical scheme, all the genes responsible for adaptive differences among closely related fish species [*pitx1*, *shh*, *twhh*, *oca2*, *eda*, *bmp4*, *dmy* (**Table 1**)] should belong in DGBs. However, six of the seven are better characterized as input/output (I/O) switches or plug-ins, both of which are classes of evolutionarily conserved components of multiple developmental networks. Davidson & Erwin hypothesize that changes in I/O switches and plug-ins explain differences at the taxonomic level of class, order, or family. Only *oca2* fits the definition of a DGB. So why do the data from fish adaptations not fit Davidson & Erwin's schema? The answer seems to lie in the degree of modular function for these I/O switch and plug-in genes. I/O switches and plug-ins can elicit major morphological change (because they regulate other genes through morphogenesis, unlike DGB genes), but the modularity of their regulation allows other pleiotropic functions of the encoded protein to remain unchanged [e.g., fin versus jaw function of *pitx1* (Shapiro et al. 2004)]. Perhaps a better prediction is that the genes involved in adaptation among closely related species will be those genes central to key morphogenetic processes (e.g., cell proliferation, differentiation, death, and migration) whose regulation across tissue- and cell-type is highly modular. In the language of GRNs, these are well-connected hubs, but the genes to which they are connected may vary across tissues and from species to species. The developmental and evolutionary flexibility of GRNs has not been examined among closely related species, but the approach is tractable in vertebrates (Tsaparas et al. 2006).

In summary, the next decade of research, highlighting these and other fish models, will surely contribute important data regarding the developmental genetic basis of adaptation. Further study fusing the power of molecular biology and genomics in fish groups of tremendous morphological, functional, physiological, and behavioral diversity will shape our understanding of how development works.

FUTURE ISSUES

1. Adaptation to new environments involves a wide range of morphological, physiological, and behavioral changes. In particular, the genetic basis of physiological and behavioral diversity has been relatively unexplored in any system. Because the fish models highlighted in this review display enormous morphological, physiological, and behavioral diversity, it should be possible to use the genetic and genomic tools developed for these systems to identify the genetic and molecular basis of any trait of interest. It will be particularly interesting to determine whether the types of mutations, genes, and pathways that are important for morphological adaptation are more generally involved in physiological and behavioral novelty.
2. As technical costs decrease, more fish lineages will become appropriate models to answer key biological questions. The richness and diversity found among teleost fishes are nearly limitless in this regard.
3. Many future research efforts will focus on traits expressed after embryogenesis or in adult life stages. New techniques and the application of standard techniques to new situations (explant culture, tissue- or stage-specific gene knockdown) will be required to rigorously evaluate functional associations between genotype and phenotype.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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