



Metamorphosis in Teleosts

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Contents

1. Introduction and Definitions	128
2. Metamorphic Diversity in Teleosts	130
2.1 Marine teleosts	130
2.2 Diadromous teleosts	135
2.3 Freshwater teleosts	138
3. Endocrine Controls of Teleost Metamorphosis	140
3.1 Thyroid hormone	141
3.2 Non-TH mediators of metamorphosis	146
4. Local Mechanisms of Morphogenetic Changes	148
4.1 Flatfish cranial asymmetry	149
4.2 Skin	149
4.3 Pigmentation	150
4.4 Fin ray formation	152
5. Conclusions	153
Glossary	153
References	154

Abstract

Teleosts are the largest and most diverse group of vertebrates, and many species undergo morphological, physiological, and behavioral transitions, “metamorphoses,” as they progress between morphologically divergent life stages. The larval metamorphosis that generally occurs as teleosts mature from larva to juvenile involves the loss of embryo-specific features, the development of new adult features, major remodeling of different organ systems, and changes in physical proportions and overall phenotype. Yet, in contrast to anuran amphibians, for example, teleost metamorphosis can entail morphological change that is either sudden and profound, or relatively gradual and subtle. Here, we review the definition of metamorphosis in teleosts, the diversity of teleost metamorphic strategies and the transitions they involve, and what is known of their underlying endocrine and genetic bases. We suggest that teleost metamorphosis offers an outstanding opportunity for integrating our understanding of endocrine mechanisms, cellular processes of morphogenesis and differentiation, and the evolution of diverse morphologies and life histories.



1. INTRODUCTION AND DEFINITIONS

Nearly half of all described vertebrates are teleosts (see [Volf, 2005](#)), and the more than 23,500 known species of teleosts exhibit a vast diversity of phenotypes, ecologies, and developmental life histories. Moreover, teleosts exhibit a tremendous range of metamorphic processes, sometimes undergoing major phenotypic and physiological transitions that allow a single species to exploit different habitats and niches during different life stages. This diversity in teleost life history has long fascinated comparative embryologists and marine ecologists, but the molecular mechanisms of these transitions remain almost entirely unexplored. With the methods of modern genetics and developmental biology, we can begin to elucidate the molecular, endocrinological, and morphogenetic processes underlying this incredibly diverse array of postembryonic transitions.

Several families of teleosts undergo spectacular morphological metamorphoses, comparable to the metamorphosis of anuran amphibians. Other teleosts undergo comparatively subtle phenotypic transformations, more analogous to the fetal-to-adult transition of mammals. Accordingly, workers in this area have adopted sometimes conflicting definitions of what should rightly constitute a “metamorphosis.” For example, some count only the most dramatic of transitions to be metamorphoses, requiring profound morphological and ecological differences between life stages, and rapid transitions between these stages ([Balon, 1990, 1999](#); [Just, Kraus-Just, & Check, 1981](#); [Manzon, 2011](#); [Youson, 1988, 2004](#)). Such restrictive definitions dismiss more subtle morphological, physiological, or ecological changes. Alternatively, others have suggested that metamorphosis of teleosts and other chordates can be defined as a conserved period of postembryonic remodeling, how extensive it might be, that is regulated specifically by thyroid hormone (TH; [Laudet, 2011](#); [Paris et al., 2008](#); [Paris & Laudet, 2008](#); [Power, Silva, & Campinho, 2008](#)). Yet, this definition precludes transformations that may rely on other hormonal axes.

For the purposes of this chapter, we define metamorphosis to be *an irreversible developmental and physiological change that affects multiple traits during post-embryonic development and is brought about by one or more systematically acting endocrine mediators, but is independent of sexual maturation, sex-specific modifications, or senescence*. This definition focuses on intrinsic features of an organism, or how the environment impacts organismal functioning, and accommodates what is clearly a phylogenetic continuum in the magnitude of

postembryonic remodeling. By excluding habitat changes *per se*, this definition allows for studies of how metamorphic processes have evolved in association with particular ecological conditions or life history modes. By our definition, metamorphosis is not necessarily a specific event, but, rather, any nonsexual, nonsenescent transition entailing developmental or physiological remodeling that is systemically controlled. Thus, our criteria allow one to pose testable hypotheses for whether any particular morphological or physiological transformation constitutes a metamorphosis; that is, whether or not it is controlled by one or more endocrine mediators. The definition deliberately excludes morphological changes (e.g., acquisition of nuptial coloration) that may be temporary, sex-specific, or both, and also does not specify any requirement for overall somatic growth. Moreover, as we have defined it, metamorphoses could occur over a range of time spans, from less than a day to periods of several months, and could, in principle, occur between a variety of life history phases, though metamorphosis is generally most prevalent during the larva-to-juvenile transition (Fig. 5.1). Finally, in being agnostic to mechanism, our definition acknowledges that additional factors mediating such transformations still may await discovery or characterization. In proposing this definition, and in the review that follows, our goal is to facilitate the study of postembryonic cellular, developmental, and physiological processes, how they intersect with endocrine mechanisms, and how they have evolved.

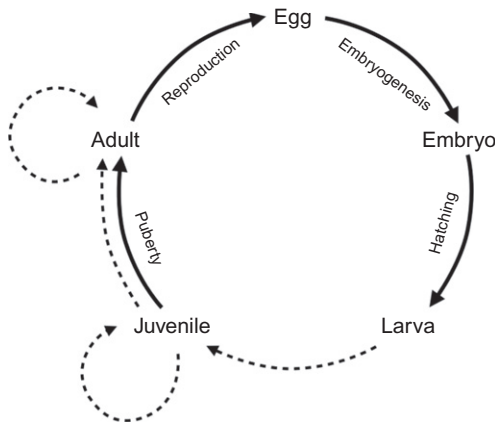


Figure 5.1 Generalized life cycle of a teleost. Dashed lines indicate potential periods of metamorphic transformations within the life cycle; the transformation from larva to juvenile represents larval metamorphosis.



2. METAMORPHIC DIVERSITY IN TELEOSTS

In this section, we briefly survey the astonishing diversity of metamorphic remodeling among teleosts, set in the context of the ecological and life history transitions that they accompany (Table 5.1). The majority of described metamorphic transitions, *sensu* our definition, are metamorphoses from larva to juvenile. These larval metamorphoses commonly include the formation of adult fins (pectoral fins generally develop during embryogenesis) and ossification of fin rays, maturation of internal organs and sensory systems, formation of scales, modifications to pigment pattern, and allometric changes in body proportions. Accompanying these alterations are a multitude of group- and species-specific morphological and physiological changes, some of which we outline below.

2.1. Marine teleosts

Marine teleosts exhibit some of the most dramatic morphological transitions seen in vertebrates. These changes in phenotype facilitate ecological transitions: most marine fish—and indeed the majority of marine organisms—exhibit a dispersive planktonic or pelagic (open water) larval stage, then undergo metamorphosis and are recruited to an adult habitat (Thorson, 1950). Pelagic larvae often possess morphological specializations that maximize survival and dispersal potential: large larval fin folds, bony plates, and long spines frequently characterize dispersive larvae. Such larval-specific features are resorbed at metamorphosis (as in the grouper, Fig. 5.2; Moser, 1981; Webb, 1999). The larval stage can last several years in some fish species, allowing larvae to disperse over long distances (Webb, 1999).

In addition to the loss of larval features, larval metamorphosis of marine fishes often involves dramatic changes in pigmentation and overall morphology, with specific alterations to head shape and body depth (de Jesus, Toledo, & Simpas, 1998; Fukuhara & Fushimi, 1988; Wittenrich et al., 2010). Flattening in the dorsoventral plane prepares many species to become “demersal” adults, which inhabit the bottom of the water column, or “benthic” adults, which live close to or in contact with the substrate or the sea floor (Webb, 1999). One remarkable group of benthic teleosts flattens laterally rather than dorsoventrally during metamorphosis (flatfish morphology citations, Table 5.1). As Pleuronectiform flatfish mature, bilaterally symmetric larvae become markedly asymmetrical as one eye translocates across the dorsal midline to the opposite side of the head, resulting in an ocular side that

Table 5.1 Characteristics of larval metamorphosis in different teleost groups

Group	Habitat	Niche shift	Duration	Additional morphological changes*	Species and references
Carp	Freshwater	None	Days–weeks	None	Zebrafish <i>Danio rerio</i> : gross morphology (Parichy, Elizondo, Mills, Gordon, & Engeszer, 2009); fin development (Cubbage & Mabee, 1996; Goldsmith, Iovine, O’Reilly-Pol, & Johnson, 2006); pigmentation (Budi, Patterson, & Parichy, 2011; Parichy & Turner, 2003a); and lateral line (Nuñez et al., 2009; Webb & Shirey, 2003)
Catfish	Freshwater	Pelagic to benthic	Days–weeks	Growth of barbels	Indian catfish <i>Mystus punctatus</i> (Ramanathan, Natarajan, & Sukumran, 1985)
Coral reef fish	Marine	Pelagic to demersal	Hours–weeks	Dramatic adult pigmentation changes in many species	Multiple species (McCormick & Makey, 1997; McCormick, Makey, et al., 2002)
Eels	Catadromous	Marine to freshwater	Months–years	Leptocephalus/glass eel to elver/silver eel transition: Salinity tolerance	American eel <i>Anguilla rostrata</i> otolith morphology (Cieri & McCleave, 2000) Japanese eel <i>Anguilla japonica</i> otolith morphology (Arai, Otake, & Tsukamoto, 1997) Australian shortfin eels <i>Anguilla australis</i> (De Silva, Gunasekera, Gooley, & Ingram, 2001) Multiple species (Raju, 1974)

Continued

Table 5.1 Characteristics of larval metamorphosis in different teleost groups—cont'd

Group	Habitat	Niche shift	Duration	Additional morphological changes	Species and references
Flatfish	Marine	Pelagic to benthic	Weeks	Cranial development and eye migration, asymmetrical pigmentation	Atlantic halibut <i>Hippoglossus hippoglossus</i> (Sæle et al., 2004) Japanese flounder <i>Paralichthys olivaceus</i> (Tanaka, Kawai, Seikai, & Burke, 1996) Senegalese sole <i>Solea senegalensis</i> (Fernández-Díaz et al., 2001) Starry flounder <i>Platichthys stellatus</i> (Policansky & Sieswerda, 1979) Summer flounder <i>Paralichthys dentatus</i> (Keefe & Able, 1993; Martinez & Bolker, 2003) Multiple species (Schreiber, 2001)
Gobies	Amphidromous	Marine to freshwater	Days–weeks	Change in mouth position and fin shape	Freshwater goby <i>Sicyopterus lagocephalus</i> (Keith et al., 2008; Taillebois et al., 2011)
Groupers	Marine	Pelagic to benthic	Months	Loss of larval spines, dorsoventral flattening	Spotted grouper <i>Epinephelus tauvina</i> (Hussain & Higuchi, 1980) Leopard grouper <i>Mycteroperca rosacea</i> (Martínez-Lagos & Gracia-López, 2009) Hong Kong grouper <i>Epinephelus akaara</i> (Fukuhara & Fushimi, 1988)
Medaka	Amphidromous	None	Days–weeks	None	Medaka <i>Oryzias latipes</i> (Iwamatsu, 1994)
Sea Breams	Marine	Pelagic to benthic	Months	None	Gilt-head sea bream <i>Sparus aurata</i> (Fukuhara, 1991)

Salmonids	Anadromous	Freshwater to marine	Days– weeks	Parr to smolt transition: Changes in lipid content and salinity tolerance; erythrocyte modifications	Atlantic salmon <i>Salmo salar</i> : Morphology (Dêbowski et al., 1999); physiology (McCormick & Saunders, 1987; Virtanen, 1987) Coho salmon <i>Oncorhynchus kisutch</i> physiology (Sullivan, Dickhoff, Mahnken, & Hersbberger, 1985) Multiple species (McCormick & Saunders, 1987; Woo, Bern, & Nishioka, 1978)
Tilapia	Freshwater	None	Days– weeks	None	Tilapia <i>Oreochromis mossambicus</i> (Ramanathan et al., 1985)
Tuna	Marine	Planktonic to pelagic	Days– weeks	None	Pacific bluefin tuna <i>Thunnus thynnus</i> (Kaji, Tanaka, Takahashi, Oka, & Ishibashi, 1996; Kawakami, Nozaki, Seoka, Kumai, & Ohta, 2008; Miyashita, Sawada, Okada, Murata, & Kumai, 2001; Tanaka, Satoh, Iwahashi, & Yamada, 2006) Yellowfin tuna <i>Thunnus albacares</i> (Kaji et al., 1999)

* At metamorphosis, all groups acquire adult fins and fin rays, internal organs and sensory systems mature, scales and adult pigment pattern form and body proportions change; additional morphological changes lists specific modifications in addition to these common changes

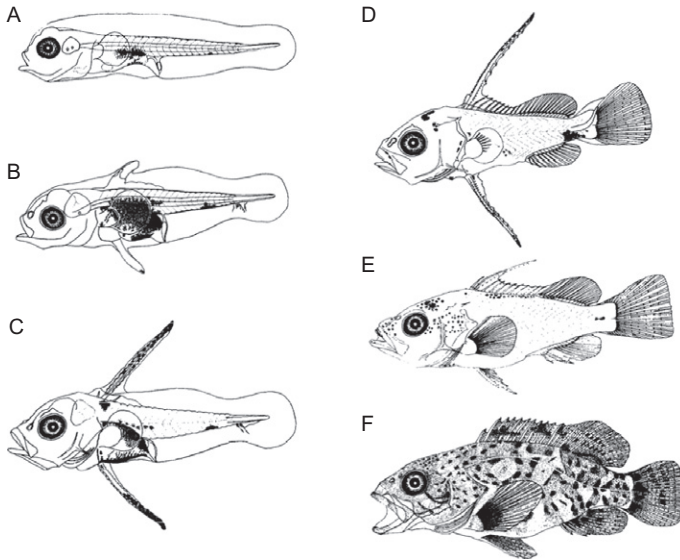


Figure 5.2 Metamorphosis of the brown-spotted grouper (*Epinephelus tauvina*). (A) Newly hatched larva, 2 mm; (B) 10-day-old larva; (C) 13-day-old larva; (D) 31-day-old metamorphosing individual; (E) 31 day old, 18 mm; and (F) 50 dpf juvenile, 31 mm. Images reprinted with permission from (Hussain & Higuchi, 1980)

will face the water column, and a blind side that will face the substrate (Fig. 5.3). During the transitional metamorphic period, fish swim at an increasing angle to ultimately settle onto the substrate. As in other teleosts, a new pattern of pigmentation develops during metamorphosis, but only on the ocular surface of the body (Table 5.1).

Particularly rapid and dramatic remodeling also occurs among coral reef fishes, which undergo changes in body shape and acquire conspicuous adult pigmentation (Leis & McCormick, 2006). Metamorphosis in reef fish enables the transition from a pelagic dispersal stage to a demersal, reef-associated adult form. This metamorphosis can be extremely rapid, with some species undergoing their metamorphic changes in pigmentation in as little as 6 h, or can last several weeks and include several intermediate stages; for example, goatfish and damselfish undergo 2–3 week metamorphic processes that include several intermediate shifts in habitat and morphology (McCormick & Makey, 1997; McCormick, Makey, & Dufour, 2002). Thus, marine teleosts exhibit an astonishing range of metamorphic transformations that often include substantial morphological changes allowing the exploitation of different spatial niches within an oceanic environment.

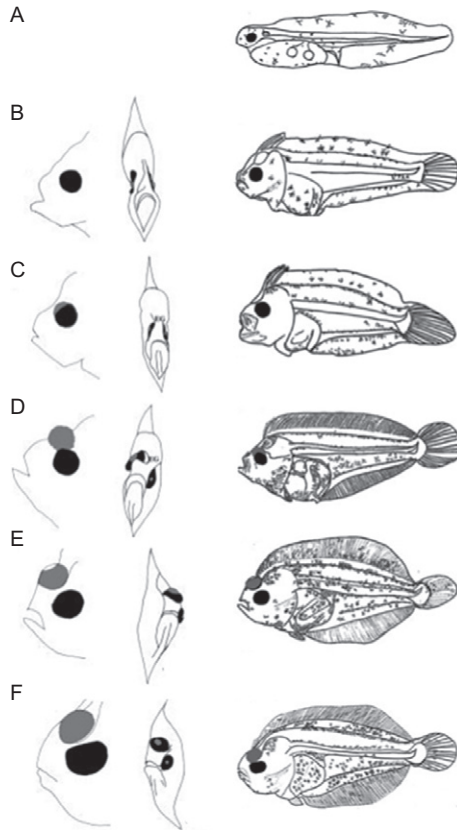


Figure 5.3 Metamorphosis of the summer flounder *Paralichthys dentatus*. (A) Hatched yolk-sac larva. (B) Pretransformation larva before eye migration commences. (C) Early metamorphosis and the beginning of eye migration. (D) Mid-metamorphosis. (E) Metamorphic climax, right eye has migrated over the dorsal midline. (F) Young juvenile. Left column in B–D shows the migration of the eye across the skull; migrating right eye is shaded in gray. Rightmost column shows whole-body morphological changes at each stage. Images reprinted with permission from (Martinez & Bolker, 2003)

2.2. Diadromous teleosts

Diadromous species migrate between salt water and fresh water environments; metamorphosis can prepare these fish to survive in their new habitat. The physical demands of a marine environment differ significantly from those of fresh water, and diadromous teleosts undergo substantial changes in morphology. These include changes in body shape, muscle, skin, and pigmentation; changes in the structure and function of numerous organs, including the kidneys, gut, eyes, and lateral line; and physiological changes in osmoregulation and metabolism.

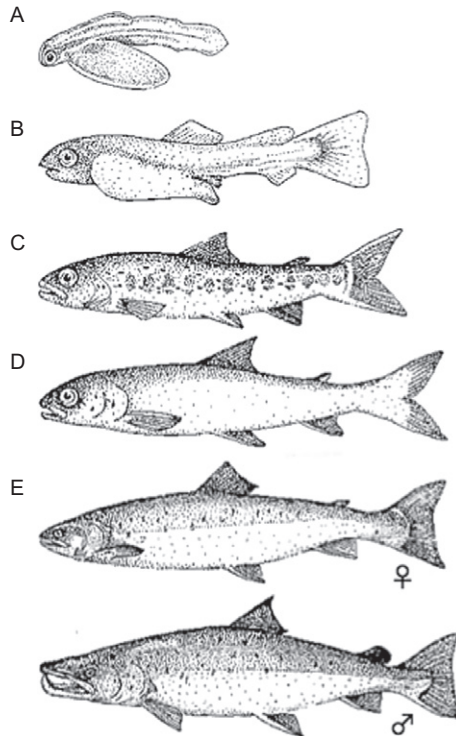


Figure 5.4 Life stages of Atlantic Salmon, *Salmo salmar*. (A) Alevin; (B) fry, 3–6 weeks old; (C) parr; (D) smolt, 1–3 years old; and (E) Breeding female and male. Images from public domain.

The best-studied example of a fresh-to-salt water (anadromous) migration is that of salmon. Salmon spawn in freshwater breeding grounds, where embryonic “alevin” hatch into larval “fry.” After months to several years of development, larval fry develop bars of pigmentation and are called “parr” (Fig. 5.4). Swimming downstream, parr undergo smoltification, which morphologically and physiologically prepares young “smolt” juveniles for the marine habitat. By our definition, the entire parr-to-smolt period constitutes a protracted larval metamorphosis, with different morphogenetic and physiological processes stimulated by different hormones (insulin, prolactin, TH, growth hormone (GH), and cortisol) that spike at different points during the months of parr development (see Björnsson, Einarsdottir, & Power, 2012; Dickhoff, Brown, Sullivan, & Bern, 1990). As fish metamorphose into smolts, purines are deposited in the skin, producing a silvery appearance, body fat decreases, gas bladder size increases, and body shape and condition change

to become leaner and sleeker (Björnsson, Einarsdottir, et al., 2012; Johnston & Saunders, 1981; McCormick & Saunders, 1987; Winans & Nishioka, 1987). In preparation for the hyperosmotic environment, smolts become able to absorb increased amounts of water through the intestine, and expression of ion channels (aquaporins) and ion pumps (Na^+/K^+ -ATPase) increases, allowing active excretion of salt (D’Cotta, Valotaire, le Gac, & Prunet, 2000; Tipsmark, Sørensen, & Madsen, 2010). During smoltification, salmon also begin synthesizing additional hemoglobin isoforms with enhanced oxygen affinity (Seear et al., 2010; Sullivan et al., 1985). If smolts do not reach salt water during a critical “smolt window,” they undergo desmoltification, which includes a loss of hypo-osmoregulatory abilities and metabolic adaptations, and a darkening of skin color (Stefánsson, Björnsson, Ebbesson, & McCormick, 2008). Although desmoltification includes the regression of certain physiological functions, fish do not revert to an overall smolt morphology; thus, desmoltification is not a reversal of metamorphosis. Returning to freshwater environments to spawn, marine salmonids undergo yet another transformation into the life stage known as “grilse,” preparing them for migration in fresh water and breeding. This transformation is controlled predominantly by the gonadotropic axes (Youngson, McLay, Wright, & Johnstone, 1988), and the majority of the morphological changes are sex-specific, so by our definition, this transformation primarily constitutes a puberty rather than a metamorphosis.

Eels represent a second well-studied instance of a diadromous life history. In contrast to salmonids, eels develop and disperse as marine larvae, then begin to metamorphose in preparation for a salt-to-fresh water (catadromous) migration. The leaf-shaped marine larvae (leptocephali) are dispersed by ocean currents and after up to 18 months of larval development, transform into transparent “glass eels” (Fig. 5.5; Wang & Tzeng, 2000). Glass eels undergo numerous morphological and physiological changes to preadapt them to freshwater environments, suggesting that the entire glass eel stage represents the metamorphic period. As glass eels are recruited to a freshwater habitat, they complete metamorphosis to become juvenile “elvers.” To return to oceanic environments for spawning, eels undergo the process of silvering and regain saltwater tolerance. Silvering has been described as a secondary metamorphic event, although it is stimulated by sex hormones and involves maturation of the gonads (Aroua et al., 2005; Rousseau, Aroua, Schmitz, Elie, & Dufour, 2009). This event may represent a second metamorphosis simultaneous with puberty.

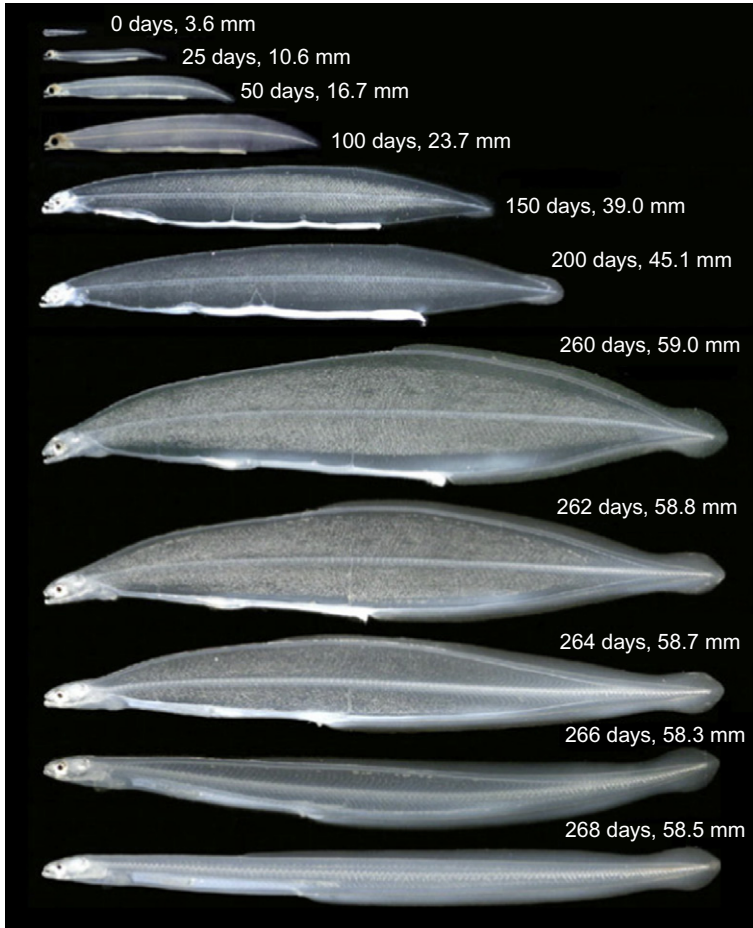


Figure 5.5 Developmental growth series of the Japanese eel *Anguilla japonica*. Larval leptocephali transform into the glass eel stage (bottom image shows a young glass eel). Reprinted with permission from (Tsukamoto et al., 2009).

2.3. Freshwater teleosts

In contrast with their marine and diadromous counterparts, freshwater teleosts generally undergo more phenotypically subtle metamorphoses. Few larva-specific adaptations are found in freshwater teleosts, reflecting the fact that freshwater fish do not generally have an explicitly dispersive larval stage. Nonetheless, freshwater teleosts undergo numerous morphological and physiological changes during larval metamorphosis, modifications that have been described most extensively in the developmental genetic model species zebrafish *Danio rerio* (Fig. 5.6; Parichy et al., 2009). Like other teleosts,

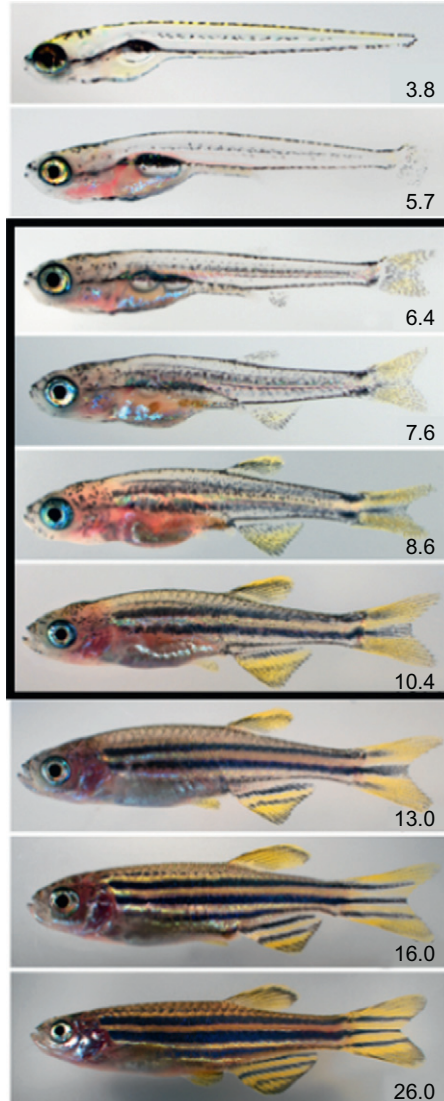


Figure 5.6 Postembryonic development in the zebrafish (*Danio rerio*). Numbers indicate standard length in mm, with the period of peak metamorphic remodeling during the larva-to-juvenile transition indicated by the black box. At standard temperature and typical rearing densities, this transition begins at about 10–14 days and takes about 2 weeks. As postembryonic fish can develop and grow at markedly different rates, days of development is an inadequate staging criterion; stages based on morphological criteria, and their size equivalents have been defined for this species and are preferable for developmental studies (Parichy et al., 2009).

zebrafish undergo significant changes in body shape, losing larval fin folds, developing or completing development of adult fins and fin rays (Cubbage & Mabee, 1996; Goldsmith et al., 2006; Patterson, Mook, & Devoto, 2008), ossifying the axial skeleton (Bird & Mabee, 2003; Elizondo et al., 2005), forming an adult pigment pattern (Budi, Patterson, & Parichy, 2008; Budi et al., 2011; Johnson, Africa, Walker, & Weston, 1995; Parichy & Turner, 2003b), acquiring scales (Sire & Akimenko, 2004), and exhibiting maturation and remodeling of many organs, including the lateral line (Ledent, 2002; Nuñez et al., 2009; Webb & Shirey, 2003), central and peripheral nervous systems (Larson, Gordon, Lau, & Parichy, 2010), gut, kidneys, and swimbladder (Parichy et al., 2009; Robertson, McGee, Dumbarton, Croll, & Smith, 2007). Freshwater teleosts tend to have less distinct periods of larval metamorphosis than marine or diadromous species, but this postembryonic process still unequivocally occurs, transforming the larval organism into a morphologically distinct juvenile form. There are at least a few identified cases of paedomorphism in freshwater species, with miniature *Paedocypris* and *Danionella* fish failing to undergo normal metamorphosis and becoming reproductively mature while maintaining a larva-like overall morphology (Britz, Conway, & Rüber, 2009; Mayden & Chen, 2010; Rüber et al., 2007). These paedomorphic genera illustrate ways in which even relatively subtle metamorphic processes may be modified to effect major morphological change.



3. ENDOCRINE CONTROLS OF TELEOST METAMORPHOSIS

The coordinated occurrence of multiple disparate organ- and tissue-specific events during teleost life-stage transitions suggests that “local” processes are likely to be coordinated by “global” signals (and so are likely to constitute bona fide metamorphoses, as defined above). Research into the endocrine controls of postembryonic transitions in teleosts has focused almost exclusively on spectacular examples of such metamorphoses; for example, salmonid smoltification and flatfish metamorphosis. Yet, there is evidence that more subtle transitional processes are controlled by conserved endocrine mechanisms as well. Here, we outline what is known about the hormonal contributions to teleost metamorphosis. TH appears to be a key regulator of teleost metamorphosis, and most endocrine studies of metamorphosis have focused on this factor. Thus, we briefly review the

metabolism of TH in teleosts, and the expression of TH-associated factors before outlining what is known about other endocrine contributions to metamorphosis.

3.1. Thyroid hormone

It became clear in the late 1980s that TH, which stimulates the metamorphosis of amphibians, also promotes metamorphosis of flatfish. Application of exogenous TH accelerates metamorphic events, including fin resorption, eye migration, and fin ray shortening (Inui & Miwa, 1985; Inui, Tagawa, Miwa, & Hirano, 1989; Klaren, Wunderink, Yüfera, Mancera, & Flik, 2008; Miwa, Yamano, & Inui, 1992). TH is also necessary for flatfish metamorphosis: treatment with TH-inhibiting goitrogens arrests metamorphosis, resulting in oversized pelagic larvae (Inui & Miwa, 1985).

Further studies showed that spikes in thyroid activity or circulating TH levels are associated with the larval metamorphosis of many teleost species, including those with spectacular transformations (salmonids, eels, flatfish) and those with more subtle metamorphoses (fatheads, greenlings, groupers, minnow, sea breams, tilapia, tuna, zebrafish; see Fig. 5.7 and hormone titer citations in Table 5.2). Treatment with exogenous TH stimulates metamorphic processes, while inhibition of TH synthesis with goitrogens inhibits metamorphosis in numerous groups: eels, gobies, greenlings, groupers, and salmon (morphological responses to TH manipulation citations, Table 5.2). Metamorphic changes in fins, pigmentation, and body size in zebrafish are inhibited by goitrogen treatment as well (Brown, 1997; D.M. Parichy, unpublished data). Evolutionary modifications of TH signaling effected by *cis*-regulatory changes at the thyroid-stimulating hormone $\beta 2$ locus have also been implicated in the adaptive divergence of marine and freshwater stickleback populations (Kitano et al., 2010). Together, these studies suggest that TH involvement in metamorphosis is widespread among teleosts, and that changes in this pathway can contribute to evolutionary diversification. Interestingly, lampreys, relatives of early teleosts, undergo a metamorphosis in which TH plays an inhibitory rather than a stimulatory role (see Youson, 1997); the mechanistic bases for this divergent TH effect, and whether other factors substitute for TH in promoting metamorphosis, remain unknown.

TH synthesis and metabolism in teleosts are similar to that of tetrapods (Yen, 2001). The genes that contribute to thyroid follicle patterning and

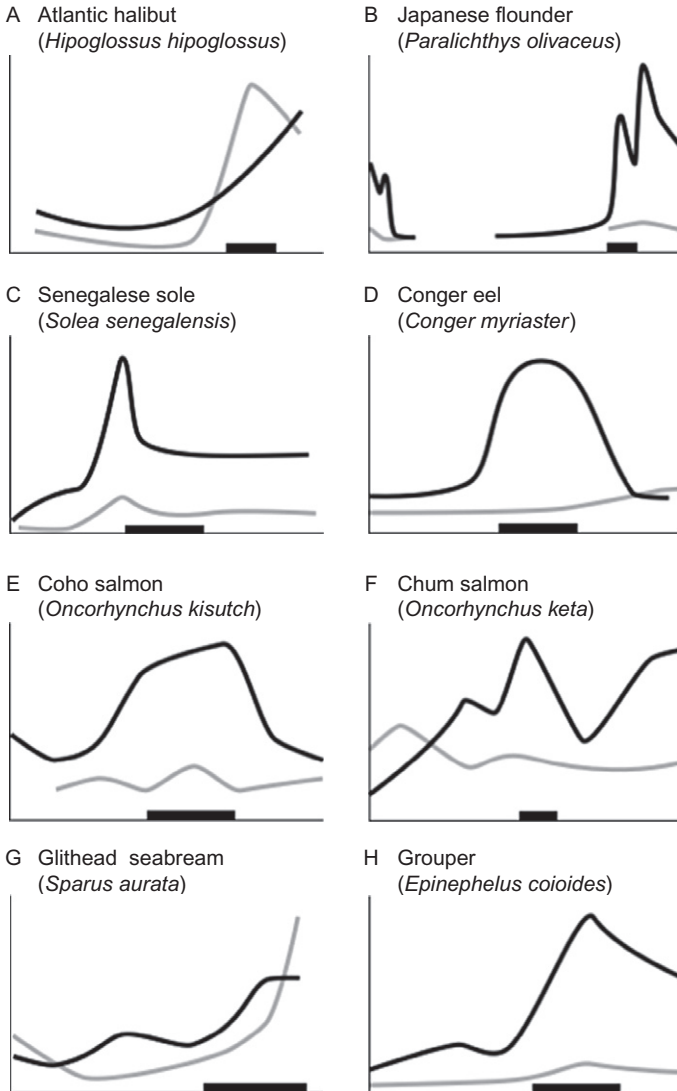


Figure 5.7 Relative whole-body concentrations of thyroid hormone in different teleosts during larval and juvenile development. Developmental stage is indicated by the x-axis and the horizontal black bar shows the approximate climax of the metamorphic period. Black line indicates relative level of thyroxine (T4); gray line indicates relative level of triiodothyronine (T3); lines redrawn from original figures. Relative concentrations shown for three flatfish: (A) Halibut (Galay-Burgos, Power, Llewellyn, & Sweeney, 2008); (B) Flounder (Yamano & Miwa, 1998); and (C) Sole (Klaren et al., 2008). Also shown are (D) Eel (Kawakami, Tanda, Adachi, & Yamauchi, 2003), two species of salmon: (E) Coho salmon (Harada, Yoshinaga, Ojima, & Iwata, 2008) and (F) Chum salmon (Parhar & Iwata, 1996); (G) Seabream (Szisch, Papandroulakis, Fanouraki, & Pavlidis, 2005); and (H) Grouper (de Jesus et al., 1998).

Table 5.2 Selected studies that have examined hormone involvement or gene expression during teleost larval metamorphosis

Family	Assessment	Species and references
Carp (Cyprinidae)	Hormone titer	TH (zebrafish <i>Danio rerio</i>) (Chang et al., 2012) TH (minnow <i>Pimephales promelas</i>) (Crane, Pickford, Hutchinson, & Brown, 2004)
	Morphological response to TH manipulation	Overall morphology: (Brown, 1989); Larval survival and growth: (Lam and Sharma, 1985)
Cichlids (Cichlidae)	Hormone titer	TH (Shiao, Wu, Hwang, Wu, & Hwang, 2008)
	Morphological response to TH manipulation	Overall morphology (Okimoto, Weber, & Grau, 1993) Otolith development (Shiao et al., 2008)
Eels (Anguilloidei)	Hormone titer	TH (Aroua et al., 2005; Jegstrup & Rosenkilde, 2003; Yamano, Nomura, & Tanaka, 2007; Yamano, Tagawa, et al., 1991) Cortisol (Yamano, Tagawa, et al., 1991) GH, TSH, and sex hormones (Aroua et al., 2005)
	Morphological response to TH manipulation	Overall morphology and pigmentation (Jegstrup & Rosenkilde, 2003; Kitajima, Sato, & Kawanishi, 1967)
Flatfish (Order: Pleuronectiformes)	Hormone titer	TH (de Jesus, Hirano, & Inui, 1991; Klaren et al., 2008; Miwa, Tagawa, Inui, & Hirano, 1988) GH and IGF (Hildahl, Sweeney, Galay-Burgos, Einarsdóttir, & Björnsson, 2007) Cortisol (de Jesus et al., 1991)
	Morphological response to TH manipulation	Eye migration and overall morphology (Inui & Miwa, 1985; Inui et al., 1989; Schreiber & Specker, 1998; Solbakken, Norberg, Watanabe, & Pittman, 1999; Tagawa & Aritaki, 2005) Gastric development (Miwa et al., 1992) Pigmentation (Yoo, Takeuchi, Tagawa, & Seikai, 2000) Muscle development (Yamano, Miwa, Obinata, & Inui, 1991) Fin rays (de Jesus, Hirano, & Inui, 1993; de Jesus, Inui, & Hirano, 1990) Erythrocyte development (Miwa & Inui, 1991)

Continued

Table 5.2 Selected studies that have examined hormone involvement or gene expression during teleost larval metamorphosis—cont'd

Family	Assessment	Species and references
	Gene expression	<p>TRs (Galay-Burgos et al., 2008; Marchand, Duffraisse, Triqueneaux, Safi, & Laudet, 2004; Yamano & Miwa, 1998)</p> <p>Deiodinases (Itoh, Watanabe, Wu, & Suzuki, 2010)</p> <p>GH receptors (Hildahl, Power, Björnsson, & Einarsdóttir, 2008; Hildahl et al., 2007; Manchado, Infante, Asensio, Planas, & Cañavate, 2008; Manchado, Infante, Rebordinos, & Cañavate, 2009)</p> <p>CK-M1 (Chen et al., 2010)</p> <p>Elongation factor 1 alpha genes (Infante, Asensio, Cañavate, & Manchado, 2008)</p> <p>Heat shock proteins (Manchado, Salas-Leiton, et al., 2008)</p> <p>Trypsinogens (Manchado, Infante, Asensio, et al., 2008)</p> <p>Keratin (Infante, Manchado, Asensio, & Cañavate, 2007)</p> <p>Myogenic regulatory factors (Andersen et al., 2009)</p>
Fatheads (Platycephalidae)	Hormone titer	TH (Taillebois et al., 2011)
	Morphological response to TH manipulation	Overall morphology (Taillebois et al., 2011)
Groupers	Hormone titer	TH (de Jesus et al., 1998)
	Morphological response to TH manipulation	Overall morphology (de Jesus et al., 1998; Trijundo, Yosedá, Hirokawa, Tagawa, & Tanaka, 2002)
Greenlings (Hexagrammidae)	Hormone titer	TH (Matsumoto & Tanaka, 1996)
	Morphological response to TH manipulation	Overall morphology and settling behavior (Matsumoto & Tanaka, 1996)

Salmonids (Salmonidae)	Hormone titer	<p>TH (Boeuf, Le Bail, & Prunet, 1989; Dickhoff, Folmar, & Gorbman, 1978; Dickhoff, Folmar, Mighell, & Mahnken, 1982; Grau, Specker, Nishioka, & Bern, 1982; Lin et al., 1988; McCormick, Moriyama, & Björnsson, 2000; Prunet, Boeuf, Bolton, & Young, 1989; Quigley, Harvey, Hayden, Dowling, & O’Keane, 2006; Specker & Schreck, 1982; Virtanen & Soivio, 1985; Young, Björnsson, Prunet, Lin, & Bern, 1989)</p> <p>GH (Ágústsson et al., 2001; Boeuf et al., 1989; McCormick et al., 2000; McCormick, Shrimpton, Moriyama, & Björnsson, 2002; Prunet et al., 1989; Sweeting & McKeown, 1989; Young et al., 1989)</p> <p>Cortisol (McCormick et al., 2000; McCormick, Shrimpton, Moriyama, & Björnsson, 2002; Specker & Schreck, 1982; Virtanen & Soivio, 1985; Young et al., 1989)</p> <p>Prolactin (Prunet et al., 1989; Young et al., 1989)</p> <p>IGF-I (Ágústsson et al., 2001; McCormick et al., 2000; McCormick, et al., 2002)</p>
	Morphological response to TH manipulation	<p>Growth and salinity tolerance (Saunders, McCormick, Henderson, Eales, & Johnston, 1985)</p> <p>Salinity preference (Baggerman, 1960)</p> <p>Adult hemoglobin expression (Sullivan et al., 1985)</p>
	Gene expression	<p>Microarray of multiple genes (Seear et al., 2010)</p> <p>Aquaporins (Tipsmark et al., 2010)</p>
Sea Breams (Sparidae)	Hormone titer	<p>TH (Campinho, Galay-Burgos, Sweeney, & Power, 2010; Deane & Woo, 2003)</p> <p>Cortisol (Deane & Woo, 2003)</p>
	Gene expression	<p>TRs and deiodinases (Campinho et al., 2010)</p> <p>HSPs (Deane & Woo, 2003)</p>
Tuna (Scombridae)	Hormone titer	<p>TH (Kawakami, Nozaki, et al., 2008)</p>
	Morphological response to TH manipulation	<p>Eye pigmentation (Kawakami, Yokoi, Kumai, & Ohta, 2008)</p>

development are highly conserved between teleosts and mammals (Alt et al., 2006; Porazzi, Calebiro, Benato, Tiso, & Persani, 2009), as are the deiodinases that regulate TH activity (Itoh et al., 2010; Orozco & Valverde-R, 2005; Power et al., 2008). In response to pituitary thyrotropin (TSH), thyroid follicles produce TH in the form of thyroxine (T4). Circulating plasma levels of T4 increase markedly at the onset of metamorphosis in several teleost species (Fig. 5.7), suggesting that the thyroid is highly active during this period. This is further consistent with the results of radioiodide uptake assays (Brown, 1997; D.M. Parichy, unpublished) and enzyme-linked immunoassays performed in zebrafish (Chang et al., 2012). T4 is converted in peripheral tissues by deiodinase enzymes (DIO1 and DIO2) into the genomically active form, tri-iodothyronine (T3). Both T3 and T4 are inactivated by a third deiodinase, DIO3. Thus, the expression and activity of deiodinases regulate TH bioactivity and availability. In teleosts, these genes are expressed in spatially and temporally specific manners during postembryonic development, with *dio1* and *dio2* increasing in expression immediately before and during metamorphic climax of several species (Campinho et al., 2010; Itoh et al., 2010).

T3 serves as the ligand for nuclear TH receptors (TRs), which typically activate expression of target genes in the presence of the hormone, and repress expression in its absence. All teleosts examined possess at least two isoforms of TRs: TR α and TR β , and many possess additional copies of these loci, possibly owing to an ancient, teleost-specific genome duplication (Hoegg, Brinkmann, Taylor, & Meyer, 2004; Ravi & Venkatesh, 2008); for example, zebrafish exhibit two TR α loci, *thraa* and *thrab*, though only a single TR β locus, *thrb*. In species that have been examined so far, TRs increase in expression prior to and during metamorphic climax (Fig. 5.8). Thus, TR-mediated TH signaling appears to play a critical role in the metamorphosis of teleosts examined. Nevertheless, although TH is by far the best-studied hormonal factor in teleosts, TSH and TH titers and expression of DIOs and TRs remain undocumented for the vast majority of teleost families. Thus, the requirement or sufficiency for TH in metamorphosis remains unknown in most fish; moreover, the genetic targets and molecular mechanisms of hormonal action remain largely unclear.

3.2. Non-TH mediators of metamorphosis

In addition to TH, other endocrine factors contribute to metamorphosis as well. GH activates insulin-like growth factor (IGF) pathways, stimulating cellular proliferation and increasing basal metabolic rate. Spikes in plasma

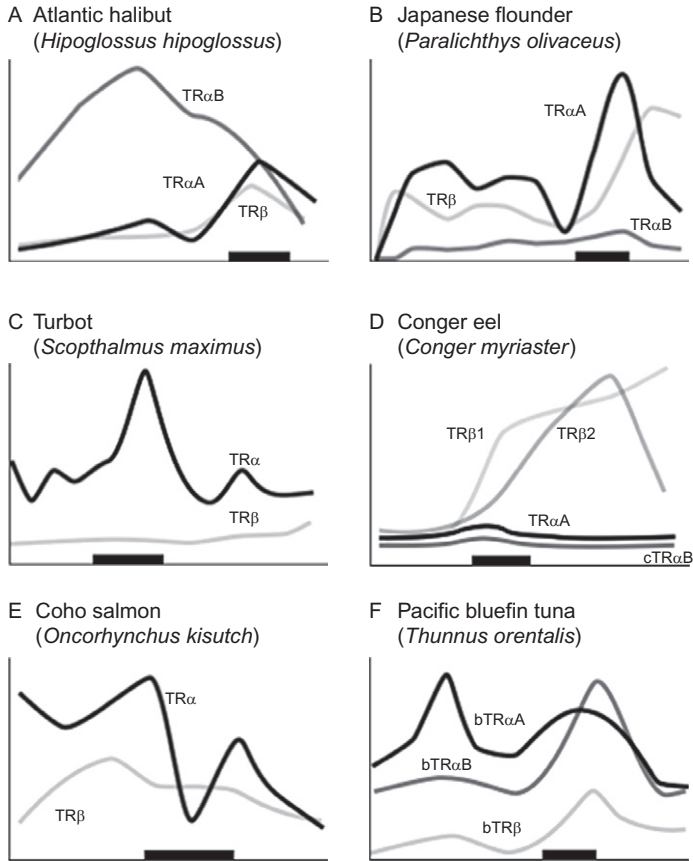


Figure 5.8 Relative different thyroid hormone receptor genes during larval and juvenile development. Expression is from whole-body assays unless otherwise noted; lines redrawn from original figures. The x-axis shows developmental progression and the thick black bar shows the approximate climax of the metamorphic period. Relative gene expression in three flatfish: (A) Halibut (Galay-Burgos et al., 2008), (B) Flounder (gene expression in head; Yamano & Miwa, 1998), and (C) Turbot (Marchand et al., 2004), and three other teleosts: (D) Eel (Kawakami et al., 2003), (E) Salmon (gene expression in brain; Harada et al., 2008), and (F) Tuna (Kawakami, Nozaki, et al., 2008). The absence of a particular receptor subtype on a graph does not necessarily mean that the species does not possess that isoform.

GH and IGF-I are observed during salmonid parr-to-smolt metamorphosis (Table 5.2). Further, treating parr with exogenous GH induces metamorphic changes, including changes in body shape, pigmentation, and seawater tolerance (Boeuf, 1993; Donaldson, Fagerlund, Higgs, & McBride, 1979; Dufour & Rousseau, 2007). Genetic loss of GH likewise delays metamorphic stage transitions in zebrafish; though this may be a secondary effect of delayed

growth (McMenamin and Parichy, unpublished). In flatfish, GH receptors peak in expression immediately prior to the onset of metamorphosis, as do concentrations of IGF (Hildahl et al., 2007). The hormone prolactin antagonizes GH, and appears to have a negative influence on salinity tolerance and overall smoltification in salmonids (Björnsson, Stefansson, & McCormick, 2011; Madsen & Bern, 1992). The GH/IGF axis thus plays important roles in promoting growth and regulating metabolism during postembryonic development in teleosts (Yousefian & Shirzad, 2011), and its potential roles in directly stimulating morphogenetic events merit further investigation.

Another factor that may contribute to metamorphic progression is cortisol, known primarily for its roles in stress response. Cortisol titer increases during salmon smoltification, and may directly contribute to physiological metamorphosis (Richman, de Diaz, Nishioka, & Bern, 1985; Specker, 1982). Flatfish also exhibit peak cortisol levels at metamorphic climax, potentially indicating a stimulatory role in this process (de Jesus et al., 1991). Indeed, stress hormones are known to contribute to metamorphosis of some anuran amphibians (Denver, 1993, 1997). In eel leptocephali, however, cortisol levels decrease prior to metamorphosis and remain low throughout metamorphosis (Yamano, Tagawa, et al., 1991). Thus, stress hormones may play synergistic roles with TH during the metamorphosis of some teleosts (Dufour & Rousseau, 2007), but these roles require further investigation and particularly experimental manipulation.

In summary, it is clear that several hormonal axes are activated immediately before, during, and following metamorphic climax in the teleosts that have been studied to date. These hormonal axes, and specifically TH pathways, likely play roles in orchestrating metamorphosis, and may integrate external environmental cues into coordinated sets of disparate morphogenetic events. Nevertheless, the evolutionary conservation of these roles, the interactions between the hormonal axes, and the proximate mechanisms of endocrine response remain unclear.



4. LOCAL MECHANISMS OF MORPHOGENETIC CHANGES

The morphogenetic changes that occur at metamorphosis include major remodeling of existing features as well as the formation of entirely new tissues and organs; thus, metamorphosis requires extensive differentiation as well as the morphogenetic processes of cellular migration, proliferation, growth, and death. For the overwhelming majority of metamorphic events, however, the underlying cellular mechanics and genetic mechanisms remain unexplored by modern methods. Here, we discuss the relatively few areas in

which the cellular or genetic bases underlying metamorphic changes are being thoroughly investigated, and we highlight some of the many outstanding questions that remain to be answered.

4.1. Flatfish cranial asymmetry

The most thoroughly studied teleost metamorphic process is undoubtedly the unique cranial transformation of the flatfish. Although flatfishes are exceptional in their external morphological asymmetry, the internal organs of all vertebrates are asymmetric to different degrees. This internal asymmetry originates during early embryogenesis with the asymmetric expression of genetic cascades that initiate asymmetric expression of the homeobox-containing transcription factor *Pitx2* (Ryan et al., 1998). Flatfishes exploit this internal asymmetry to ultimately achieve external asymmetry at metamorphosis (Hashimoto et al., 2002; Suzuki et al., 2009). *Pitx2* is reexpressed at metamorphosis in a fundamentally asymmetric portion of the brain, and this reexpression appears to initiate eye migration (Suzuki et al., 2009). Cellular proliferation in the suborbital tissue of one side of the cranium may “push” one eye across the dorsal midline (Bao et al., 2011). Whether this proliferation is stimulated by TH directly or whether intermediary signals are involved remains unknown, but GH and IGF pathways likely serve as more proximal factors (Hildahl et al., 2008). In several flatfish mutants, cranial asymmetry is decoupled from internal organ asymmetry, suggesting that the two are regulated by independent mechanisms (Hashimoto et al., 2002). Elucidating the local pattern-forming and morphogenetic cues that determine the definitive form of the adult craniofacial skeleton, and how these factors depend on global hormonal effectors, clearly represents an exciting area for future research.

4.2. Skin

Larval teleosts have a simple integumentary structure, composed primarily of epidermis; at metamorphosis, the skin becomes increasingly stratified and complex (Chang & Hwang, 2011; Hawkes, 1974; Rakers et al., 2010). Collagen fibrils are deposited in orthogonal arrays under the epidermis (Le Guellec, Morvan-Dubois, & Sire, 2004) and the acellular stroma is then invaded by fibroblasts of unknown origin (but potentially originating from the neural crest; Matsumoto et al., 1983). Later, in metamorphosis, these fibroblasts initiate scale formation, potentially regulated

by expression of sonic hedgehog among other factors (Sire & Akimenko, 2004). The processes of skin stratification have been studied in greatest detail in zebrafish, but appear at least structurally similar in cichlids (Sire & Géraudie, 1983). Keratins mediate some of the skin restructuring events, and in flatfish, keratin expression is regulated directly by TH (Infante et al., 2007), decreasing after metamorphic climax (Campinho, Silva, Sweeney, & Power, 2007). The metamorphic transformation of flatfish skin resembles the metamorphic restructuring seen in amphibians (Power et al., 2008), in which keratin loci are also under TH control (Page et al., 2007). Nevertheless, further research is needed to determine the precise roles of TH in promoting integumentary metamorphosis of teleosts. In this regard, genetically tractable species such as zebrafish offer outstanding potential for studying skin metamorphosis; indeed, a variety of mutants with defects in the formation of scales and other postembryonic integumentary cell lineages have been identified (Harris et al., 2008; Lang, Patterson, Gordon, Johnson, & Parichy, 2009). As many features of skin development are conserved even with mammals, and mammalian skin undergoes a similar period of increased stratification and barrier function acquisition during fetal stages, studies of teleost skin metamorphosis may have translational relevance as well (Hoath & Maibach, 2003; Rakers et al., 2010).

4.3. Pigmentation

The formation of adult pigmentation is another common feature of teleost metamorphosis. Some of the genetic mechanisms underlying metamorphic pigmentation have been dissected in zebrafish, in which adult pigment patterns result from the spatial arrangements of neural crest-derived black melanophores, yellow xanthophores, and iridescent iridophores. During embryonic stages of neural crest migration, precursors to adult pigment cells are established in part owing to ErbB signaling (Budi et al., 2008; Hultman et al., 2009). Subsequently, these precursors are associated with peripheral nerves and, at metamorphosis, migrate to the skin along stereotypical pathways to form the adult pigment pattern, a process that can be directly visualized owing to the existence of fluorescent lineage reporters and the relative transparency of even metamorphic stage zebrafish (Budi et al., 2011). Embryonic and adult pigment cells have partially nonoverlapping genetic requirements, demonstrated by the phenotypes of several zebrafish mutants in which normal embryonic pigment cells develop yet adult precursors

either fail to be established or fail to be recruited. In these mutants, pigment pattern metamorphosis is effectively decoupled from overall somatic metamorphosis (e.g., Budi et al., 2008; Larson et al., 2010; Parichy & Turner, 2003b). Once latent precursors have been recruited, a variety of genes acting both within the pigment cells and in the tissue environments through which these cells migrate are required to organize the different pigment cell classes into distinct juvenile and adult stripes (Eom et al., 2012; Iwashita et al., 2006; Lang et al., 2009; Parichy, Rawls, Pratt, Whitfield, & Johnson, 1999; Parichy & Turner, 2003a; Watanabe et al., 2006).

Phylogenetic comparisons reveal that adult pigment patterns of zebrafish relatives similarly depend on the recruitment of latent pigment cell precursors at metamorphosis. Interestingly, however, these cells have been mostly lost in the closely related *Danio nigrofasciatus*, in which the adult pigment pattern arises at metamorphosis largely through the rearrangement of embryonic/early larval melanophores that persist into the adult. Interspecific cell transplantation shows that the difference in adult melanophore development between zebrafish and *D. nigrofasciatus* lies extrinsic to the pigment cells, implicating a change in a still-unidentified tissue or cell type that influences metamorphic processes within the pigment cell lineage (Quigley et al., 2004). This example highlights the potential for comparative studies to reveal the cellular, and ultimately genetic, bases underlying evolutionary changes in metamorphic transformations.

In contrast to other teleosts, flatfish develop pigmentation in an asymmetric manner at metamorphosis, with only the ocular (upper) side normally developing adult melanophores. In flounder, pigment cell precursors migrate symmetrically to both lateral sides from the bases of fins at the dorsal and ventral margins of the flank, yet these cells differentiate as melanophores only on the ocular side (Watanabe et al., 2008; Yamada, Okauchi, & Araki, 2010). The genetic bases for this differential response of pigment cells remain unknown.

Development of metamorphic pigmentation in zebrafish is retarded by goitrogens that prevent TH synthesis (Brown, 1997). Whether TH is directly required by pigment cells or their precursors, or whether the hormone exerts an influence indirectly through other cellular intermediaries, is an active area of investigation. Treatment with high (hyper-physiological) levels of T4 actually inhibits adult melanophore development in flatfish (Yoo et al., 2000), eels (Jegstrup & Rosenkilde, 2003) and zebrafish (D.M. Parichy, unpublished data), but the biological significance of these observations remains obscure. Likewise, the genetic and cellular mechanisms

of metamorphosis giving rise to the many and varied adult pigment patterns of other teleosts are largely unknown, though mutational and transgenic resources for some (Kelsh, 2004; Kelsh et al., 2004; Odenthal et al., 1996; Parichy, 2006), and evolutionary genetic strategies for others (Miller et al., 2007; Roberts, Ser, & Kocher, 2009), offer significant potential for future advances in this area.

4.4. Fin ray formation

Before and during metamorphosis, mesenchymal cells give rise to the fin endoskeleton, with rays growing from proximal to distal. Numerous pathways regulate positioning and outgrowth of these rays and the joints within the rays (Marí-Beffa & Murciano, 2010; Sims, Eble, & Iovine, 2009). Early proximo-distal patterning in the fin bud, largely controlled by Fgf signaling, is thought to establish a “prepattern” for ray positioning. Sonic hedgehog receptors are expressed in the proximal blastema, potentially inducing the differentiation of bone-forming cells (Laforest et al., 1998). Many of these morphogenetic processes are reactivated during fin regeneration (Iovine, 2007), and studying the normal metamorphic processes can lend insight into regenerative processes. Interestingly, fin regeneration in zebrafish is accompanied by enhanced expression of DIO3 and regenerative progress is retarded when DIO3 activity is blocked pharmacologically (Bouzaffour, Rampon, Ramaugé, Courtin, & Vríz, 2010), suggesting that local T3 degradation promotes regeneration. By contrast, growth cone formation of the regenerating lateral line is stimulated by TH (Bouzaffour et al., 2010). Remaining unknown is the extent to which hormonal mediators associated with normal metamorphosis are required during regeneration of other tissues and how precisely these contribute to particular cellular behaviors. The roles of these factors during normal fin development remain largely unknown, but will be interesting to uncover, particularly in light of the diversity of fin morphologies among teleosts more generally.

In summary, larval metamorphosis in teleosts involves coordinated morphological changes to many different organs; we now understand only a few of the genetic requirements for these transitions. The mechanisms by which these cascades are hormonally activated and coordinated remain largely unknown. Particularly, considering the growing number of molecular resources for nonmodel organisms (Sarropoulou, Nousdili, Magoulas, & Kotoulas, 2008; Voff, 2005), the genetics of metamorphic events and transitions in teleosts represents a promising field for future study.



5. CONCLUSIONS

Teleosts undergo a spectacular diversity of postembryonic metamorphic transitions, but most of these transitions have been described only superficially. Even in the most familiar teleosts, the proximate endocrine and genetic mechanisms for different elements of metamorphosis have yet to be described. Nonetheless, this period of profound remodeling encompasses many inherently interesting developmental phenomena involving fundamental processes of morphogenesis and differentiation. Moreover, this period of coordinated tissue modification offers the opportunity to examine differential tissue responses to global endocrine signals. Genetic modifications to these postembryonic processes have contributed to the spectacular diversity in adult morphology seen within teleost lineages, and elucidating their attendant molecular mechanisms will lend considerable additional insight into this diversification (Harris, 2012). Although the weight of evidence supports roles for TH signaling in promoting metamorphosis in teleosts, roles for other factors remain likely but uncertain, and the precise mechanisms by which TH effects particular morphogenetic or physiological outcomes remain largely unknown. Given the diversity of teleost metamorphoses and the particular tractability of some species (such as zebrafish) for analyses of developmental, genetic, and endocrine mechanisms, it seems certain that further studies of teleosts will provide important insights into the evolution of metamorphosis and, more generally, the diversification of physiology, behavior, and form.

GLOSSARY

Adult Reproductively mature form of an organism, possessing all adult organs and mature gonads. Adults are not always in breeding condition as many species are seasonal spawners.

Amphidromous Fish that migrate back and forth between fresh and salt water habitats, not necessarily for the purposes of breeding.

Anadromous Fish that spawn in fresh water, then migrate to marine habitats.

Benthic Associated with the lower layers of the water column, just above the substrate.

Catadromous Fish that spawn in marine environments, then migrate to fresh water habitats.

Demersal Associated with the very bottom of the water column, close to or in physical contact with the substrate.

Diadromous Fish that migrate between salt water and fresh water environments (catadromous and anadromous).

- Embryo** Developmental stage characterized by yolk sac and chorion. Non-feeding; acquires nutrients exclusively from yolk. Sometimes called *alevin*, *yolk sac fry*, or *sac fry*.
- Juvenile** Developmental stage at which the majority of adult organs have developed and organism is proportionally similar to an adult, but is not yet sexually mature. Salmonid juveniles are called *smolts*; eel juveniles are called *elvers* and *yellow eels*.
- Larva** Developmental stage characterized by free swimming and active feeding. Larvae are able to obtain and digest exogenous food and are often transparent or lightly pigmented. Generally show substantial morphological differences from adults. Larvae may also be called *fry*, salmonid larvae may be called *fingerlings* or *parr*, eel larvae are called *leptocephali*.
- Metamorphosis** An irreversible developmental and physiological change that affects multiple traits during postembryonic development and is brought about by one or more systematically acting endocrine mediators, but is independent of sexual maturation, sex-specific modifications, or senescence. May occur multiple times throughout during a life cycle, and may be simultaneous with puberty. The most common type of metamorphosis is larval metamorphosis, during which time a teleost transforms from larva to juvenile.
- Pelagic** Associated with the upper layers of the water column and open water. Many marine organisms have a pelagic open ocean larval stage of life.
- Puberty** The process of transforming from juvenile to adult, involving the maturation of the gonads and reproductive organs. Controlled by sex hormones in the gonadotropic axis.

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