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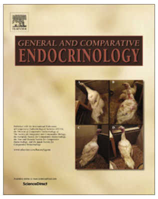

Minireview

# Primary males guide the femaleness through the regulation of testicular Dmrt1 and ovarian Cyp19a1a in protandrous black porgy

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ABSTRACT

Controlling the development of the sexes is critically important for the broodstock management in aquaculture. Sex steroids are widely used for sex control of fish. However, hermaphroditic fish have a plastic sex, and a stable sex is difficult to maintain with sex steroids. We used the black porgy (*Acanthopagrus schlegelii*) as a model to understand the possible mechanism of sexual fate decision. Low exogenous estradiol (E2) induced male development. In contrast, high exogenous E2 induced the regression of the testis and the development of the ovary and resulted in an unstable expression of femaleness (passive femaleness, with ovaries containing only the primary oocytes). The removal of testicular tissue by surgery resulted in the early development of vitellogenic oocytes and active femaleness. Our data also demonstrated that the male-to-female sex change is blocked by the maintenance of male function with gonadotropin-induced *dmrt1* expression in the testis. Furthermore, our data also indicated that ovarian *cyp19a1a* expression is regulated by the testis through epigenetic modifications. Therefore, the primary male guides the femaleness in the protandrous black porgy and the transition of sexual fate from male to female is determined by the status of the testicular tissue.

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## 1. Introduction

Hermaphroditism rarely occurs in tetrapods, and this intersex status in mammals results in infertility (Policansky, 1982). Unlike in amphibians, reptiles, birds, and mammals, sex change is common in a variety of fish and invertebrates (Policansky, 1982). In teleost fishes, hermaphroditism has been documented in more than 1500 species (de Mitcheson and Liu, 2008). Most hermaphroditic fishes develop through a sequence of three primary forms (protogyny, which is a female-to-male sex change; protandry, which is a male-to-female sex change; and serial bidirectional sex change) (Mank and Avise, 2009). Conversely, simultaneous hermaphroditism is only present in the following two fish species: *Kryptolebias marmoratus* and *Hypoplectrus nigricans* (de Mitcheson and Liu, 2008). In the protandrous wrasse (*Thalassoma bifasciatum*), protogynous anemone fish (genus *Amphiprioninae*), and some bidirectional sex-change goby (genera *Gobiodon* and *Paragobiodon*), the timing of the sex change is determined by social cues (relative body size within the population) (Mank and Avise, 2009; Munday et al., 2006). Conversely, in most fish with sequential sex change, the sex change is determined by age or body size (Mank and Avise, 2009). In the protandrous black porgy, *Acanthopagrus schlegelii* (Lee et al., 2004; Wu et al., 2008a) and the protogynous grouper, *Epinephelus coioides* and *Epinephelus malabaricus* (Murata et al., 2014; Wu et al., 2015), the estrogen-induced secondary sex (compared to the primary male in the black porgy and the primary female in the grouper) is transient, and a reversible sex change occurs after the suspension of steroid administration. These data showed that the sexual phase is tightly regulated by the endogenous parameters (age in black porgy and size in grouper) of the hermaphroditic fish (Lee et al., 2004; Wu et al., 2008a, 2015; Murata et al., 2014). Thus, sex in hermaphroditic fish is determined by the early stage of initial gonadal differentiation (maleness) and later stage of sex change (femaleness). However, even though the "size-advantage hypothesis" is widely used to explain the timing of sex change in hermaphroditic fish (Ghiselin, 2006), the mechanisms that control the timing of the sex change remain unknown. Thus, we used the protandrous black porgy as a model to understand the mechanisms of male-to-female sex change.

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## 2. Black porgy as a unique model for sexual fate decision

In hermaphroditic fish, the sexual fate is decided by many different cues. Thus, a stable sex change pattern is helpful for understanding the mechanism of sexual fate decision. Black porgies are functional males for the first two spawning seasons of life, and then, one-half of the fish change sex into functional females during the third spawning season (Chang and Yueh, 1990; Chang et al., 1994). The ovarian tissue (with the primary oocytes) and testicular tissue are well separated by connective tissue in the gonad (a digonic gonad) before the sex change (Lee et al., 2008). No clear difference exists in the body length/size or outer characteristics between a male and female in the 3-year-old fish (Wu et al., 2005, 2010b). Therefore, black porgies are a unique model to study the sexual fate decision, especially due to the close interaction of the testicular and ovarian tissues in the digonic gonad.

### *2.1. Maleness, passive femaleness, and active femaleness*

Two components of the digonic gonad (testis and ovary) are formed during the same period, and then, the gonads differentiate and develop to male phase (Lee et al., 2008). The fish are functional males during the first two spawning seasons, and the testis exists at different stages of the reproductive cycle until the fish change to the female sex. In addition, plasma estradiol-17β (E2) levels are the important endocrine regulator for the natural sex change because higher plasma E2 levels were detected in the male-to-female sex-changing fish compared to the male fish in 2–3-year black porgy (Chang et al., 1994). Reversible sex change can occur in the E2 (4–6 mg/kg feed)-induced female, where fish younger than 2 years of age can switch from a dominant ovary with a regressed testis (female phase) to a dominant testis with a regressed ovary (male phase) following the end of 2–3 months of E2 administration (Lee et al., 2004; Wu et al., 2008a). Moreover, vitellogenic oocytes were infrequently observed following long-term treatment with E2 in fish less than 2 years of age (Lee et al., 2004; Wu et al., 2008b). Thus, we identified the fish during the first two reproductive cycles as expressing "maleness" and those that underwent an E2-induced male-to-female sex change as expressing "passive femaleness," with primary oocytes in the ovary (Fig. 1). However, surgical approaches revealed vitellogenic oocytes and female function in the digonic gonad following removal of the testis (Wu et al., 2008a). The gonads will naturally change the sex fate from male to functional female in certain portion of 3-year-old fish (Chang and Yueh, 1990; Chang et al., 1994; Lee et al., 2004). Therefore, we identified the fish as expressing "active femaleness" in the testis-removal fish and the natural sex-change fish (Fig. 1).

### *2.2. Dual roles of estrogen and Cyp19a1a in the gonadal development*

Unlike the way in which sex is determined by genetic factors in eutherian mammals, sex determination and differentiation are very sensitive to the endogenous levels of estrogen in the noneutherian vertebrates (Guiguen et al., 2010). In most fish, the blockage of Cyp19a1a activity by the aromatase inhibitor (AI) and the induction of E2 administration results in masculinization and feminization, respectively (Devlin and Nagahama, 2002; Guiguen et al., 2010). E2 administration induced a dominant ovary with a regressed testis but not a vitellogenic ovary in black porgy that are less than 2 years old (Wu et al., 2008a,b). Interestingly, AI administration also resulted in a morphology of the digonic gonad that is similar to E2-treated fish, with a dominant ovary and a regressed testis in the 10-month-old fish (Wu et al., 2008b). In addition, Pcna (a proliferation marker) staining revealed that cell proliferation is arrested in the testicular part of the digonic gonad during the E2 and AI administration (Wu et al., 2008b). Furthermore, according to the immunohistochemical staining, Cyp19a1a was not only observed in the follicle cells of the ovary but also in the interstitial cells of the testis (Wu et al., 2008b). Altogether, these data revealed that Cyp19a1a (or E2) is required for the early development of the testis. Furthermore, Cyp19a1a was more important for the early testicular development than the early ovarian development because the AI induced the regression of early testicular tissue and the development of early ovarian tissue (Wu et al., 2008b).

Plasma E2 levels are stable during the sexual phase alternation from an individual with a dominant ovary with a regressed testis to an individual with a dominant testis with a regressed ovary in

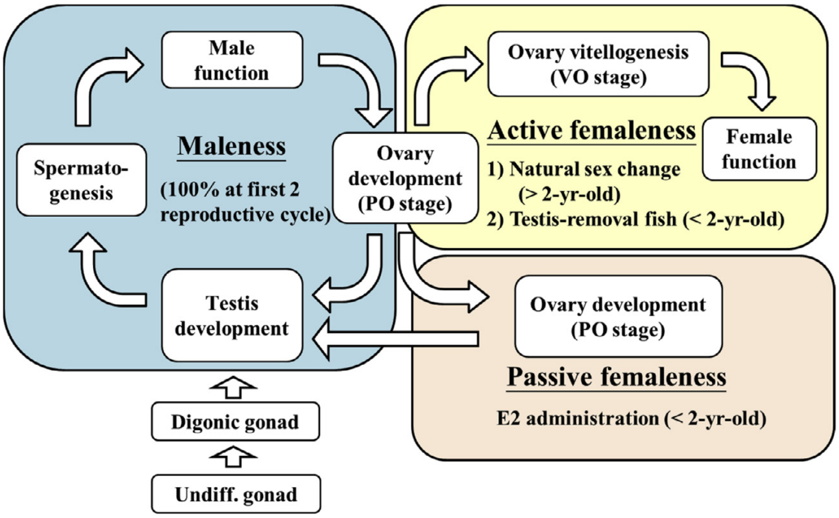

**Fig. 1.** The profiles of gonadal development in three different sexual phases. Maleness: The fish are functional males in the first two spawning seasons. The testis exists at all stages of the reproductive cycles in maleness. Active femaleness: The fish are functional females following the natural sex change that occurs in fish older than 2 years or when induced by the removal of the testis of the digonic gonad. The ovary could reach to the stage of vitellogenesis, vitellogenic and mature oocytes. Passive femaleness: Long-term E2 (4–6 mg/kg feed) administration for 2–3 months results in the appearance of a dominant ovary (with the primary oocytes) with a regressed testis in fish younger than 2 years old, and no vitellogenic oocytes are observed in E2-induced sex-change fishes). A reversible sex change (from passive femaleness to maleness) exists after E2 administration has been withdrawn. Undiff. gonad, undifferentiated gonad; E2, estradiol-17β; PO, primary oocytes stage; VO, vitellogenic oocytes stage.

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