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REVIEW
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The Regulatory Mechanism of Sexual Development in Decapod Crustaceans

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Crustacean culture has been developing rapidly in various parts of the world. Therefore, it is important to understand their reproductive biology. Insulin-like androgenic gland hormone (IAG) secreted from the androgenic gland (AG) is widely accepted as a key regulator of sexual differentiation in male crustaceans. However, recently several sex-related genes (i.e., *CFSH*, *DEAD-box* family, *Tra-2*, *Sxl*, *Dsx*, *Fem-1*, *Sox* gene family, *Foxl2*, and *Dmrt* gene family) have been identified via transcriptomic analysis in crustaceans, indicating that sexual differentiation in crustaceans is more complicated than previously expected. It has been found that several non-coding RNAs (i.e., miRNAs, lncRNAs, and piRNAs) and IAG receptors may be involved in the sexual development of decapods. Identification and study of the regulation mechanism of sex-related genes, non-coding RNAs, and IAG receptors will provide valuable information regarding sexual development in decapods. In this review, the roles of hormonal and genetic factors in both males and females are discussed. In males, crustacean female sex hormone (CFSH), *Sxl*, *Dmrt* gene family, *Dsx*, *Sox* gene family, *GEM*, *Fem-1*, I-GnRH-III, and corazonin play important roles in *IAG* regulation in the "eyestalk-IAG-testis" endocrine axis. Unlike males, the regulation mechanism and interaction of sexual genes are relatively unknown in females. However, *CFSH*, *IAG*, *Fem-1*, *FAMeT*, *Slo*, *UCHLs*, *Erk2*, *Cdc2*, *EGFR*, *Vg*, *VgR*, and *VIH* seem to play crucial roles during ovarian development. This study summarizes the available information in the field, highlights gaps, and lays the foundations for further studies and a better understanding of the regulatory mechanism of sexual development in decapods.

Keywords: decapods, gametogenesis, sex-related genes/non-coding RNAs, sexual differentiation, regulatory mechanism

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INTRODUCTION

The order Decapoda includes approximately 17,000 species of crayfish, shrimps, crabs, and lobsters (De Grave et al., 2009). Some decapods are economically cultivated and some maintained in domestic aquariums, but some are invasive and are considered as pathogenic vectors. Crustacean culture is a rapidly developing industry, due to the high economic value as a source of animal

protein, employment, and foreign exchange gains. Crustaceans production reached 9.4 million tons in 2018 (6.4 and 3 million tons were provided from capture fisheries and aquaculture, respectively), with an estimated sale value of US$ 69.3 billion (FAO, 2020).

Understanding the reproductive biology and mechanism of sexual differentiation are key issues for sexual manipulation and improving the reproductive efficiency of decapods. Male and female decapods have different growth performances at different growth stages, which is important in artificial selective breeding and farming (Shi X. et al., 2019). For example, in crayfish and prawns (freshwater Palaemonidae), males grow larger and faster, and as such, all-male individual rearing is desired. In contrast, females grow larger and faster than males in shrimps (marine Penaeidae) and crabs (Ventura and Sagi, 2012). In hatcheries, females are considered more valuable than males for increasing the size of the population since males can copulate with more females with no negative effect on the percentage of berried females (Harlıoğlu and Farhadi, 2017b). Studies showed that male and female decapods have different biochemical composition, nutritional value, and flesh quality (Wu et al., 2019). Another benefit of sexual manipulation is the ecological application of non-reproductive and mono-sex crustaceans in controlling invasive species. For example, all-male specimens of some *Macrobrachium* genus have been successfully used as biocontrol vectors on snails in some African countries (Sokolow et al., 2014). The advantages of sexual manipulation in decapod crustaceans are summarized in **Table 1**.

TABLE 1 | The advantages of sexual manipulation in decapod crustaceans.

Purpose	Advantage/Description/ Example	References
Monosex culture	Selective harvesting in *M. Rosenbergii*	Sagi and Aflalo, 2005
	Increasing stability of mating systems (e.g., sex change in groupers)	Harlıoğlu and Farhadi, 2017a
	Avoiding energy diversion (e.g., lipids) toward reproductive processes.	Rodgers et al., 2006
All-female monosex culture	Females grow larger and faster than males in shrimp (marine Penaeidae) and crab	Ventura and Sagi, 2012
	In hatcheries, females are considered more valuable	Harlıoğlu and Farhadi, 2017a
All-male monosex culture	In crayfish and prawns (freshwater Palaemonidae), males grow larger and faster	Ventura and Sagi, 2012
Ecological application	Mono-sex culture of non-indigenous crustaceans	Policar and Kozák, 2015
	Mono-sex crustaceans in controlling invasive species, for example, all-male specimens of some *Macrobrachium* genus have been successfully used as biocontrol vectors on snails in some African countries	Sokolow et al., 2014
Flesh quality	Male and female decapods have different biochemical composition, nutritional value, and flesh quality	Wu et al., 2019

SEXUAL DEVELOPMENT IN DECAPODS

Sex Determination

The sexual development in crustaceans begins with a sex-specific genetic cascade mediated by a chromosomal mechanism of sex determination. In Penaeidae shrimp and prawns a general ZZ/ZW (homogametic male) mechanism seems to exist (Aflalo et al., 2006; Coman et al., 2008; Staelens et al., 2008). In other decapods such as freshwater crayfish (Astacidea) and true crabs (Brachyura), both ZZ/ZW and XY/XX mechanisms occur (Parnes et al., 2003; Cui et al., 2015; Mlinarec et al., 2016). Recently, various genetic techniques have been successfully applied to identify the sex-specific DNA sequences and markers in decapods. Restriction-site associated DNA sequencing (RAD-seq) is based on NGS technology and can discover massive single nucleotide polymorphisms (SNPs) in various species by sequencing parts of the genome at high depth, without a reference genome. RAD-seq has been successfully applied to develop sex-specific markers in several decapod species (Zhang et al., 2018). For example, sex-specific SNP markers and high-density genetic linkage maps showed male homogamety and female heterogamety, presenting reliable genetic evidence for a WZ/ZZ sex-determination system in mud crabs, *Scylla tranquebarica*, and *Scylla serrata* (Shi et al., 2018; Waiho et al., 2019b). The discovery of five male-specific SNP markers in crucifix crab (*Charybdis feriatus*) provided reliable genetic evidence for a XX/XY sex-determination system in *C. feriatus* (Fang et al., 2020).

The sexual determination process in Drosophila species is controlled through alternative splicing of pre-mRNA of a series of genes involved in the sex determination pathway, including *Tra-2*, *Sxl*, and *Dsx*. A homologue gene of *Tra-2* has been identified in *Penaeus monodon*, however, no sex dimorphism on the expression and alternative splicing patterns was observed (Leelatanawit et al., 2009). Up to now, the sex determination mechanisms in crustacean species are still largely unknown. Kato et al. (2011) identified two *Dsx* homologues (*DapmaDsx1* and *DapmaDsx2*), which act as a key regulator of the male phenotype in *Daphnia magna*. However, in contrast to *Dsx* for *Tra* no significant difference was detected in the splicing or expression patterns (Kato et al., 2010). In ornate spiny lobster (*Panulirus ornatus*), *Sxl* and *Tra-2* isoform-encoding transcripts showed broad tissue expression, with no clear bias between males and females, suggesting that *Sxl-Tra-Dsx* may be unique to Drosophilidae and not conserved among decapods. However, the male-specific *iDMY* was conserved between the eastern (*Sagmariasus verreauxi*) and ornate spiny lobsters (*P. ornatus*), indicating a conserved central function in sex determination (Ventura et al., 2020).

Sexual Differentiation and Maturation

The complex process of sexual differentiation results in sex-specific phenotypic development. Our understanding of sexual differentiation in the decapods far exceeds what is known about sex determination. Neuropeptides from the eyestalk and mandibular organ regulate the sexual development in decapods (Khalaila et al., 2002; Alfaro-Montoya, 2010). Eyestalk is the

major neuroendocrine control center and eyestalk ablation influences gonadal development in crustaceans (Fingerman, 1987). The CHHs (crustacean hyperglycemic hormones) secreted from the X-organ have been classified as subfamily I peptides containing a CHH precursor related peptide (CPRP) and the subfamily II peptides lack the CPRP (Jia et al., 2012). The subfamily II peptides including moult inhibiting hormone (MIH), gonad/vitellogenesis-inhibiting hormone (GIH or VIH), and mandibular organ-inhibiting hormone (MOIH) control the moulting and gonadal maturation (Lacombe et al., 1999; Böcking et al., 2002). Serotonin (5-HT), dopamine, and gonadotropin-releasing hormones (l-GnRH-III) are other important factors affecting the sexual development pathway of decapods (Tinikul et al., 2008, 2011; Siangcham et al., 2013).

The insulin-like androgenic gland hormone (IAG) secreted from androgenic gland (AG) is a key regulator in sexual differentiation. Recent studies have shown that IAG itself is controlled by several genes and hormonal factors (Shen et al., 2014; Shi L. et al., 2019; Zhong et al., 2019). The detailed mechanisms and the role of sex-related genes and miRNAs in the IAG regulation are discussed in detail in other sections of the present review. In the present review, we focus on the downstream mechanisms such as novel sex-related genes and miRNAs that play important role in the sexual development process. The present review aims to highlight gaps in knowledge that must be filled to allow further development of sexual manipulation techniques.

SEXUAL MANIPULATION IN DECAPOD CRUSTACEANS

Androgenic gland is the key regulator of primary and secondary sexual characters in male decapods. It controls behavior, spermatogenesis, and sexual differentiation by secretion of IAG. AG is associated with the subterminal part of the sperm duct and attached to the posterior vas deferens in male decapods. *IAG* silencing had adverse effects on sexual development (i.e., spermatogenesis) in male *Macrobrachium rosenbergii* (Ventura et al., 2009). Silencing accomplished via double-stranded RNA (dsRNA) injection caused considerable sex-related changes such as ovarian activation and testicular degeneration in male *Cherax quadricarinatus* (Rosen et al., 2010). Similar results were observed in *M. rosenbergii* and *C. quadricarinatus* after AG ablation (Barki et al., 2006).

At present, sexual manipulation in decapods only applies through the manipulation of AG. Such as AG ablation and *IAG* suppression in males, which produce neofemales (phenotypically female but genetically male) in *M. rosenbergii* (Aflalo et al., 2006; Ventura et al., 2009). Neofemale *M. rosenbergii* (complete and functional sex reversal) was obtained by long-term *IAG* silencing at PL30 stage (Ventura et al., 2012). AG implantation into females induced sex reversal in females, called neomales (phenotypically male but genetically female) (Aflalo et al., 2006; Ventura et al., 2009).

Until now, the only successful AG manipulation that led to complete and functional sex reversal has been recorded in *M. rosenbergii* (Aflalo et al., 2006; Ventura and Sagi, 2012). In *Macrobrachium* sp., *IAG* is expressed exclusively and abundantly in the AG rather than in the testis or other tissues (Ventura and Sagi, 2012; Ventura et al., 2012; Ma et al., 2013). However, studies showed that in other decapod groups such as shrimps (Mareddy et al., 2011; Li et al., 2012b), crayfish (Shi X. et al., 2019), and crabs (Zhang et al., 2014; Jiang et al., 2020a) the *IAG* is expressed not only in the AG, but also in other tissues. The AG-specific expression pattern of *IAG* could explain why AG manipulation led to complete sex reversal only in *M. rosenbergii*. The broad tissue expression pattern of *IAG*s in other decapods indicates that *IAG*s may have some additional functions.

Recently, several sex-related genes and non-coding RNAs have been identified in decapods, suggesting that sexual differentiation mechanisms in decapods are more complicated than previously expected (Chandler et al., 2018). Further studies are required to identify more sex-related factors such as genes, non-coding RNAs and IAG hormones, which could be involved in the sexual development of decapods. Understating the function of these genetic factors may provide novel insights into the development of new sexual manipulation techniques. Sex-related genes, hormones, and their potential roles in decapods are summarized in **Table 2**.

HORMONAL AND GENETIC FACTORS IN MALE DECAPODS

Insulin-like Androgenic Gland Hormone

Insulin-like androgenic gland hormones have been isolated from several decapod species including *M. rosenbergii* (*Mr-IAG*) (Ventura et al., 2009), *C. quadricarinatus* (*Cq-IAG*) (Manor et al., 2007), *Portunus pelagicus* (*Pp-IAG*) (Sroyraya et al., 2010), *P. monodon* (*Pem-IAG*) (Mareddy et al., 2011), *Marsupenaeus japonicus* (*Maj-IAG*) (Banzai et al., 2011), *F. chinensis* (*Fc-IAG*1, *Fc-IAG*2) (Li et al., 2012a), *Cherax destructor*, *Callinectes sapidus* (*Cas-IAG*) (Chung et al., 2011), *Scylla paramamosain* (Huang et al., 2014), *Procambarus clarkii* (Shi L. et al., 2019), and *Eriocheir sinensis* (Liu Z. et al., 2019). There is remarkable structural similarity in encoded amino acids from *IAG*s and all consist of a signal peptide, a B chain, a C peptide, and an A chain (Chung et al., 2011). Recent studies showed that *IAG* has a more complex expression pattern and AG is not the only organ for the expression of *IAG* (Manor et al., 2007; Sroyraya et al., 2010; Mareddy et al., 2011). For example, in *C. sapidus IAG* is not only expressed in AG but also in the hepatopancreas (Chung et al., 2011). In *Fenneropenaeus chinensis*, *IAG* was expressed in both nerve cord and hepatopancreas of female and male individuals at relatively low levels (Li et al., 2012a).

Sox Gene Family

The *Sox* (Sry-related high-mobility group (HMG) box) family of transcription factors is extensively distributed in different animal groups, and plays crucial roles in development processes including cell pluripotency, neurogenesis, and sex determination. To date, the *Sox* gene has been isolated from several decapods including *Macrobrachium nipponense* (Hu et al., 2020), *Penaeus*

TABLE 2 | Sex-related genes and their roles in different decapod species.

Gene	Species	Role	References
IAG	Has been identified in many decapod species	Key regulator of sexual differentiation in male	Barki et al., 2006; Manor et al., 2007; Rosen et al., 2010
CFSH	*Scylla paramamosain* *Callinectes sapidus* *Sagmariasus verreauxi* *Cherax quadricarinatus* *Procambarus clarkii* *Chorismus antarcticus* *Marsupenaeus japonicus*	Play a crucial role in female phenotypes and acts as a negative regulator inhibiting the development of AG	Ventura et al., 2014; Zmora and Chung, 2014; Veenstra, 2015; Nguyen et al., 2016; Toullec et al., 2017; Kotaka and Ohira, 2018; Liu C. et al., 2018; Jiang et al., 2020b
Vitellogenin (*Vg*) and vitellogenin receptor (*VgR*)	*Scylla paramamosain*	Play important roles in egg yolk protein synthesized and ovarian development in female	Jia et al., 2013
Vitellogeneis inhibiting hormone (VIH)	*Penaeus vannamei*	Inhibiting *VTG* mRNA expression. Regulate reproduction.	Chen et al., 2014
	Scylla paramamosain	Regulate ovarian maturation	Liu C. et al., 2018
Sox gene family	*Penaeus vannamei*	Expression testis > ovary	Peng et al., 2015
	Palaemon serratus	Up-regulated in the testis	González-Castellano et al., 2019
	M. nipponense	Involved in gonadal differentiation and development, especially testis development	Hu et al., 2020
	Scylla paramamosain	Plays an important role during gonadal development	Liao et al., 2020; Lin et al., 2020
	Eriocheir sinensis	*SoxB2* is required for the maturation of the sperm nucleus during spermiogenesis	Liu et al., 2016
Tra-2	*Penaeus monodon*	Increasing with development and gonad biased in adults	Leelatanawit et al., 2009
	F. chinensis	The expression level suddenly increased at the mysis stage	Li et al., 2012b
	Macrobrachium nipponense	Broad male, female and developmental expression	Zhang et al., 2013
	Eriocheir sinensis	Broad male and female expression	Cui et al., 2015
Dmrt	*Macrobrachium nipponense*	Increasing in developmental stages	Ma K. et al., 2012
	Sagmariasus verreauxi	Significant male-biased expression patterns	Chandler et al., 2015
	Palaemon serratus	Testis-specific expression of the *Dmrt1* gene.	González-Castellano et al., 2019
	Macrobrachium rosenbergii	Testis biased in adults *MroDmrt11E* stimulates expression of *MroIAG*	Yu et al., 2014
	Eriocheir sinensis	Testis specific and greater in immature testis	Zhang and Qiu, 2010
	Scylla paramamosain	Testis specific	Gao et al., 2014
Fem-1	*Macrobrachium nipponense*	*MnFem-1* specific to the ovary (immature and mature) and have a role in oogenesis/vitellogenesis	Rahman et al., 2016
	P. serratus	*Fem-1* genes are involved in sexual development	González-Castellano et al., 2019
	Penaeus vannamei	*Fem-1-like* expression in testis > ovary	Peng et al., 2015
	Peneaus monodon	The pattern of SNP segregation suggests gene is within the sex-determining locus region on chromosome	Robinson et al., 2014
	Scylla paramamosain	Equally expressed in testis and ovary	Gao et al., 2014
	Eriocheir sinensis	*EsFem-1* might function in crab early sex determination and late gonad development	Liu et al., 2015; Song et al., 2015
Sxl	*Macrobrachium nipponense*	*Mnsxl1* and *Mnsxl2* play complex and important roles in the sexual differentiation of *M. nipponense*	Zhang et al., 2013
	Penaeus vannamei	In the male gonad during spermatogenesis, mostly occurring in the cytoplasm from spermatogonia and spermatocytes	López-Cuadros et al., 2018
	Cherax quadricarinatus	Higher expression levels in testis than in ovary	Zheng et al., 2019
	Eriocheir sinensis	*Sxl1* and *Sxl2* show broad male and female expression	Shen et al., 2014
VASA	*Scylla paramamosain*	Expressed in male and female gonads. Play role in germ cell formation.	Wang et al., 2012
	M. rosenbergii	Transcripts were specifically detected in the germ cells	Nakkrasae and Damrongphol, 2007

(Continued)

TABLE 2 | Continued

Gene	Species	Role	References
	Fenneropenaeus chinensis	Fc-vasa plays an important role in germ-line development and has utility as a germ cell lineage marker	Zhou et al., 2010
	Penaeus vannamei	Is a gonad specific germline cell marker that could be exploited to enhance our understanding of developmental and reproductive processes in the germline	Aflalo et al., 2007
BMPs	*Eriocheir sinensis*	Play role during spermatogenesis	Xu et al., 2018
	Scylla paramamosain	Had an impact on ovarian development, presumably via the autocrine/paracrine way	Shu et al., 2016
UCHLs	*Scylla paramamosain*	The expression is higher in ovaries than testes during gonadal development	Han et al., 2018
Erk2	*Scylla paramamosain*	Expression increased gradually with ovarian development	Ma A. et al., 2012
	Fenneropenaeus chinensis	Play role in controlling embryogenesis	Li et al., 2013
SUMO	*Penaeus monodon*	The expression is higher in mature females	Rotllant et al., 2015
14-3-3 zeta	*Scylla paramamosain*	The expression level in the ovary was higher than that in the other tissues	Xiaowei et al., 2013
Slo	*Scylla paramamosain*	Highly expressed in ovary	Gong et al., 2014
CKS1	*Penaeus monodon*	Highly expressed in the ovaries	Qiu et al., 2018
Cdc2	*Penaeus monodon*	Play role in ovarian development	Phinyo et al., 2013
	Eriocheir sinensis	High expression was found at previtellogenic, late vitellogenic and germinal vesicle breakdown (GVBD) stages	Qiu and Liu, 2009
	Scylla paramamosain	The positive signals were localized in the cytoplasm of oogonia and ooplasm of previtellogenic and primary vitellogenic oocytes and intense signals in spermatids and secondary spermatocytes following primary spermatocytes	Han et al., 2012
Dsx	*Penaeus vannamei*	Expression in testis > ovary	Peng et al., 2015
MAPK1	*Penaeus monodon*	Abundantly expressed in ovaries than in testes	Ponza et al., 2011
FAMeT	*P. monodon; Penaeus indicus*	Play important roles during ovarian development	Buaklin et al., 2016; Saikrithi et al., 2019
EGFR	*Scylla paramamosain*	Promote ovarian development	Lu et al., 2020
GEM	*Macrobrachium nipponense*	Negatively controls the expression of *IAG*; play important roles in oogenesis and spermatogenesis	Jin et al., 2019

vannamei (Peng et al., 2015), *Palaemon serratus* (González-Castellano et al., 2019), *E. sinensis* (Liu et al., 2016), and *S. paramamosain* (Liao et al., 2020; Lin et al., 2020). *SoxE1* is involved in testis development in *M. nipponense* (Hu et al., 2020). In a recent study, Lin et al. (2020) reported that the *SoxB2* gene plays a key role during gonad development in the mud crab. *Sox* gene plays critical roles in sexual dimorphism and participates in the formation of brain nerves and is involved in the regulation of body segments (Liao et al., 2020). In *E. sinensis*, Sox protein was exclusively localized in the nucleus of spermatid and spermatozoa even at the end of acrosome reaction and was bound to the uncondensed chromatin in the nucleoplasm of mature spermatozoa. *SoxB2-1* knockdown leads to an abnormal transformation of the nucleus during spermiogenesis. These results revealed the importance of the *Sox* gene family in testis development and spermatogenesis in males (Liu et al., 2016; Lin et al., 2020).

Dmrt Gene Family

The *Dmrt* gene family plays essential roles in sexual differentiation. This gene family has been widely studied in vertebrates, nematodes, and insects, however, limited information is available regarding the molecular function of the *Dmrt* gene family in decapods (Zhong et al., 2019). To date, *Dmrt* has been isolated from different crustacean species including *E. sinensis* (Zhang and Qiu, 2010), the water flea *D. magna* (Toyota et al., 2013), *S. verreauxi* (Chandler et al., 2015), *F. chinensis* (Li et al., 2012b), *M. nipponense* (Wang et al., 2019), *P. serratus* (González-Castellano et al., 2019), the giant freshwater prawn *M. rosenbergii* (Yu et al., 2014; Zhong et al., 2019), and mud crab *S. paramamosain* (Gao et al., 2014). Targeting the coding region of the *Dmrt* gene by repetitive injection of dsRNA revealed that *Dmrt* plays important roles in the spermatogenesis and testicular development of *E. sinensis* (Ma et al., 2016a). RNAi-targeting of *MroDmrt*99B in male *M. rosenbergii* did not affect the expression level of *IAG*, while *MroDmrt11E* silencing resulted in a significant reduction in the expression level of *IAG* (Yu et al., 2014), indicating that *IAG* is positively regulated by *MroDmrt11E*. In *M. rosenbergii*, eyestalk removal significantly increased the expression level of *Dsx* in the testis and AG. Putative Dsx/Mab-3 binding site was identified on the promoter region of male sexual differentiation effector gene *IAG* (Yu et al., 2014).

Vasa Gene

Vasa is an important regulatory gene for reproductive system development (Lasko and Ashburner, 1988). In decapod crustaceans, the *Vasa* gene has been identified in *F. chinensis*

(Zhou et al., 2010) and *P. vannamei* (Aflalo et al., 2007), *M. rosenbergii* (Nakkrasae and Damrongphol, 2007), and mud crab *S. paramamosain* (Wang et al., 2012). *Vasa* gene can be used as a specific germ cell marker to track the origin and precise route of germ cell migration toward the gonad, and elevates our knowledge on the reproductive and developmental processes of the germline in decapods (Wang et al., 2012). In *F. chinensis*, the strongest hybridization signal was detected in the spermatogonia and the intensity gradually declined toward the centre of testis tubules indicating that the transcript level of *Vasa* progressively decreased from spermatogonia to spermatids (Zhou et al., 2010). *Vasa* RNA was detected in the nucleus and the cytoplasm of the spermatozoa in *M. rosenbergii* (Nakkrasae and Damrongphol, 2007). It seems that *Vasa* gene plays various roles in the regulation of spermatogenesis. Further studies are required to investigate the exact role of the *Vasa* gene in the germ cells of decapods.

Sex-lethal (*Sxl*)

It has been documented that *sex-lethal* (*Sxl*) is involved in the sex determination process of insects. In Drosophila, female embryos expressed a fully functional *Sxl* protein while males produced a shorter peptide lacking an RNA binding domain. In males, the truncated *Sxlm* has no regulatory effect, leading to the production of an equally inactive default splice variant of *Tra* (Mullon et al., 2012). In decapods, *Sxl* has been isolated from Chinese mitten crab (Shen et al., 2014), redclaw crayfish *C. quadricarinatus* (Zheng et al., 2019), red swamp crayfish *P. clarkii* (Shi L. et al., 2019), *S. verreauxi* (Chandler et al., 2015), *M. nipponense* (Zhang et al., 2013), and *P. vannamei* (López-Cuadros et al., 2018). *Sxl* plays crucial roles in sexual differentiation, embryonic development, and gonad development but not in the sex determination of decapods (Shen et al., 2014; López-Cuadros et al., 2018; Zheng et al., 2019). In *E. sinensis*, *Sxl* was expressed in different stages of embryos development. The expression of *Sxl* had a gradual increase from the cleavage stage to the egg-nauplius stage, however, *Sxl* rapidly increased in the original zoea stage. The increase of *Sxl* at the last stages of embryos indicates that *Sxl* may play a role in embryonic development (Shen et al., 2014). Among the four isoforms of *Sxl* in *P. clarkii*, *CqSxl*3 demonstrated tissue specificity with a higher expression level in the testis than in the ovary. *CqSxl4* and *CqSxl1* were extensively expressed in various tissues while *CqSxl*2 was almost undetectable. The transcript levels of *CqSxl1/3/4* slowly increased along with embryonic development (Zheng et al., 2019). The transcript pattern of *Sxl* in females and males show that *Sxl* may not be sex-specific in decapods (Shen et al., 2014; López-Cuadros et al., 2018; Zheng et al., 2019).

Corazonin

Corazonin (Crz) was first found in insects and is a peptide with the sequence pGlu-Thr-Phe-Gln-Tyr-Ser-Arg-Gly-Trp-Thr-Asn-amide (Nässel, 2002). In crustaceans, Crz has been characterized from *Cancer borealis* (Li et al., 2003), *Carcinus maenas* (Ma et al., 2009), *Homarus americanus* (Ma et al., 2008), and *M. rosenbergii* (Siangcham et al., 2013). Some studies have shown that Crz is involved in various physiological functions, including stress (Boerjan et al., 2010), heart beat in cockroaches (Veenstra, 1989), pigment production in locusts (Hua et al., 2000), and reduction of silk making in caterpillar (Tanaka et al., 2002).

Bone morphogenetic proteins (*BMPs*)

It has been demonstrated that *bone morphogenetic proteins* (*BMPs*) such as *BMPRIB* and *BMPRII* play an important role in the development of ovary in *S. paramamosain* (Shu et al., 2016). *BMP7* may also play a role in the testis development of *E. sinensis*, probably by promoting the germ cell differentiation/meiotic mitosis and maintaining the self-renewal of spermatogonia or facilitating the successful fertilization (Xu et al., 2018).

Gem-associated Protein 2-like Isoform X1 (*GEM*)

In *M. nipponense*, *gem-associated protein 2-like isoform X1* (*GEM*) was highly expressed in the testis and ovary and during larval development indicating that *GEM* plays important roles in gonad and larval development. *In situ* hybridization showed that *GEM* may promote oogenesis and spermatogenesis. RNAi experiment revealed that *GEM* negatively controls the expression of *IAG* in *M. nipponense* (Jin et al., 2019).

REGULATORY MECHANISM OF SEX IN MALE DECAPODS

The "eyestalk-AG-testis" endocrine axis is the main regulatory mechanism of sex in male decapods. The X-Organ-Sinus-gland complex (XO-SG) of the eyestalk regulates the activity of AG through the XO-SG-AG-Gonad axis (Rodríguez et al., 2007). Eyestalk ablation causes hyperplasia and hypertrophy in AG cells (Khalaila et al., 2002), elevates *IAG* expression, and accelerates the testicular development in males (Nagaraju, 2011). XO-SG secretes neurohormones such as GIH, CHH, MIH, and VIH which are suspected to directly regulate the expression of *IAG* (Li et al., 2015b) and have inhibitory effects on reproduction and sexual development (Suwansa-ard et al., 2015).

Recently, several sexual genes have been identified to be involved in the "eyestalk-IAG-testis" endocrine axis (Guo et al., 2019). It has been revealed that some of these genes are regulated by the eyestalk neurohormones and are located at the upstream of IAG and the sexual differentiation cascade (Shen et al., 2014; Ma et al., 2016a; Shi X. et al., 2019; Zheng et al., 2019; Zhong et al., 2019).

Upstream Mechanisms of Sex in Male Decapods

Crustacean female sex hormone (CFSH) (Liu A. et al., 2018), *Sxl* (Shi L. et al., 2019; Zheng et al., 2019), *Dmrt* gene family (Abayed et al., 2019), *Dsx* (Yu et al., 2014), *Sox* gene family (Li et al., 2012a; Zhang et al., 2014), *GEM* (Jin et al., 2019), *Fem-1* (Ma et al., 2016b), l-GnRH-III, and Crz (Siangcham et al., 2013) may play key roles in *IAG* regulation at the upstream of *IAG* in the "eyestalk-IAG-testis" endocrine axis.

Liu C. et al. (2018) suggested that *CFSH* is not a female-specific hormone and the expression pattern of *CFSH* is opposite

to the expression pattern of *IAG* during the development of AG in males. Recombinant *CFSH* (r*CFSH*) reduced the expression of *IAG* in AG by approximately 60% (Liu A. et al., 2018). *CFSH* from the eyestalk is a negative regulator and inhibits AG development in decapods. Jiang et al. (2020b) found no difference in the expression level of *Sox*-5 and AP-1 in AG exposed to r*CFSH*, however, STAT significantly declined, indicating that *CFSH* controls the expression of STAT, inhibiting its function to control *IAG* in the mud crab. Further experiment showed that RNAi mediated STAT gene knockdown lowered *IAG* expression indicating that *CFSH* regulates *IAG* by inhibiting STAT. In a study by Jiang et al. (2020b), promoter activity was significantly increased in pGL3-pSp-IAG1 (*Sox*-5-binding site) and pGL3-pSp-IAG6 (*Sox*-5-binding site) than in previous plasmids (pGL3-basic and pGL3-pSp-IAG5), indicating that the Sox-5-binding site is probably involved in enhancing this activity, consistent with site-directed mutation (SDM) results of decreased promoter activity in pGL3-pSp-IAG6-Mut (Jiang et al., 2020b).

The *Sox* gene plays a crucial role in male sexual differentiation and sex determination of vertebrates (Ma K. et al., 2012). In zebrafish, *Sox*-5 binds to the *Dmrt*1 promoter (double sex and mab-3-related transcription factor 1) and inhibits *Dmrt*1 expression that may affect sexual differentiation (Gao et al., 2005). In medaka, *Sox*-5 knockout reverses female to male by controlling dmrt1bY expression (Schartl et al., 2018). In decapods, 5′ flanking regions for *IAG* have only been studied in *F. chinensis*, *M. nipponense*, and *S. paramamosain*, which contains a cis-acting element of *Sox*-5-binding site, indicating that the transcriptional regulation mechanism of *IAG* may be conserved in decapods (Li et al., 2012a; Zhang et al., 2014). The finding of transcription factor binding sites of *Sox* in the 5′ flanking region of *IAG* indicates a regulatory role of *Sox* at the upstream of *IAG*.

Sxl is regulated by neuropeptide hormones from the eyestalk (Shen et al., 2014) and acts as the upstream regulator of *IAG* (Shi L. et al., 2019; Zheng et al., 2019). *Sxl* transcription in the testis was downregulated 3 days after eyestalk removal while in the ovary it was upregulated 7 days after eyestalk removal (Shen et al., 2014). *Sxl* silencing significantly decreased the *IAG* level in *C. quadricarinatus* and *P. clarkii* (Shi L. et al., 2019; Zheng et al., 2019). In *P. clarkii*, no direct relation was observed between the *Sxl* and *IAG* and the expression level of *Sxl* was not affected by *IAG*-dsRNA injection (Shi L. et al., 2019). In contrast, after *IAG* silencing, the expression level *Sxl1*, and *Sxl2* decreased significantly in *M. rosenbergii* (Tan et al., 2020b).

Similarly, *Dsx* is likely to be negatively regulated by the neuropeptide hormones from the eyestalk and *Dsx* may be involved in the regulation of *IAG* in *M. rosenberg*ii (Zhong et al., 2019). *Dsx* knockdown induced a significant decrease in the expression of *IAG* (Yu et al., 2014; Li et al., 2018). *IAG* silencing significantly reduced the expression of two genes, *MroiDmrt1b* and *MroiDmrt1c* in *M. rosenbergii*, thereby indicating their possible roles in the *IAG*-switch (Abayed et al., 2019; Tan et al., 2020a). Nevertheless, the up-regulation of *Dsx* at the nauplius stage before the first up-regulation of *IAG* (Li et al., 2018) indicate that *Dsx* may act as an upstream regulator of *IAG* (Yu et al., 2014; Li et al., 2018). Abayed et al. (2019) suggested that *Mr-IAG* is correlated with *MroiDmrt1b* and *MroiDmrt1c*, however, it is difficult to conclude whether the relationship is downstream or upstream.

The *Fem-1* gene might be at the upstream of the sex determination cascade when compared with *IAG* in *M. nipponense* (Ma et al., 2016b), since *IAG* was first expressed at the blastula stage (Ma et al., 2013). In contrast to *IAG*, the *Fem-1* showed a high expression level from the unfertilized egg to cleavage, and then the expression declined to a low level from blastula to zoea. *Fem-1* probably influences sexual development by interacting with cathepsin L in embryogenesis and vitellogenesis (Ma et al., 2016b). Silencing of *IAG* results in testicular degeneration and sexual shifts in decapods (Rosen et al., 2010). The insulinase domain protein in *Drosophila willistoni* may hydrolyze insulin protein in individual development (Clark et al., 2007), indicating that *Fem-1* probably controls *IAG* indirectly and feminizes male-related phenotypes similar to *IAG* silencing (Ma et al., 2016b).

Crz and l-GnRH-III are other regulatory factors at the upstream of *IAG*, In *M. rosenbergii*, Crz has inhibitory effects on the AG through significant decreases in AG size, proliferation of AG cells, and *IAG* suppression. In contrast, it seems that *IAG* is positively regulated by l-GnRH-III (Siangcham et al., 2013).

Downstream Mechanisms of Sex in Male Decapods

To better understand the multiple functions of *IAG*, it is necessary to clarify the mechanisms of how *IAG* is transported. An insulin family-based signaling system has been proposed based on the structure similarity of *IAG* to the insulin/IGF family (Sharabi et al., 2016). Several peptide receptors including tyrosine kinase insulin receptor (TKIR), G-protein-coupled receptor (GPCR), insulin receptor (IR), and insulin-like growth factor-binding peptide (IGFBP) have been identified to be the receptor for *IAG* (Rosen et al., 2010; Aizen et al., 2016; Chandler et al., 2017; Jiang et al., 2020c; Ventura et al., 2020).

IGFBPs act not only as carriers of IGFs to release at the target site, but also function as modulators of IGF availability and activity (Govoni et al., 2005). *In vitro* study of IGFBP in the red claw crayfish *C. quadricarinatus* revealed that recombinant Cq-IGFBP protein interacts with the IAG hormone (Rosen et al., 2013). In *M. rosenbergii*, the highest expression level of *IAGBP* was detected in AG (Yang et al., 2020). *IAGBP*-dsRNA significantly reduced the transcript level of *IAG* in *M. rosenbergii* and *M. nipponense* (Li et al., 2015a; Yang et al., 2020). These results indicate that *IAGBP* probably participates in *IAG* signaling.

Aizen et al. (2016) suggested that IAG hormone in *S. verreauxi* is regulating phosphorylation through a tyrosine kinase insulin receptor (Sv-TKIR). The Sv-TKIR receptor signaling pathway is mediated through the MAPK/ERK pathway and IAG activates this signaling pathway in a dose-dependent manner (Aizen et al., 2016). This activation confirms the existence of receptors in the testis which can bind to AG ligands, coinciding with the testis regression in response to *IAG* silencing (Rosen et al., 2010; Aizen et al., 2016).

Insulin receptors (IRs) belong to the large class of tyrosine kinase receptors. IRs play important roles in signaling pathways, which mediate insulin and insulin-like peptides (ILP) signaling (Jin Chan and Steiner, 2000). The expression of *IR* in *M. rosenbergii* (*Mr-IR*) was detected in most tissues in both males and females, including the AG and gonads (Sharabi et al., 2016). *Mr-IR* silencing resulted in hypertrophy of AG and increased the expression level of *Mr-IAG*, with an unusual mass of immature spermatozoa cells in the distal vas deferens. RNAi experiments revealed that *MrIR* functions as a receptor for *MrIAG*; and the knockdown of *MrIR*, using both siRNA and dsRNA approaches, induced sex reversal (neofemales) in *M. rosenbergii* (Tan et al., 2020a). *Mr-IR* could also regulate *Mr-IAG* expression, possibly through cross-talk with eyestalk-borne neuropeptide (s) or potentially via auto/paracrine feedback with the AG itself (Sharabi et al., 2016). The regulatory mechanism of the eyestalk-IAG-testis endocrine axis, sex-related genes, hormones, and miRNAs are presented in **Figure 1**.

HORMONAL AND GENETIC FACTORS IN FEMALE DECAPODS

CFSH

CFSH has been identified in several decapod species including *C. sapidus* (Zmora and Chung, 2014), *S. verreauxi* (Ventura et al., 2014), *C. quadricarinatus* (Nguyen et al., 2016), *P. clarkii* (Veenstra, 2015), *Chorismus antarcticus* (Toullec et al., 2017), *M. japonicus* (Kotaka and Ohira, 2018), *S. paramamosain* (Liu A. et al., 2018), and *M. rosenbergii* (Thongbuakaew et al., 2019). It has been reported that *CFSH* plays an important role in the development of reproductive phenotypes of female blue crab (*C. sapidus*) (Zmora and Chung, 2014). The expression pattern of *CFSH* has been evaluated in several decapod species. In *C. sapidus* and *S. verreauxi*, *CFSH* was exclusively expressed in the eyestalk (Ventura et al., 2014; Zmora and Chung, 2014). In *P. clarkii CFSH* had the highest expression level in the ovary (Veenstra, 2015). In *M. rosenbergii*, the expression of *CFSH* was not exclusive to the eyestalk, but also expressed in several tissues including the CNS, gonads (testis and ovaries), hepatopancreas, stomach, gill, heart, and muscle (Thongbuakaew et al., 2019). However, in some species including shrimps (*M. japonicus*), prawns (*M. rosenbergii*), lobsters (*S. verreauxi*), and crayfish (*P. clarkii*) *CFSH* is expressed in both females and males at roughly the same level (Ventura et al., 2014; Veenstra, 2015; Kotaka and Ohira, 2018; Thongbuakaew et al., 2019). These results indicate that *CFSH* might regulate sexual development only in some crab species and is not a female sex hormone in other decapods.

Fem-1 Gene Family

Fem-1 gene family includes three members, *Fem-1a*, *Fem-1b*, and *Fem-1c* (Ventura-Holman et al., 2003). It has been demonstrated that the sex determination pathway in the roundworm *Caenorhabditis elegans* is controlled by *Fem-1*, together with *Fem-2* and *Fem-3* (Doniach and Hodgkin, 1984). *Fem-1* is known to be required for sexual development, involving both somatic and germline sex determination together with other *Fem* genes (*Fem-2* and *Fem-3*) in *C. elegans*. *Fem-1* negatively regulates *Tra-1*, which is a key gene for sexual development in females (Doniach and Hodgkin, 1984; Mehra et al., 1999). To date, *Fem-1* has been isolated from several decapod species including *P. serratus* (González-Castellano et al., 2019), *E. sinensis* (Song et al., 2015), *P. vannamei* (Galindo-Torres et al., 2019), *M. nipponense* (Ma et al., 2016b,a), *S. paramamosain* (Gao et al., 2014), and *P. monodon* (Robinson et al., 2014). Based on the high expression of *Fem-1* in early embryonic development it might be maternal genes in decapods (Song et al., 2015; Ma et al., 2016b). The high expression level of *Fem-1* in unfertilized eggs and embryos at the cleavage stage and the low expression level from blastula to zoea in *M. nipponense*, indicate that *Fem-1* in early embryos is maternal. The expression of *Fem-1* significantly increased in the larvae, an important stage of sexual differentiation. Fem-1 protein can be potentially interactive with cathepsin L and proteins containing the domains of insulinase, ankyrin or ubiquitin (Ma et al., 2016b). Galindo-Torres et al. (2019) suggested that a negative post-transcriptional regulation controls the expression of *Fem-1* in female gonads, which allows the occurrence of sexual differentiation in female *P. vannamei*. The expression of *Fem-1* in spermatogonia indicates it's also requirment for differentiation of the male gonad (Galindo-Torres et al., 2019). In *E. sinensis*, the expression pattern of *Fem-1* shows a certain degree of sexually dimorphic expression in some tissues. The higher expression level of *Fem-1* consistently detected in the testis, ovary, hepatopancreas, and muscles shows its potential role in the last stages of gonadal development (Song et al., 2015).

Tra-2

Transformer-2 (*Tra-2*) plays important roles in the regulation of pre-mRNA splicing and a pivotal downstream component of the genetic somatic sex determination pathway in Drosophila (Salvemini et al., 2009). In decapods, *Tra-2* has been isolated from *P. monodon* (Leelatanawit et al., 2009), *F. chinensis* (Li et al., 2012b), *P. serratus* (González-Castellano et al., 2019), *M. nipponense* (Zhang et al., 2013), *S. verreauxi* (Chandler et al., 2015), and *E. sinensis* (Luo et al., 2017). It has been reported that *Tra-2* plays key roles in sexual differentiation and embryonic development of *M. nipponense* (Zhang et al., 2013). In *F. chinensis*, *Tra-2c* expression levels suddenly increased at the mysis stage. In addition, *FcTra-2c* showed a significantly higher expression level in females than in the male. *Tra-2* might therefore be involved in the sex determination of female *F. chinensis*. Luo et al. (2017) isolated four *Tra-2* isoforms, designated as *EsTra-2a*, *EsTra-2b*, *EsTra-2c*, and *EsTra-2d* from *E. sinensis*. Remarkably, *EsTra-2a* had a higher expression level in somatic tissues of males, while *EsTra-2c* had a higher expression level in the ovary.

Ubiquitin C-Terminal Hydrolases (*UCHLs*)

Ubiquitin C-terminal hydrolases (*UCHLs*) are involved in several physiological processes. However, little information is available regarding the role of *UCHLs* in gonadal development of crustaceans. *UCHLs* have been identified

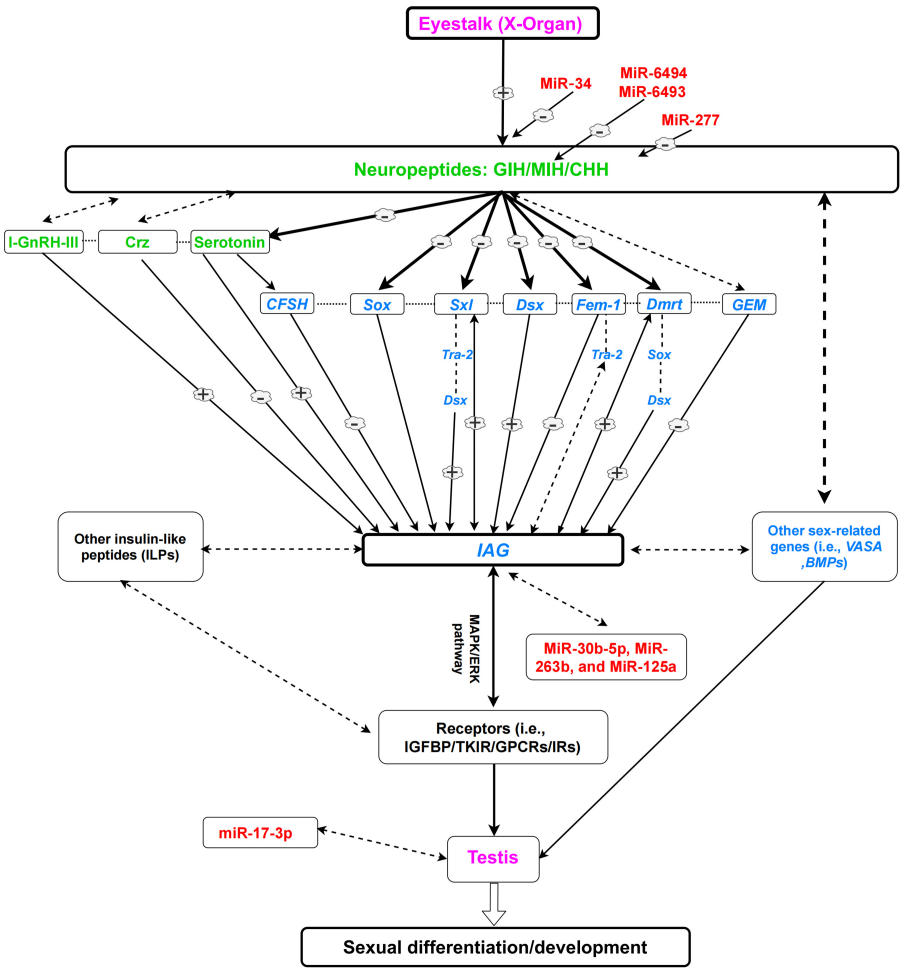

FIGURE 1 | A simplified view of the eyestalk-IAG-testis endocrine axis and its role in the sexual development of male decapods, based on previous literature. Dotted lines indicate possible regulations which are not proved. (–) Shows downregulation. (+) Shows upregulation. Neuropeptides and hormones (green); sex-related genes (blue); miRNAs (red); organs (purple). Note: Every species (or group of species) is unique and could have variable regulatory networks.

only in *S. paramamosain* (Han et al., 2018). Han et al. (2018) reported that the expression level of *UCHL3* and *UCHL5* in the ovary was significantly higher than in other tissues which provides basic data indicating that *UCHL3* and *UCHL5* may play important roles in the ovarian development of *S. paramamosain*.

Epidermal Growth Factor Receptor (EGFR)

Epidermal growth factor receptor (*EGFR*) is a member of the tyrosine kinase receptor superfamily found in many species. EGFR is a pleiotropic glycoprotein that plays a role in regulating cell proliferation, migration, and differentiation. In mud crab, *EGFR* is mainly localized in the oocyte perinuclear region with notably obvious signals. *EGFR* might promote ovarian development by stimulating the expression of *VgR* and *Cyclin B* (Lu et al., 2020). The role of *EGFR* in *M. rosenbergii* seems to be mostly related to growth control. *EGFR*-dsRNA injection resulted in delay in the appearance of a male secondary sexual characteristic, growth reduction, and affected eye formation. It seems that Mr-IAG is probably not a ligand of Mr-EGFR (Sharabi et al., 2013).

REGULATORY MECHANISM OF SEX IN FEMALE DECAPODS

Upstream Mechanisms of Sex in Female Decapods

The upstream regulation mechanisms in female decapods include the role of several neurohormones and neuropeptides such as methyl farnesoate (MF), ecdysone, ecdysone receptor (EcR), CHH, GIH, MIH, 5-HT, DA, VIH, octopamine, and red pigment concentrating hormone (RPCH). The major source of these neuropeptides is the X-organ located in the eyestalk ganglia. These neuropeptides involved in carbohydrate and lipid metabolism, moulting, and ovarian development (Böcking et al., 2002; Zhou et al., 2019). The RPCH is not only

involved in the regulation of pigmentation but also the regulation of ovarian maturation in crustaceans (Fingerman, 1997). *EcR* and *farnesoic acid O-methyltransferase* (*FAMeT*) are important genes and have a high expression in the eyestalk (Gong et al., 2015). FAMeT is an important rate-limiting enzyme for the conversion from Farnesoic acid (FA) to methyl farnesoate (MF) in the final stage of MF synthesis (Holford et al., 2004). MF is synthesized from the mandibular organ. MF plays important roles in ovarian development (Rodríguez et al., 2002). Based on the high structural similarity, MF is considered to be the homologue of juvenile hormones (JH) from insects (Xie et al., 2015). Localization studies indicated that *FAMeT* is co-localized in the neurosecretory cells that produce CHH and MIH. Higher levels of *FAMeT* mRNA transcript and protein levels were reported along with higher levels of CHH and GIH (Zhou et al., 2019). MF biosynthesis is regulated by secreted neuropeptides from the X-organ which regulates the activity of *FAMeT* and thereby vitellogenesis (Gunawardene et al., 2002).

Downstream Mechanisms of Sex in Female Decapods

CFSH, *IAG*, *Vg*, *UCHLs*, *Erk2*, *SUMO*, *14-3-3 zeta*, *Slo*, *CKS1*, *Cdc2*, *MAPK1*, *FAMeT*, *Wnt4*, and *EGFR* probably play important roles in the sexual development of females. Unlike males, the downstream mechanisms in females are relatively unknown. Except for *CFSH* and *IAG*, the regulation mechanism of other genes is unknown and information is limited to the molecular characterization and expression profile.

The bilateral eyestalk ablation and silencing of *CFSH* altered reproductive structures (i.e., sharper abdomens, absent or misplaced gonopores, fewer and shorter setae on pleopods) and impaired mating in female *C. sapidus* (Zmora and Chung, 2014). It seems that *CFSH* plays an important role in sexual differentiation rather than sex determination because the absence of *CFSH* neither resulted in sex reversal nor ovarian degeneration (Zmora and Chung, 2014). The expression level of *CFSH* changed at different moulting stages and the highest expression level was detected in the pre-moult stage. Moreover, the expression of *CFSH* increased at the beginning of gonopore development in females and decreased in males, indicating that the expression of *CFSH* affects the formation of gonopores in *S. paramamosain* (Jiang et al., 2020a). *CFSH* may also participate in the regulation of sexual differentiation of early juveniles (Jiang et al., 2020a).

The role of *IAG* is not limited to males, *IAG* may play an inhibitory role in ovarian development in female decapods. The expression level of *IAG* is maintained at low levels during the undeveloped stage (stage I) to late vitellogenic stage (stage IV) and then increased at the mature stage (stage V), indicating that *IAG* participates in inhibiting oocyte growth and vitellogenesis (Huang et al., 2014). In *C. sapidus*, ovarian development and season affected the expression level of both *IAG* and insulin-like peptide binding protein (*ILPBP*) in the ovary. These results indicated that ovarina *IAG* and *ILPBP* may be involved in the ovarian development (Huang et al., 2017).

The interaction of sex-related genes in females is poorly understood. Therefore, further studies are required to study the function and interaction of these genes. The regulatory mechanism of sexual development in female decapods and the roles of sex-related genes, hormones, and miRNAs are presented in **Figure 2**.

NON-CODING RNAS (NCRNAS)

MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are small non-coding RNA with a length of about 22 bp. miRNAs inhibit gene expression through translational repression by binding to the 3′-untranslated regions (UTRs) of the target mRNAs (Christensen et al., 2009). Moreover, one miRNA can control numerous genes, and one gene can be regulated by multiple miRNAs (Jingsheng et al., 2015). There are two main stages for miRNAs generation. The first step is the synthesis of the 70-100 bp precursor-miRNA which has a characteristic hairpin structure generated from a primary miRNA transcript by the Drosha and its RNA-binding cofactor DiGeorge syndrome critical region gene 8 (DGCR8) in the nucleus. In the second step, Exprotin5-RAN-GTP carries the pre-miRNA to the cytoplasm for further processing by Dicer (a RNAse III endonuclease) to form the mature miRNA (Zeng, 2006; Winter et al., 2009). In mammals, miRNAs control gonad development (ovary and testis), induce differentiation and maturation of oocytes and spermatozoa, and influence zygote development (Scherr et al., 2007). In the rat, miR-141-3p inhibits ovarian granulosa by targeting DAPK1 gene and participates in the etiology of polycystic ovary syndrome (Li et al., 2017). It has been reported that miR-143 plays a key role in follicle stimulating hormone (FSH) which induces estradiol production and granulosa cell proliferation via binding to the 3′-UTR of Kirsten rat sarcoma (KRAS) mRNA (Zhang et al., 2017). miRNAs are also essential for ovulation and oocyte maturation in invertebrates (Kadener et al., 2009). In decapods, several sex-related miRNAs have been identified in *S. paramamosain* (Jia et al., 2018; Waiho et al., 2019a; Zhou et al., 2019, 2020), *Portunus trituberculatus* (Meng et al., 2018, 2020), *E. sinensis* (Song et al., 2014; He et al., 2015), *M. rosenbergii* (Liu X. et al., 2019; Qiao et al., 2019) *M. nipponense* (Sb et al., 2015; Jin et al., 2017), *P. monodon* (Zhao et al., 2018), and *Fenneropenaeus merguiensis* (Saetan and Chotigeat, 2019). The roles of sex-related miRNAs in decapods are summarized in **Table 3**.

Transcriptomic analysis revealed that miRNAs may affect the sexual development of decapods through several pathways. The most important predicted pathways are ERK, MAPK, necroptosis pathway, GnRH signaling pathway, *Wnt* signaling pathway, ovarian steroidogenesis, TGF-beta signalling pathway, gluconeogenesis pathway, glycolysis pathway, estrogen signaling pathway, ovarian steroidogenesis, and insulin signaling pathway (He et al., 2015; Jia et al., 2018; Meng et al., 2018; Zhao et al., 2018; Liu X. et al., 2019; Zhou et al., 2019).

In males, miRNAs such as miR-17-3p, let-7c, and miR-21-5p demonstrated different expression levels during different stages of testicular development indicating their probable involvement

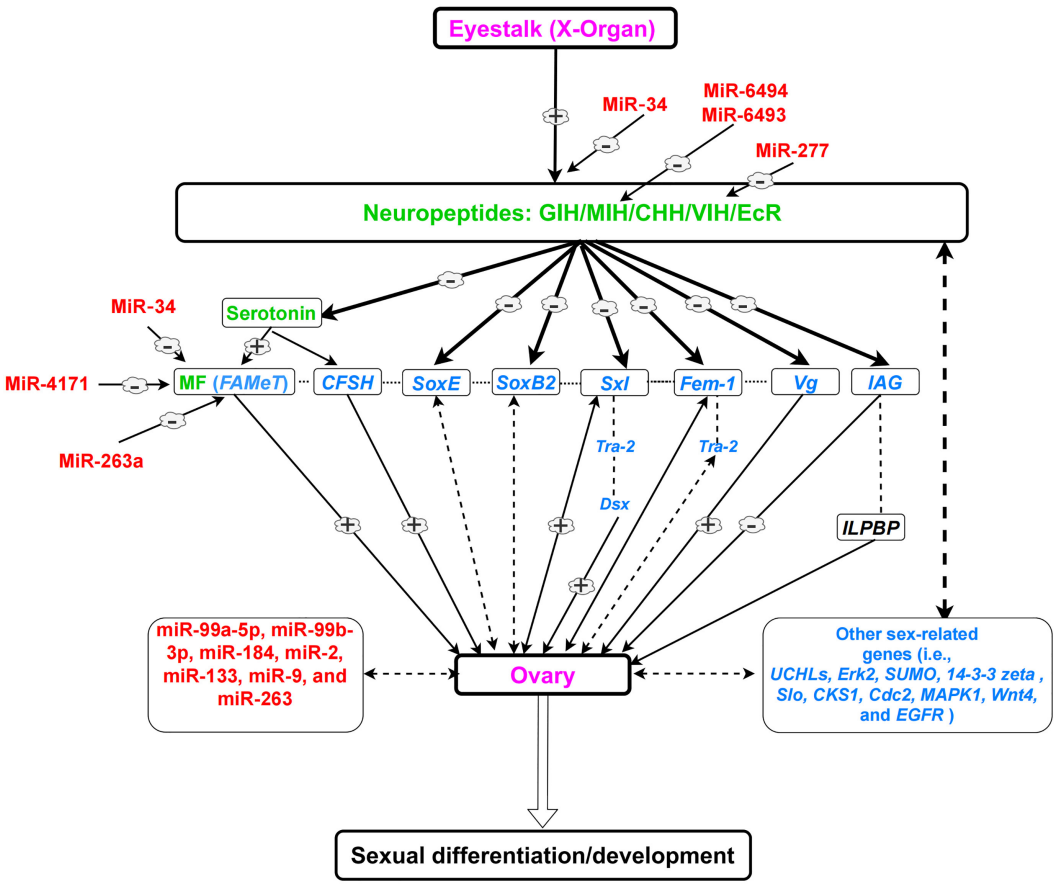

FIGURE 2 | A simplified view of the eyestalk-ovary endocrine axis and its role in sexual development in female decapods, based on previous literature. Dotted lines indicate possible regulations which are not proved. (–) shows downregulation. (+) shows upregulation. Neuropeptides and hormones (green); sex-related genes (blue); miRNAs (red); organs (purple). Note: Every species (or group of species) is unique and could have variable regulatory networks.

in spermatogenesis (He et al., 2015). MiR-34 probably regulates the reproductive function via binding to the 3′-UTRs of *MIH*, *EcR*, *FAMeT*, and *CHH* genes (Zhou et al., 2019).

In females, miR-34 and miR-277 may play a key role in the ovarian development of *S. paramamosain*. AgomiR-34 reduced the expression level of *MIH*, *CHH*, *VIH*, *EcR*, *RPCH*, and *FAMeT* genes, whereas antagomiR-34 elevates the expression level of these genes (Zhou et al., 2019). Injection of agomiR-277 in female mud crab increased the expression of the *Spvtg* gene in the ovary and hepatopancreas of mud crab. On the contrary, the expression of *Spvih* was significantly decreased after injection with agomiR-277, indicating that miR-277 could positively regulate the expression of the *Spvtg* gene in mud crab indirectly (by negative regulation on *VIH*) (Jia et al., 2020). It has been demonstrated that miR-133 and miR-2 downregulated cyclin B gene expression during meiotic oocyte maturation in *E. sinensis* (Song et al., 2014). In addition, the expression level of miR-87 and miR-7 was significantly increased and they were predicted to target cyclin-dependent kinase 2 (Cdk2)7 and cell division cycle4 (Cdc4), which are important for regulation of the G1-to-S-phase transition during the cell cycle (Schnackenberg et al., 2007). Meng et al. (2020) showed that MF synthesis and *FAMeT* expression are directly regulated by miR-4171 and miR-263a. Also, miR-317, miR-2b, and miR-466f-3p repress the expression of *calcium signal transduction* (*CaM*). The eyestalk ablation showed a negative association between miR-263a, miR-4171, and *FAMeT* and between miR-2b, miR-317, and *CaM*. Taken together, these results indicate that multiple miRNAs operate cooperatively to regulate the expression of *FAMeT* and *CaM*, and thereby participate in inducing ovarian maturation after eyestalk ablation.

PIWI-Interacting RNAs (piRNAs)

PIWI-interacting RNAs (piRNAs) are widely presented in germ cells and are involved in gonad development and gametogenesis. piRNAs play a key role in the gametogenesis processes by silencing transposable elements (Rastetter et al., 2015). piRNAs are longer (26-31 nt) than miRNAs (21-23 nt). However, piRNAs are seldom expressed in somatic cells and show a higher composition present compared to miRNAs during gametogenesis (Aravin et al., 2006). Small RNAs function by guiding a crucial co-factor–an Argonaute/PIWI family of proteins to target RNAs (Hilz et al., 2016). Two major pathways are known for piRNA synthesis: (A) primary biogenesis: piRNAs synthesis from several

TABLE 3 | Sex-related miRNAs and their potential effects in different decapod species.

Study	miRNA	Description	Species
Waiho et al., 2019a	The most important miRNAs were let-7, miR-100, miR-8, miR-8*, miR-9* and miR-315	54 miRNAs were differentially expressed (approximately 72.2% were ovary-related)	*S. paramamosain*
Jia et al., 2018	The most important miRNAs were spa-miR-9c, −279e, −263a, −263b, and −9	108 miRNAs were differentially expressed (13 only in the testis and two only in the ovary and 93 miRNAs were coexpressed). Based on the matching results many sex-related genes such as *FAMET*, *VASA*, *Sox* genes, and eyestalk neuropeptide genes could be regulated by these miRNAs	*S. paramamosain*
Zhou et al., 2019	miR-34	miR-34 may indirectly regulate reproduction via binding to the 3′−UTRs of *MIH*, *CHH*, *EcR*, and *FAMeT* genes and suppressing their expression	*S. paramamosain*
Zhou et al., 2020	miR-9 and miR-263	miR-9/miR-263 can negatively regulate the expression of the ERK pathway genes (*ERK2*, *MEK2*, and *Rap-1b*) in the ovary	*S. paramamosain*
Jia et al., 2020	miR-277	miR-277 could inhibit Spvih gene expression by targeting the 3′UTR of the Spvih gene	*S. paramamosain*
Meng et al., 2018	The most abundant miRNAs were let-7, let-7c, let-7f, mir-2, mir-184, and mir-276	Obtained 187 and 225 miRNAs from ovary and testis, respectively, including 188 known and 65 novel miRNAs. Significantly enriched in 14 KEGG pathways, including several pathways important in reproduction, such as GnRH signaling pathway, Wnt signaling pathway, ovarian steroidogenesis, and TGF-beta signaling pathway.	*P. trituberculatus*
Meng et al., 2020	The most important miRNAs were miR-263a, miR-4171, miR-2b, miR-317, and miR-466f-3p	31 miRNAs were differentially expressed in eyestalk ablation and eyestalk-intact. Multiple miRNAs could function cooperatively to regulate *FAMeT* and *CaM* expression, and thereby participate in inducing ovarian maturation after eyestalk ablation.	*P. trituberculatus*
Song et al., 2014	The most abundant miRNAs were miR-2 and miR-133	miR-2 and miR-133 exhibit differential expression during the meiotic maturation of the oocytes and have activity in regulating the 3′-UTR of the crab cyclin B gene.	*E. sinensis*
He et al., 2015	The most important miRNAs were miR-99a-5p, miR-99b-3p, miR-184, and miR-17-3p	miR-99a-5p, along with miR-99b-3p and miR-184, were preferentially expressed during the ovarian development (stage III-2). miR-17-3p highly expressed during spermatogonial differentiation	*E. sinensis*
Liu Z. et al., 2019	The most important miRNAs were miR-194-5p, miR-148a-5p, miR-24-3p, cgr-miR-122, miR-145	Identified 17 ovary-biased and 24 testis-biased miRNAs in terms of expression patterns. Significantly enriched in many reproduction-related pathways including the GnRH pathway, ovarian steroidogenesis, estrogen signaling pathway, MAPK pathway, and Wnt pathway	*M. rosenbergii*
Sb et al., 2015	The most important miRNAs were mir-2a, miR-33, miR-71-5p, miR-965, miR-315, miR-184, miR-184-3p, and Let-7	mir-2a, miR-33, miR-71-5p, miR-965, and miR-315 were predicted to regulate the expression of *Sxl* and *Tra-2*. miR-184 and miR-184-3p were predicted to be involved in the regulation of Sst and Sti expression	*M. nipponense*
Jin et al., 2017	miR-30b-5p, miR-263b, and miR-125a were highly expressed	Higher expression levels of miR-30b-5p, miR-263b, and miR-125a in the androgenic gland might indicate important functional roles of these three miRNAs for male differentiation and development	*M. nipponense*
Qiao et al., 2019	The most important miRNAs were miR-124, miR-14, miR-7, miR-316-5p, miR-278, miR-125, and miR-3885-5p	bmo-miR-316-5p/opsin protein, ame-miR-125/skeletal muscle actin 8, dmo-miR-278/sugar transporter, and tca-miR-3885-5p/5-HT1 receptor play important roles in reproduction regulation	*M. nipponense*
Zhao et al., 2018	Several important miRNAs were identified	Pm-miR-1260-5p, Pm-miR-3741-3p, Pm-miR-3960-3p, Pm-miR-466-3p, Pm-miR-6238-3p, and Pm-miR-669-3p were all identified as negative regulators of Pm-14-3-3-like mRNA.	*P. monodon*
Saetan and Chotigeat, 2019	The most important miRNAs were miR-6489, miR-6491, miR-6492, miR-6493, and miR-6494	Result demonstrated that miR-6493 and miR-6494 can down-regulate the 3′UTR of *GIH* and *HSP70* genes which were predicted as their target	*F. merguiensis*

portions of long single-stranded precursor RNAs transcribed from both uni-directional and bi-directional piRNA clusters in the genomic loci (Mohn et al., 2014), and (B) secondary biogenesis, also known as the ping-pong cycle, selectively amplifies specific piRNAs targeting active transposon (Brennecke et al., 2007). Scarce information is available regarding the role of piRNAs in the sexual development of crustaceans. Waiho et al. (2020) identified gonadal piRNAs of *S. paramamosain* and out of 115,491 novel piRNAs, 596 were differentially expressed. Furthermore, 389,887 potential piRNA-target genes were predicted. The expression level of four piRNAs and nine genes with high piRNA interactions were validated with the inclusion of additional immature specimens including low-density lipoprotein receptor-related protein 2 (LRP2) that is involved in reproduction and growth, midasin (MDN1) in ribosome biogenesis pathway and gametogenesis, and PRKDC, a DNA repair gene involved in gonad development and differentiation.

Long Non-coding RNAs (lncRNAs)

Long non-coding RNAs (lncRNAs) are non-protein-coding RNAs longer than 200 nt (Rinn and Chang, 2012). lncRNAs are divided into genic and intergenic based on their proximity to the protein-coding genes in a genome (Gibb et al., 2011). Unlike small non-coding RNAs, the annotation and identification of lncRNA are difficult due to their low expression level (Derrien et al., 2012). Similar to protein-coding genes, they are mostly transcribed by RNA polymerase II and can be post-transcriptionally modified by splicing, capping, and polyadenylation (Guttman and Rinn, 2012). lncRNAs usually have a small number of exons and a shorter transcript size (average of 800 nt) compared to protein-coding genes (Derrien et al., 2012). lncRNAs often demonstrate tissue-specific expression patterns and even sometimes are localized in a specific cellular compartment (Ginger et al., 2006). Although several lncRNAs have been identified, the molecular function of only a small number of lncRNAs has been experimentally validated. lncRNAs play an important role in gene regulation in three ways including serving as decoys, scaffolds, and guides. Many lncRNAs serve as decoys and affect the transcription of genes by preventing access to DNA by regulatory proteins (Hung et al., 2011). Some lncRNAs act as scaffolds and bring proteins into a discrete complex. Other lncRNAs regulate different developmental and cellular processes by guiding a specific protein complex to a specific promoter in response to certain molecular signals (Tsai et al., 2010). In addition, lncRNAs regulate several molecular processes such as alternative splicing and mRNA transport (Tripathi et al., 2010).

In decapods, little information is available regarding the sex-related lncRNAs. Yang et al. (2018) provided fundamental resources for further studies on the roles of lncRNAs in decapod sexual development. Several lncRNAs negatively regulated the expression of some genes, indicating their potential role in the sexual differentiation of mud crab. lncRNAs including lncRNA-ncr2, lncRNA-ncr10, and lncRNA-ncr14 suppressed the expression of their target genes (Yang et al., 2018).

CONCLUSION AND FUTURE PERSPECTIVE

Although relatively adequate information is available regarding molecular mechanisms of sexual development in males, limited information is available in females. Several sex-related genes have been identified to be involved in the "eyestalk-IAG-testis" endocrine axis in males. Most of these genes are negatively regulated by the eyestalk neurohormones and have a regulatory effect on the AG and *IAG* expression. For example, it has been documented that *CFSH*, *Sox*, *Dsx*, Slx, *Dmrt*, *GEM*, and *Fem-1* regulate the expression of *IAG*. *IAG* expression is negatively regulated by *GEM*, *Fem-1*, and *CFSH*. In contrast, *Slx*, *Dsx*, and *Dmrt* silencing significantly decrease the expression of *IAG* indicating the existence of positive regulation. *IAG*, *Sox*, *Dmrt*, *Dsx*, *Vasa*, *BMPs*, and *Slx* exhibit male-biased expression patterns and play crucial roles in testis development and spermatogenesis. In contrast, *CFSH*, *Fem-1*, *FAMeT*, *Slo*, *Tra-2*, *UCHLs*, *Erk2*, *Cdc2*, *EGFR*, *Vg*, *VgR*, and *VIH* have female-biased expression patterns and play important roles during ovarian development.

Also, it has been revealed that several non-coding RNAs (i.e., miRNAs, lncRNAs, and piRNAs) may affect the sexual development of decapods. Studies on non-coding RNAs are limited to some miRNAs and further studies are needed to clarify the roles of other non-coding RNAs (i.e., piRNA and lncRNAs) in the regulation mechanism of sex in decapods. For example, miR-34 indirectly regulates the reproductive function via binding to the 3′-UTRs of *MIH*, *CHH*, *EcR*, and *FAMeT* genes and suppresses their expression.

Further research is required to (1) identify more sex-related genes and non-coding RNAs; (2) investigate the role and function of sex-related genes and non-coding RNAs; (3) understand the interaction of these sex-related genes together and with non-coding RNAs, (4) understand the role and regulation mechanism of *IAG* in female decapods, and (5) identify more *IAG* receptors.

AUTHOR CONTRIBUTIONS

AF designed the framework of the draft and collected the literature. AF and HM drafted the manuscript. Other authors revised and finalized the manuscript. All authors read and approved the final manuscript.

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