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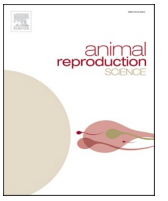

Review article

Hormonal symphony: The dynamic duo of IGF and EGF in gonadotropin-induced fish ovarian development and egg maturation

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ABSTRACT

Fish oocyte maturation (FOM) is a critical biological process that occurs before ovulation and is influenced by gonadotropins, particularly luteinizing hormone (LH). The release of LH stimulates the ovarian follicle to produce a maturation-inducing hormone (MIH), specifically 17α, 20β-dihydroxy-4-pregnen-3-one (17α, 20β-DP), which initiates the formation of maturation-promoting factor (MPF) through the activation of cyclin B and cdc2 kinase. Insulin-like growth factor I (IGF-I) significantly regulates ovarian functions, including steroidogenesis, by activating its membrane receptors and the tyrosine kinase pathway. IGF-I influences oocyte maturation directly via the PI3 kinase pathway, independent of steroid hormones. Additionally, epidermal growth factor (EGF) promotes cell growth and differentiation by binding to its receptor (EGFR). It is implicated in mediating human chorionic gonadotropin (hCG)-induced DNA synthesis in ovarian follicles while suppressing apoptosis. The presence of EGF in follicle cells and oocytes, along with its higher expression in oocytes, suggests it may act as a paracrine signal regulating somatic cell activity. Recent studies indicate that the activin system in follicle cells could be a target for EGF activity. The EGFR signaling pathway enhances gonadotropin-induced steroidogenesis and governs the transition of oocyte maturation stages, essential for successful fertilization. This review synthesizes current research on the roles of gonadotropins, IGFs, and EGFs in fish oocyte maturation and ovarian steroid production.

1. Introduction

The vertebrate ovary is one of the most active and complex organs in the body, playing a critical role in reproductive health (Rowlands and Weir, 1977; Angelini and Ghiara, 1984; Wallace, 1985; Callard et al., 1989; Ditewig and Yao, 2005; Norris and Lopez, 2011). Its regulation is primarily controlled by gonadotropins, which are hormones secreted by the pituitary gland, often referred to as the master gland due to its central role in endocrine functions (Redshaw, 1972; Licht et al., 1977; Patiño et al., 2001; Ge, 2005 a, b; Okubo and Nagahama, 2008). Among these gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are particularly important (Norris and Lopez, 2011; Aizen et al., 2012; Nyuji et al., 2016; Takahashi et al., 2016; Kanda et al., 2019; Takahashi and Ogiwara, 2023). These hormones drive essential ovarian processes, including the production of steroids (steroidogenesis) and the maturation of oocytes, which are the cells that develop into eggs (Senthilkumaran et al., 2004; Nagahama and

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Yamashita, 2008; Pham et al., 2008; Yaron and Levavi-Sivan, 2011; Shang et al., 2019; Eslamizadeh et al., 2024). The regulation of these processes is crucial for the proper development and reproductive capacity of vertebrates (McGee and Hsueh, 2000).

Recent scientific research has significantly expanded our understanding of ovarian regulation, revealing that the effects of gonadotropins are not solely direct but are also mediated or modulated by a range of growth factors produced within the ovary itself. Notably, insulin-like growth factor (IGF) (Mukherjee et al., 2006; Peyton and Thomas, 2011; Jia et al., 2019; Weber, 2023; Canón-Beltrán et al., 2024) and epidermal growth factor (EGF) (Pang and Ge, 2002; Wang and Ge, 2004; Van Der Kraak and Lister, 2011; Xie et al., 2016; Song et al., 2022; Canón-Beltrán et al., 2024) have emerged as critical players in this complex regulatory network. These growth factors have been extensively studied for their ability to act independently of gonadotropins or in concert with them, enhancing their effects. IGF and EGF are known to influence various stages of ovarian function, including the growth and development of ovarian tissues, the synthesis of steroid hormones, and the maturation of oocytes (Hsueh et al., 1994; Mukherjee et al., 2014).

In light of these findings, the present review aims to examine how gonadotropins regulate ovarian steroidogenesis and oocyte maturation in fish, a group of vertebrates where these processes are vital for reproductive success. Additionally, this review explores the role of intra-ovarian growth factors, particularly IGF and EGF, in these regulatory pathways. These growth factors may operate independently or synergistically with gonadotropins, thereby contributing to the intricate control of ovarian reproduction. By synthesizing current research, this review enhances our understanding of the molecular and physiological processes underlying fish reproduction. It identifies potential areas for further investigation, paving the way for future scientific advancements.

2. Regulation of fish ovarian development, steroidogenesis, and maturation by gonadotropins

In the piscine community, reproduction often follows the rhythm of the seasons, with hormonal orchestration ensuring the right timing for female gonadal growth, vitellogenesis, and the FOM. This intricate process is influenced by geographical and environmental factors, with the endocrine system playing a decisive responsibility in bridging the environment and reproductive organs. Ecological cues like daylight and temperature are sensed via the brain, triggering the discharge of gonadotropin-releasing hormone (GnRH), a well-known master conductor of reproductive events across vertebrates (Fig. 1). GnRH stimulates the pituitary gland to release gonadotropic hormone (GTH), which drives the growth and maturation of germ cells. By attaching to receptors on Leydig cells in the testes and theca and granulosa cells in the ovaries, GTH exerts its effects on both organs. Initially, GTH induces 17β-estradiol (E2) production in ovarian cells or 11-ketotestosterone in testicular Leydig cells. As germ cells mature, GTH promotes the synthesis of 17α,20β-dihydroxy-4-pregnen-3-one (17,20β-P), a critical maturation-inducing steroid (MIS) in many piscine species.

Oocyte growth, as well as its maturation, have been extensively studied across various vertebrates, including amphibians (Masui and Clarke, 1979; Maller and Krebs, 1980; Hammes, 2004), mammals (Mehlmann, 2005) and fish (Thomas, 1994; Nagahama et al.,

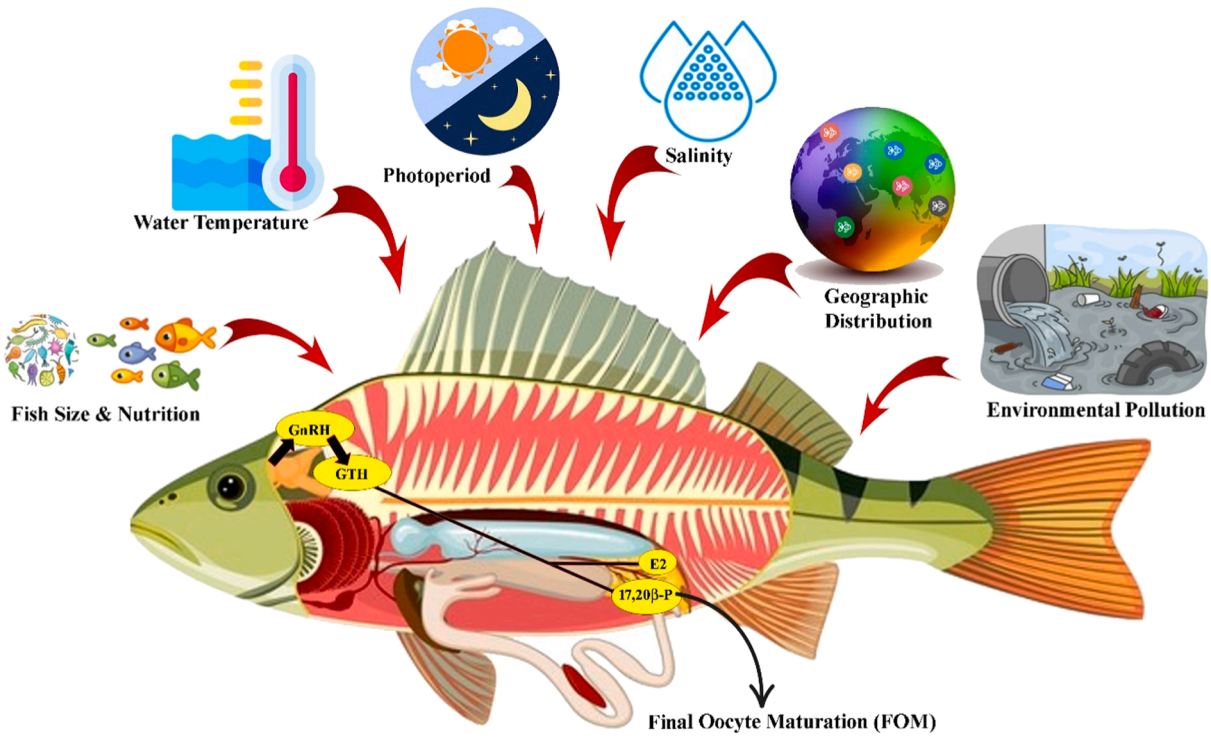

Fig. 1. Environmental and geographic factors influencing final oocyte maturation in fish.

1994; Nagahama, 1997; Bhattacharyya et al., 2000; Sen et al., 2002; Mukherjee et al., 2006). Fish has offered the most thorough insights regarding the endocrine control of oocyte development and maturation. Oocyte development and maturation in fish are controlled by a symphony of LH, FSH, MIS, and MPF, according to research employing well-characterized *in vitro* and *in vivo* systems.

In chub Mackerel (*Scomber japonicus*), the final maturation of oocytes involves a switch from FSHR to LHR expression and alterations in steroid production, regulating the effects of LH and FSH on vitellogenesis in theca and granulosa cells (Nyuji et al., 2013). In grey mullet, OM is triggered by a combination of hormones and growth factors rather than a single hormone. The process begins with the steroidogenic actions of gonadotropins (human chorionic gonadotropin [hCG], luteinizing hormone [LH]), gonadal steroids (T, DHP, 17α-OHP, E2 and P4), and non-gonadal hormones like insulin and IGF-I. E2 and DHP play significant roles in OM triggered by LH, IGF-I, and hCG (Das et al., 2014). In rainbow trout (*Oncorhynchus mykiss*), the steroidogenic shift during vitellogenesis involves the transcriptional regulation of steroidogenic proteins and gonadotropin receptor genes, with FSH and IGFs losing their stimulatory effects on cyp19a1a expression and LH inhibiting cyp19a1a transcription (Nakamura et al., 2016).

In vitro administration of hCG induced the final meiotic OM in post-vitellogenic immature follicles of tilapia via induction of 20β-HSD mRNA expression occurred only in the ovary (Senthilkumaran et al., 2002). The temporal progression of hCG-induced FOM and ovulation in chub mackerel mirrors the regular timeline instigated by endogenous pituitary LH (Shiraishi et al., 2008). In catfish species like *Clarias batrachus* and *Clarias gariepinus*, sexual maturation is induced by hCG administered via an osmotic pump, elevating the levels of transcripts related to gonadal growth (Murugananthkumar et al., 2017). hCG has been shown to induce OM and ovulation when injected unilaterally into the ovary of orange-spotted grouper (*Epinephelus coioides*) (Tang et al., 2020). Nguyen et al. (2020) suggested that hCG may indirectly influence ovarian development in previtellogenic eels, as a notable elevation in plasma levels of 11-ketotestosterone (11-KT) was observed in eels administered hCG. Using recombinant follicle-stimulating hormone (rec-FSH) and hCG may facilitate the induction of puberty in captive eels and, more broadly, in teleost fish. A study involving the single-spawning European cyprinid (ide) showed that hCG-induced final OM, with the latency period being nearly twice as long in females treated with hCG compared to those administered other spawning agents (Kucharczyk et al., 2020). In zebrafish, LH maintains OM by initiating MIH synthesis from cholesterol and inducing downstream LH signaling in steroidogenesis through the StAR protein (Shang et al., 2019). In common carp, LH alone can regulate both vitellogenesis and final OM, while FSH has an unclear role (Hollander-Cohen et al., 2019).

To control fish reproduction, one must be aware of how pituitary gonadotropins (FSH and LH) contribute to gonad development in their unique ways. Only by combining species-specific assays with target hormones can this be accomplished. Approximately eleven different fish species have Ag-Ab quantitative assays available for either GTHs alone or in combination. By studying the architecture of the pituitary gonadotrope, the steroidogenic activity of both GTHs, their function in gametogenesis, and the patterns of interaction between GTHs and their conspecific receptors, functional recombinant gonadotropins have been developed for more than 20 teleost species. More research, including a wider variety of species, is needed to have a complete picture of the physiological roles of GTHs in connection to evolution, different reproductive strategies, and gonad growth patterns (Molés et al., 2020).

3. Role of gonadotropins in fish oocyte growth

Vitellogenesis is crucial to FOM. Its primary role is sequestering and packaging vitellogenin (Vtg) and absorbing VLDL. Vtg is liver-produced and only produced in developing females. Growth-promoting ovarian follicles selectively sequester this via VtgRs that generate Vtg-coated vesicles. Vesicles combine with lysosomes to produce multivesicular bodies. Gonadotropins stimulate theca cells to produce T, which is aromatized to E2 in the ovarian follicle's granulosa cells during vitellogenesis. After stimulation, plasma E2 levels rise, causing the liver to produce Vtg, which VtgR recognizes and incorporates into the oocyte. After vitellogenesis, plasma LH rises, and E2 falls. This temporarily raises plasma T and MIS levels, which trigger FOM in follicular layers. Ovulation occurs when the follicle ruptures, releasing the oocyte. Following ovulation, follicular cells alter morphologically and release P4 and E2. Vitellogenesis and the FOM are essential in female reproductive physiology (Gabilondo et al., 2022).

The process of vitellogenesis is the primary catalyst for the extraordinary development of fish oocytes. The liver produces and deposits yolk proteins into the oocytes, supplying the embryos with the necessary nutritional reserves for development (Nagahama, 1994; Tyler and Sumpter, 1996). This mechanism is similar to that of fish and other animals that lay eggs. Gonadotropins (GTHs) directly affect the ovary to generate E2, which regulates the whole process (Nagahama, 1994). Nowosad et al. (2015) studied the biochemical changes in muscles and ovaries of maturing female European eels during hormonal stimulation with carp pituitary homogenate. They found differentiation in oocyte size, changes in body and gonad composition, and decreased relative fat content in muscles and ovaries. They also observed different trends for polyunsaturated fatty acids. LH plays a more critical role in red seabream than FSH, potentially regulating these progressions (Gen et al., 2000; Kagawa et al., 1998, 2003). During vitellogenesis, GTHs can distinctly regulate vitellogenin and estrogen receptors. Regulating E2 production is crucial during vitellogenesis, and the ovarian cytochrome P450 aromatase plays a critical role as a key enzyme for E2 biosynthesis (Tanaka et al., 1992; Gen et al., 2001; Kagawa et al., 2003).An earlier study revealed a significant association between 17,20β-P and the oocyte maturational story of *Tenualosa ilisha*, highlighting a strong correlation between plasma E2 and T during the vitellogenic and post-vitellogenic stages (Pramanick et al., 2013). In addition, the study found that most teleosts achieve oocyte maturation competence (OMC) and produce MIS via de novo protein synthesis. However, there is no change from estrogenic to progestational steroid production when transitioning from vitellogenic to post-vitellogenic phases occurs (Pramanick et al., 2013).

Photothermal treatment modulates gonadotropin regulation in the pituitary, accelerating the seasonal profiles of testosterone (T) and E2, leading to gonadal development in Atlantic salmon (female), *Salmo salar* (Taranger et al., 2015). During different developmental stages, the expression of GnRH and GnIH (inhibitory form) varies in the ovarian follicles of zebrafish. In the late-vitellogenic

stage, an in vitro study showed that GnRH and GnIH stimulate germinal vesicle breakdown (GVBD). Caspase-3 activity increased with GnRH but was inhibited by GnIH, showing an opposite effect to GVBD. These results show that GnRH3 and GnIH are required for LH-induced OM to resume (Fallah et al., 2020).

A preliminary study was conducted on the application of rGTHs (rFSH and rLH) in the teleost species flathead grey mullet (*Mugil cephalus*) to stimulate the process of oogenesis, starting from previtellogenesis and continuing until maturity in order to produce eggs and larvae. The research findings indicate that both rGTHs exhibit efficacy in stimulating oogenesis in female flathead grey mullets and facilitating the production of flowing sperm in males. These results contribute additional evidence to support the involvement of Gths in teleost gametogenesis (Ramos-Judéz et al., 2021). In earlier studies, both in vitro and in vivo models were used to illustrate the effects of eel-specific rGTHs on oocyte development. In this in vitro investigation, mature European eel (*Anguilla anguilla*) oocytes were examined for their dose-effect responses to CPE and recombinant luteinizing hormone (rLH) at several time points: pre-, during, and post- a 12- and 18-hour incubation period (Jéhannet et al., 2023).

4. Role of gonadotropins in FOM

LH plays a decisive responsibility in the final maturation of gametes, primarily by triggering the production of the MIS (Nagahama et al., 1994; Nagahama, 1994). The release of LH from the master gland triggers the production of MIS by the thecal and granulosa cell layers of the ovarian follicle, specifically 17,20β-P in various piscine species (Planas et al., 2000; Mishra and Joy, 2006; Zapater et al., 2012; Crespo et al., 2012). A complicated interaction between inhibitory G-proteins mediating signal transduction pathways and MIS receptors on the oocyte allows MIS to affect OM. This MIS signaling prompts the construction of an MPF through a phosphorylated complex of cyclin B and cdc2. MPF then drives the process of GVBD and OM (Nagahama and Yamashita, 2008; Mukherjee et al., 2014; Das et al., 2017; Nath et al., 2018) (Fig. 2).

IGF-III performs a crucial function by acting on the IGF type I receptor to promote the consequences of gonadotropin on multiple aspects of oogenesis and spermatogenesis in various fish species. The recently acquired data from IGF-III offer valuable insights into the molecular mechanisms behind fish reproduction. Additionally, it underscores the significance of the IGF classification in facilitating the impact of gonadotropin signaling on animal reproduction (Li et al., 2021).

Findings from a recent study on Medaka (*Oryzias latipes*) show that while FSH is required for follicle development and LH is required for OM, neither is necessary for spermatogenesis in Medaka (Kitano et al., 2022).

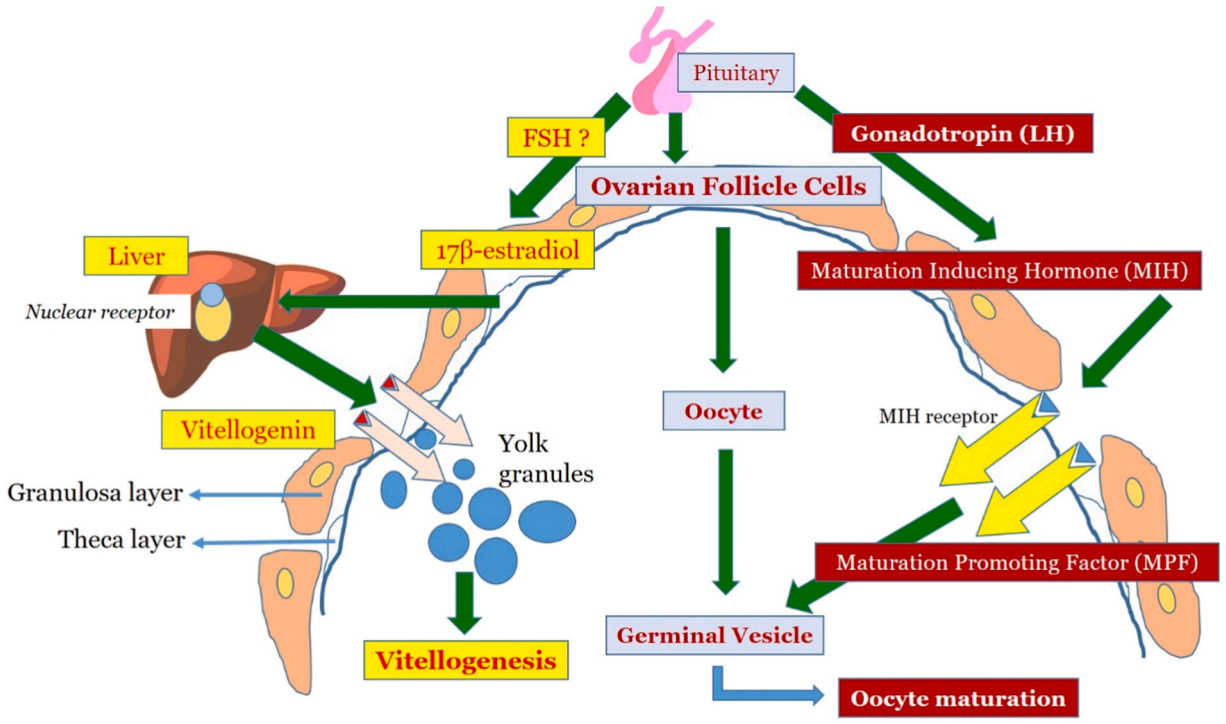

Fig. 2. Schematic diagram of hormonal regulation of oocyte growth and oocyte maturation. The major event responsible for fish oocyte growth is known as vitellogenesis which is very common among egg-laying species, including fish. Vitellogenesis is characterized by copious deposition of yolk proteins within the oocytes via hepatic production, thus affording the main nutritional reserves required for embryonic development. After being released from the pituitary, gonadotropin (luteinizing hormone, LH) stimulates the production of maturation-inducing hormone (MIH) (17α, 20β-dihydroxy-4-pregnen-3-one, 17α, 20β-DP in majority fishes) by the theca and granulosa cell layers. The MIH signal induces maturation-promoting factor (MPF) production leading to germinal vesicle breakdown and oocyte maturation. (Reproduced from Senthilkumaran et al., 2004).

5. Endocrine control of FOM

OM marks a critical re-entry into meiosis, occurring just before ovulation and subsequent fertilization. This process encompasses the GVBD, meiotic spindle assemblage, chromosome abridgement, and construction of the initial polar body. Meiotic maturation of post-vitellogenic oocytes, accelerated by gonadal steroids and luteinizing hormone, is essential in sexual development in fish and other lower vertebrates (Nagahama, 1997). As vertebrates, fish have been the subject of most research into LH-induced MIS synthesis and subsequent MPF generation. MIS is produced solely in the granulosa cell layer of the ovary under the effect of LH, triggering the maturation process (Nagahama, 1997; Planas et al., 2000). 17,20β-P is the MIS in many teleosts, as stated by Nagahama in 1997. In sciaenid fish, 17α,20β,21-trihydroxy-4-pregnen-3-one (20β-S) fulfils this function, according to Thomas in 1994.

In catfish (*Heteropnuestes fossilis*), vasotocin, an oligopeptide hormone, is reported to induce final OM, oocyte hydration, ovulation, and prostaglandin secretion. When binding to its receptor located in the follicular layer/ oocyte membrane, Vasotocin regulates the shift in steroid production by suppressing E2 and promoting 17,20β-DP. This leads to a positive autocrine feedback loop inside the ovary. (Joy and Chaube, 2015). In *Cyprinus carpio*, G-protein coupled estrogen receptor protein and mRNA are absent in follicular cells but present in oocytes, with their expression peaking in late vitellogenic oocytes. Removal of follicular cells led to spontaneous OM induced by 17,20β-P, which E2 inhibited. E2-induced cAMP production in oocytes was reversed by treating them with 17,20β-P (Majumder et al., 2015).

Fascinatingly, zebrafish research revealed the functional regulation of zinc in OM mediated via androgens (Li et al., 2019). An OM assay in zebrafish also predicted the triumph of in vitro OM subsequent in vivo revelation. However, it remains unclear if reductions in MIH-induced OM in vitro correlate with reproductive performance losses (Miller et al., 2022). Additionally, an optimal amount of vitamin D3 was shown to influence vitellogenin synthesis and stimulate ovarian development in zebrafish through the *vdr/cyp19a1a/er/vtg* gene axis (Yang et al., 2024).

6. Maturation-inducing steroid (MIS) in fish

In teleosts, the steroid 17,20β-P has long been celebrated as the critical MIS for species like salmon (Nagahama and Adachi, 1985), common carp, freshwater perch, *Anabas testudineus* (Bhattacharyya et al., 2000), and *Labeo rohita* (Sen et al., 2002). Recently, another potent MIS, 17α,20β,21-trihydroxy-4-pregnen-3-one (20β-S), also known as 20β-dihydroxy-11-deoxy cortisol, has been identified in *Micropogonia undulatus* (Atlantic croaker), *Cynoscion nebulosa* (spotted sea trout) (Trant et al., 1986; Trant and Thomas, 1988, 1989), and in *Morone saxatilis* (striped bass) (King et al., 1997). This steroid has shown remarkable efficacy in inducing in vitro GVBD.

A fascinating study on *Tenualosa ilisha* revealed that the OM triggered by 17,20β-P could be effectively inhibited by LY294002 and Wortmannin (PI3 kinase inhibitors). The research demonstrated that 17,20β-P reached peak activation of PI3 kinase after 90 minutes and cdc2 kinase after 16 hours. The research directed to appraise the roles of PI3 kinase, mitogen-activated protein kinase (MAP

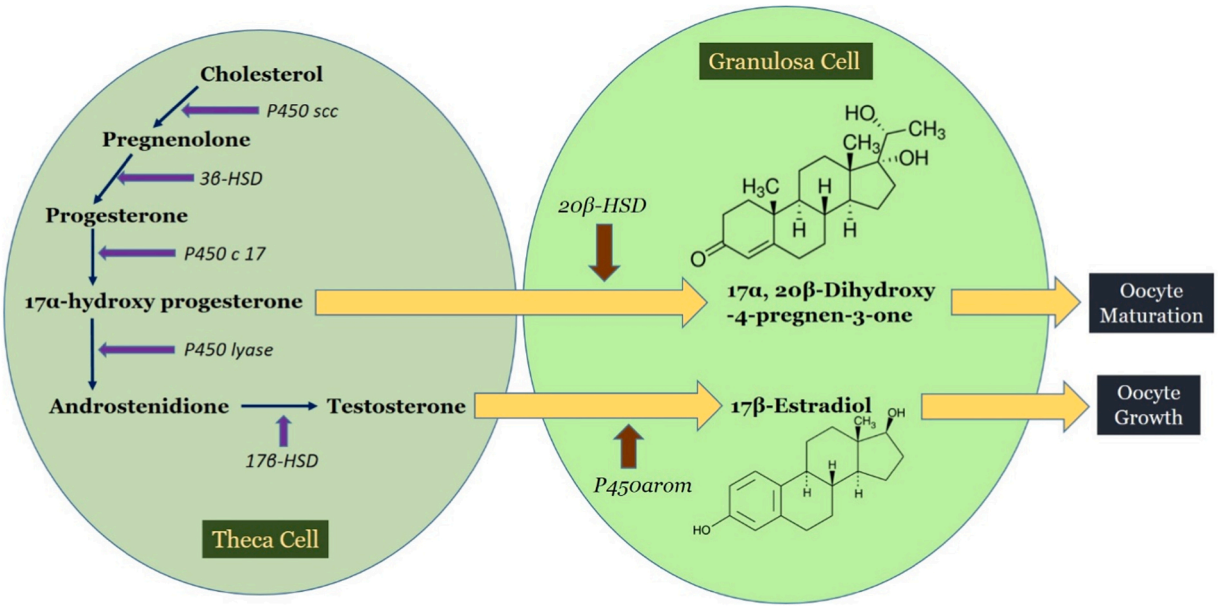

Fig. 3. Two-cell type model: Schematic representation of shift in steroidogenesis from theca to granulosa cells. GTH appears to stimulate the activity of cholesterol side-chain cleavage cytochrome P450 (P450scc). Fish granulosa cells lack the P450scc system. 17α-hydroxyprogesterone, produced by theca cell layer, navigates through basal lamina and is converted to 17α, 20β-DP by the granulosa cell layer, where GTH induces de novo synthesis of 20β-hydroxysteroid dehydrogenase (20β-HSD), the crucial enzyme which converts 17α-hydroxyprogesterone to 17α, 20β-DP. (Reproduced from Nagahama, 1997; Senthilkumaran et al., 2004).

kinase), and cdc2 kinase in 17,20β-P-induced OM. It found that MAP kinase underwent rapid phosphorylation and activation within 1–2 hrs of treatment with MIS, occurring hours before cdc2 kinase activation. Notably, the selective MAP kinase inhibitor PD98059 blocked MAP kinase phosphorylation and activation but did not affect cdc2 kinase activation and GVBD induced by MIS. This indicates that the activation of PI3 kinase is necessary to activate cdc2 kinase and OM induced by 17,20β-P in *T. ilisha*. On the other hand, although MAP kinase is active, it is not crucial for cdc2 activation and OM in *T. ilisha* (Pramanick et al., 2014).

Further research on European eel (*Anguilla anguilla*) has shown that high concentrations of steroids like E2 and 17α,20β-dihydroxy-4-pregnen-3-one (DHP) in eggs negatively impact embryonic developmental competence. Conversely, high transcript levels for genes *dio1* and *cpt1b* were positively correlated with embryonic developmental success. This study highlights the significant influence of maternal steroid and mRNA transcript transfer on embryonic survival variability in captive European eel reproduction (Kottmann et al., 2021).

The MIS, DHP and 20β-S have been categorised across various teleosts. Assays revealed that DHP, 17α-hydroxyprogesterone (17OHP), a DHP precursor, 17α,20α-dihydroxy-4-pregnen-3-one (αDHP), and 20β-S all exhibit convincing maturation-inducing endeavour judged with other C21 steroids. Nevertheless, the amounts of 17OHP, αDHP, and other C21 steroids produced during OM were meagre, indicating that 20β-S may be formed from DHP after OM through metabolism (Hasegawa et al., 2024).

7. Two-cell type model of sex steroid secretion in fish

The maturation and growth of ovarian follicles in vertebrates hinge on the intricate molecular dance of sex steroid hormone secretion. Two major steroid hormones, E2 induced by FSH and 17,20β-P stimulated by LH, play pivotal responsibilities in fish ovarian follicle development. These hormones provide a thorough investigation of the involvement of the follicular layer in their production (Fig. 3). In other vertebrates, a basement membrane separates a teleost ovarian follicle's two main cell layers: the thecal layer on the outside and the granulosa layer on the inside (Nagahama, 1983). Naive separation procedures developed for salmonid fish ovarian follicles enable the separation of these layers, facilitating the study of each layer's contributions and the role of gonadotropic hormones (GTH) in 17,20β-P production (Nagahama, 1994; Nagahama et al., 1994).

The thecal layer responds to GTH by producing significant quantities of 17α-hydroxyprogesterone (17α-OHP). This precursor then migrates to the granulosa cells, where GTH II activates 20β-HSD, the enzyme crucial for converting 17α-OHP to 17,20β-P. Cloning of cDNAs from rainbow trout and medaka ovarian samples identified the steroidogenic enzymes essential for 17,20β-P and E2 biosynthesis (Nagahama et al., 1995). Investigations using northern blot and whole-mount in situ hybridization with these cDNA clones

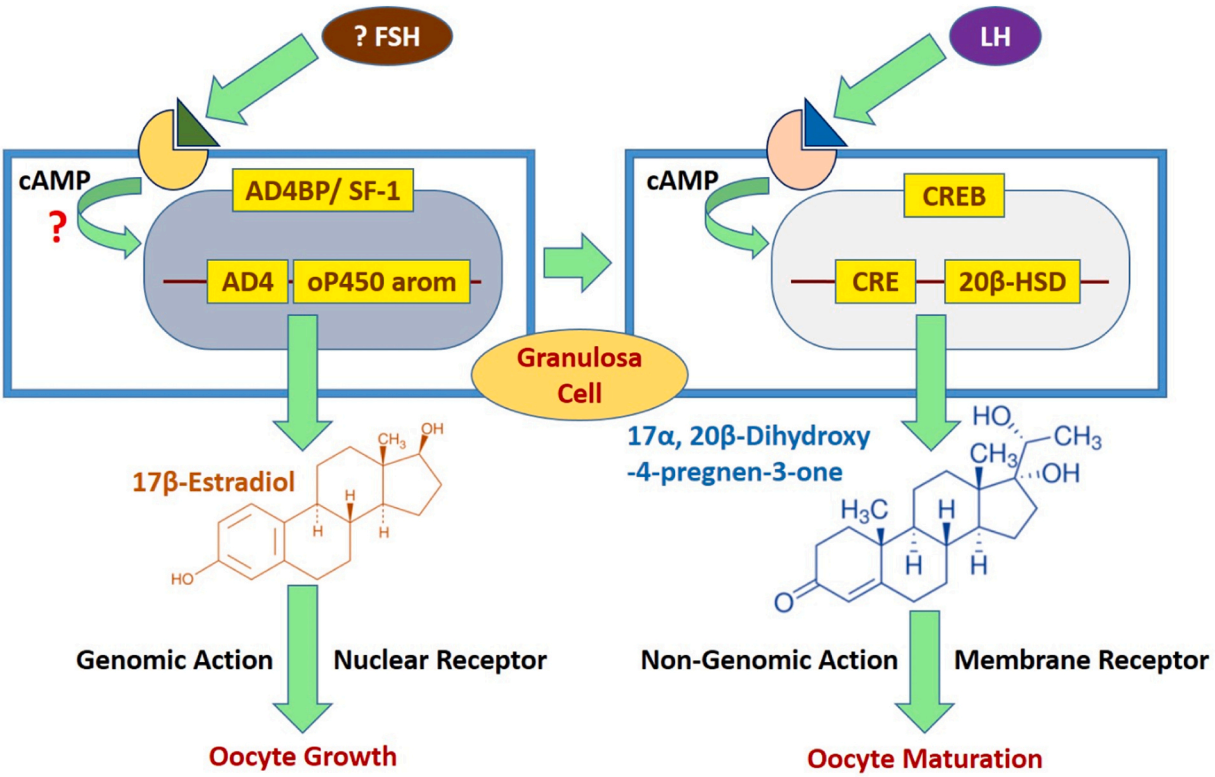

Fig. 4. Steroidogenic shift and its molecular pathway in granulosa cells of ovarian follicles: transcriptional regulation of oocyte growth and maturational events. GTH creates a cross-talk among genes including transcription factors to accelerate the shift from E2 to 17α, 20β-DP. (Reproduced from Senthilkumaran et al., 2004).

revealed increasing trends in follicular p450scc, 3β-HSD, and p450c17 mRNA transcripts during oocyte growth and maturation. When isolated thecal layers were incubated with gonadotropin, p450scc mRNA levels rose significantly. Gonadotropin's effect was even more pronounced in granulosa cells, dramatically enhancing p450scc mRNA expression, which was otherwise undetectable without gonadotropin. The upregulated expression of p450scc, 3β-HSD, and p450c17 transcripts in granulosa cells explains the substantial increase in 17,20β-P production during natural and gonadotropin-induced OM. Conversely, p450arom mRNA levels, higher during oocyte growth, rapidly declined as maturation progressed, correlating with the follicle's reduced capacity to produce E2.

8. Mechanism of the steroidogenic shift in fish

In fish ovaries, E2 production dominates throughout oocyte growth, while MIH takes the stage during OM. This fascinating transition in the steroidogenic trail from E2 to 17,20β-P or 20β-dihydroxy-11-deoxy cortisol happens just before OM (Fig. 4). Developing ovarian follicles contain genes that code for proteins involved in steroidogenesis, which is thought to govern variations in the amounts of certain steroidogenic enzymes (Nagahama and Yamashita, 2008). Part one of this process involves switching from testosterone to 17α-hydroxyprogesterone in the production of precursor steroids. Part two involves changing the final steroidogenic enzymes from P450arom (which produces E2) to 20β-HSD (which produces 17,20β-P or 20β-S) (Fig. 4). The selective increase in 17, 20β-P is accomplished by boosting the transcription of 20β-HSD, the critical enzyme for 17,20β-P biosynthesis (Senthilkumaran et al., 2004). Conversely, reducing E2 production after oocyte growth involves targeting P450arom (Yoshiura et al., 2003).

GTHs orchestrate this steroidogenic shift by interacting with multiple genes, including transcriptional regulators. The specific mediators of cAMP are still unknown in teleosts, even though it is a second messenger in the production of E2 and 17,20β-P (Nagahama, 1994, 1997) and several other GTH-related activities (Planas et al., 1993, 1997). The granulosa cell cAMP transactivation and the R2C Leydig cell basal transactivation in mammals is regulated by a synergistic effect of CREB and steroidogenic factor-1 (SF-1) (Carlone and Richards, 1997). Steroidogenic tissues contain genes that are controlled by thyroid and steroid hormones. Members of the orphan nuclear receptor family, like Ad4BP/SF-1, play an essential role as transcription factors for these genes (Lala et al., 1992; Morohashi et al., 1992; Honda et al., 1993; Omura and Morohashi, 1995; Zhu et al., 2000). GTHs probably use these transcriptional factors during teleost meiotic development to trigger the steroidogenic transition.

Many gonadotropin-releasing hormones and the duality of gonadotropins influence gonadal function differently. The Δ4 pathway is mainly used to synthesise sex hormones through the steroidogenic pathway; however, the Δ5 pathway was also clearly visible. Another factor to consider is the change in steroidogenesis that often happens in the developing follicles when the oocytes reach their final stages of maturation. However, the exact process is unclear in males (Tenugu et al., 2021).A recent research investigation showed that the ratio of sex reversal caused by levonorgestrel (LNG) varies across concentration ranges, suggesting that LNG exhibits estrogenic and androgenic effects. The protocol of this study presents a substitute for the conventional animal model employed to evaluate the potential of substances to disrupt the endocrine system. The findings demonstrate that when medaka fish (*Oryzias latipes*) are exposed to LNG, it can cause both masculinization and feminization, depending on the relative levels of androgenic and estrogenic effects (Watanabe et al., 2023).

9. MIS receptors in fish

MIS has been demonstrated to bind to a specific progestin receptor on the oocyte plasma membrane, thereby initiating OM through a nongenomic mechanism, culminating in the development of a fully mature oocyte that can be ovulated and fertilized (Nagahama and Yamashita, 2008; Thomas, 2012). While the involvement of three different types of receptor proteins in the mediating of nongenomic progestin actions in reproductive tissues has been established, the precise roles of these proteins in the induction of OM by MIS in amphibians and fish are still not fully understood (Aizen et al., 2018). These proteins include nuclear progesterone receptors (nPRs) (Boonyaratanakornkit et al., 2001), seven-transmembrane progesterone membrane receptors (mPRs) (Thomas, 2006) and a single transmembrane progesterone receptor membrane component 1 (PGRMC1) (Peluso et al., 2006; Thomas, 2006).

Multiple studies have identified the nuclear progesterone receptor (nPR) as essential for ovulation in fish. In periovulatory periods, nPR influences prostaglandin production and function by regulating the expression of phospholipase A2 (PLA2G4A) and an isoform of the prostaglandin receptor (EP4b), mediated by the actions of 17,20β-P (Baker and Van der Krakk, 2019; Baker et al., 2021). The role of nPR in modulating the beginning of OM in teleosts remains uncertain. While the overexpression of nPR in zebrafish oocytes was observed to expedite ovulation maturation in response to DHP (Hanna and Zhu, 2011), the elimination of nPR in zebrafish by TALEN technology did not hinder ovulation maturation in this species (Zhu et al., 2015).

Binding experiments have verified the existence of MIS receptors on oocyte membranes. The distinct attachment of 17,20β-P to the plasma membrane of defolliculated rainbow trout oocytes, *Oncorhynchus mykiss*, was discovered and detailed by Yoshikuni and colleagues (1993). A high-affinity site with a Kd of 0.8 nM and a Bmax of 0.2 pmol/mg protein was identified by their Scatchard analysis, whereas a low-affinity site with a Kd of 0.5 pM and a Bmax of 1 pmol/mg protein was reported. This pattern of receptor attachment has also been observed in salmonids, flounder, and major carp. Notably, MIS receptors are more abundant in oocytes as they mature, and treatment with GTH significantly boosts MIS receptor levels, suggesting that GTH not only enhances MIS production but also promotes MIS receptor synthesis (Sen et al., 2002). Zhu et al. (2003) made a significant discovery by identifying a novel family of membrane-bound progestin receptors (mPR) from an ovarian cDNA library of spotted seatrout. This discovery further enhanced our understanding of the molecular characteristics of the MIS receptor. These receptors, known as G-protein-coupled receptors (GPCRs) and consisting of mPRα, mPRβ, and mPRγ, appear to play a crucial role in facilitating the non-genomic impacts of steroids. The increased sensitivity of oocytes to MIS and their maturation process under GTH influence are likely reflected in the fact that mPRα

expression increases in fully mature oocytes and continues to rise in response to GTH treatment (Yoshikuni et al., 1993; Zhu et al., 2003; Berg et al., 2005). When levels of mPRα were reduced via microinjection of antisense morpholino oligonucleotides specific to goldfish mPRα, an inhibition of OM induced by MIS was observed (Tokumoto et al., 2006). This finding unequivocally established mPRα as the indispensable MIS receptor for OM in goldfish, highlighting its pivotal role in the reproductive process.

The finding that testosterone has significant binding affinity for recombinant zebrafish mPRα and may activate MAPK in mPRα-transfected cells (Hanna et al., 2006) suggests that mPRα may facilitate androgen-induced OM in fish. However, this finding also underscores the need for more research, as evidence is lacking concerning the correlation between the binding affinity of testosterone for zebrafish mPRα and its effectiveness in inducing OM. Likewise, the lack of documented findings on the efficacy of selective nPR and mPR agonists in the induction of zebrafish OM, which would elucidate the relative significance of each receptor in regulating OM (Aizen et al., 2018), highlights the importance of further investigation in this area.Several new vertebrate species have recently been shown to have seven transmembrane span proteins named GPR30 and mPR^3, which stand for membrane estrogen receptor and membrane progestin receptor, respectively. A paper summarizes all the evidence that these receptors behave as GPCRs and activate G-proteins. There appears to be a separate steroid receptor in fish gonads, which may also function as a GPCR, according to preliminary research on ligand binding, G-protein activation, and molecular size of a membrane androgen receptor (mAR) in croaker ovaries (Thomas et al., 2006).

Progesterone receptor membrane component 1 (PGRMC1) is a protein composed of 194 amino acids, with a molecular weight ranging from 26 to 28 kDa, distinguished by a solitary transmembrane domain. PGRMC1 and its closely related counterpart, PGRMC2, belong to the membrane-associated progesterone receptor (MAPR) family (Thomas, 2012). The PGRMC1 gene is linked to various functions, such as axonal guidance in embryogenesis, steroid synthesis and cholesterol metabolism, modulation of reproductive behaviours, endocytosis, interaction with PAIRBP-1, a component of the progesterone receptor, and functioning as an adapter protein. PGRMC1 may play a role in progestin-induced OM in fish, based on the discovery that *pgrmc1* mRNA expression in rainbow trout ovaries is upregulated during oocyte development (Mourot et al., 2006). PGRMC1 interacts with other proteins, including SCAP and Insig-1, essential for sterol production and activation of steroidogenesis. A range of ligands has been identified or proposed to interact with PGRMC (Thomas, 2012). Recent findings utilizing AG205, a solid and selective inhibitor of PGRMC1, indicate that PGRMC1 may function as an adapter protein for EGFRs in zebrafish oocytes (Aizen and Thomas, 2015).

10. Oocyte Maturational Complex (OMC) in response to gonadotropin

Early studies primarily explored how MIH and LH control OM in fish and amphibians. However, recent evidence highlights that LH is pivotal in regulating OM in two distinct phases (Patiño et al., 2001; Patiño and Sullivan, 2002). In the first stage, OMC is achieved by the oocyte when the follicle (somatic) cells learn to synthesize MIS. The second phase is characterized by the oocyte's release from meiotic arrest, triggered by MIS produced by the somatic follicle cells. MIS initiates this process by activating the maturation-promoting factor (Nagahama et al., 1994; 1997).

Initial studies on LH-dependent OMC were conducted with Atlantic croaker. By culturing ovarian follicles in vitro and applying LH or HCG, it was found that the acquisition of OMC depends on new transcription and translation, rather than steroid production (Patiño and Thomas, 1990 a,b; Sen et al., 2002). These findings refuted earlier beliefs that follicular steroid production, an LH effect, was crucial for OMC in *Xenopus laevis* (LaMarca et al., 1985). In addition, they established a two-step model of LH-dependent OM, whereby the absorption of MIS is the first step, and MIS production and meiosis restart are the second (Review by Patiño et al., 2001). It was further noted that OMC falls under LH's maturational influence, not FSH's follicular growth action (Patiño et al., 2001). In Atlantic Croaker, adenylate cyclase activity and cAMP analogues are potent inducers of OMC, with HCG's effect on OMC being blocked by protein kinase A inhibitors (Chang et al., 1999). In the Indian freshwater catfish, *Heteropneustes fossilis*, an inhibitory mechanism for LH surge and secretion is crucial for meiotic resumption and ovulation. This suggests that two regulatory systems-peptidergic and aminergic-control OM in this species (Kumari et al., 2021).

The transcriptomic analysis proposed that a new functional LHR2 in the Orange-Spotted Grouper (*Epinephelus coioides*) may work with LHR1 to transmit LH signals. This new LHR2 may have a significant role in the process of OM triggered by HCG in the organism's body. Both DHP and 20βs are putative MIH of this species. The substantial rise in npr levels during OM indicates that it may function not only in ovulation but also in maturation. To facilitate the hydration of oocytes, cathepsins, ion pumps, and ion channels were stimulated, resulting in water absorption through both AQP1 subtypes (Tang et al., 2019). Xiong et al. (2020) showed that microRNA 200 (miR 200) can control OM in a knockout female zebrafish model (chr23-miR-200 KO). This regulation occurs through the modulation of LH production and the regulation of oxytocin and vasotocin, possibly involved in fish ovulation. Recently, it has been shown that insulin-like growth factors IGF-I and IGF-II did not trigger the OM process in rainbow trout follicles. IGF1 did not enhance the oocyte's ability to undergo maturation in vitro. IGFs were not discovered to control either of these processes in the rainbow trout (Weber, 2023). Thyroxin, along with GnRH, has been shown to accelerate OM in *Labeo rohita*, suggesting the role of thyroxine in inducing spawning, fecundity and survivability of larval stages (Eslamizadeh et al., 2024).

11. Maturation Promoting Factor (MPF) in fish

The discovery of receptors on fish oocyte surfaces suggests the presence of a crucial cytoplasmic factor known as MPF, first identified in oocytes of amphibians by Masui and Clark in 1979. Like its amphibian counterpart, fish MPF is composed of two key elements: the catalytic cdc2 kinase (34 kDa) and the regulatory cyclin B (46–48 kDa) (Nagahama, 1994). When MIH triggers a signaling cascade in oocytes, it ultimately leads to the formation of MPF, which then drives the resumption of meiosis halted in

prophase I (Balamurugan and Haider, 1998). In goldfish, cyclin B degradation is initiated by ubiquitin-independent cleavage via the 26S proteasome and completed through ubiquitin-dependent proteolysis (Tokumoto et al., 2020). This study found that the 26S proteasome from immature oocytes could cleave cyclin B, unlike mature oocytes, highlighting differences in proteasome activity across developmental stages.

In zebrafish, a potent hepatotoxin, Microcystin-LR, has been shown to degrade ovarian structures and reduce cAMP levels in oocytes. It also up-regulates ERK and MPF protein phosphorylation to induce OM without activating PKA (Zhan et al., 2020). Research on the spotted steed (*Hemibarbus maculatus*) revealed that the Anti-Müllerian hormone significantly enhances in vitro GVBD, cyclin B expression, and MPF levels. Concurrently, there is a decrease in *Cyp19a1a* expression and E2 production (Liu et al., 2021).

12. Development and initiation of MPF in fish

While cyclin B is missing from immature oocytes, the 35 kDa cdc2 is present. A mechanism initiated by signal transduction from the surface receptor mPRα leads to the production of cyclin B through the translational activation of incognito mRNA. This pathway involves cyclic AMP (cAMP), inhibitory G-protein (Gi), and protein kinase A (PKA). Cyclin B interacts with preexisting cdc2, which triggers cdk activating kinase (CAK) phosphorylation at T161 (T), activating cyclin B. The mobility cdc2 changes from 35 to 34 kDa due to its activation (Fig. 5).

Like in other vertebrates, FOM involves multiple signaling pathways converging to trigger the MPF, which drives the development process. Although MPF's role in OM is consistent across species, the signaling mechanisms steering to its activation vary (Schmitt and Nebreda, 2002; Voronina and Wessel, 2004). LH acts as a gonadotropin in fish, facilitating MPF activation by promoting the production of MIH (Balamurugan and Haider, 1998; Nagahama and Yamashita, 2008).Research has extensively explored the molecular machinery behind MPF development and initiation in fish and amphibians (Hirai et al., 1992; Yamashita et al., 1992; Kajiura et al., 1993; Katsu et al., 1993; Nagahama, 1994; Balamurugan and Haider, 1998; Yamashita, 1998; Basu et al., 2004; Nagahama and Yamashita, 2008; Jessus et al., 2020). MIH in fish has been identified as a steroid, similar to 17,20-DP, 17–20,21-trihydroxy-4-pregnen-3-one (20S), and 11-deoxycorticosterone (Nagahama and Adachi, 1985; Trant et al., 1986; Trant and Thomas, 1989; Patiño and Thomas, 1990; King et al., 1994; Unal et al., 2008; Tokumoto et al., 2011). In addition to steroids, other endogenous factors such as activin (Pang and Ge, 1999), insulin (Dasgupta et al., 2001; Das et al., 2016a), growth hormone (Sarang and Lal, 2005), and IGF-I (Grigorescu et al., 1994; Kagawa et al., 1994; Duan, 1997; Weber and Sullivan, 2000, 2001; Mukherjee et al., 2006; Das et al., 2016b) also play roles in stimulating OM. Recent research has revealed that conspecific vitellogenin regulates OM onset in catfish by

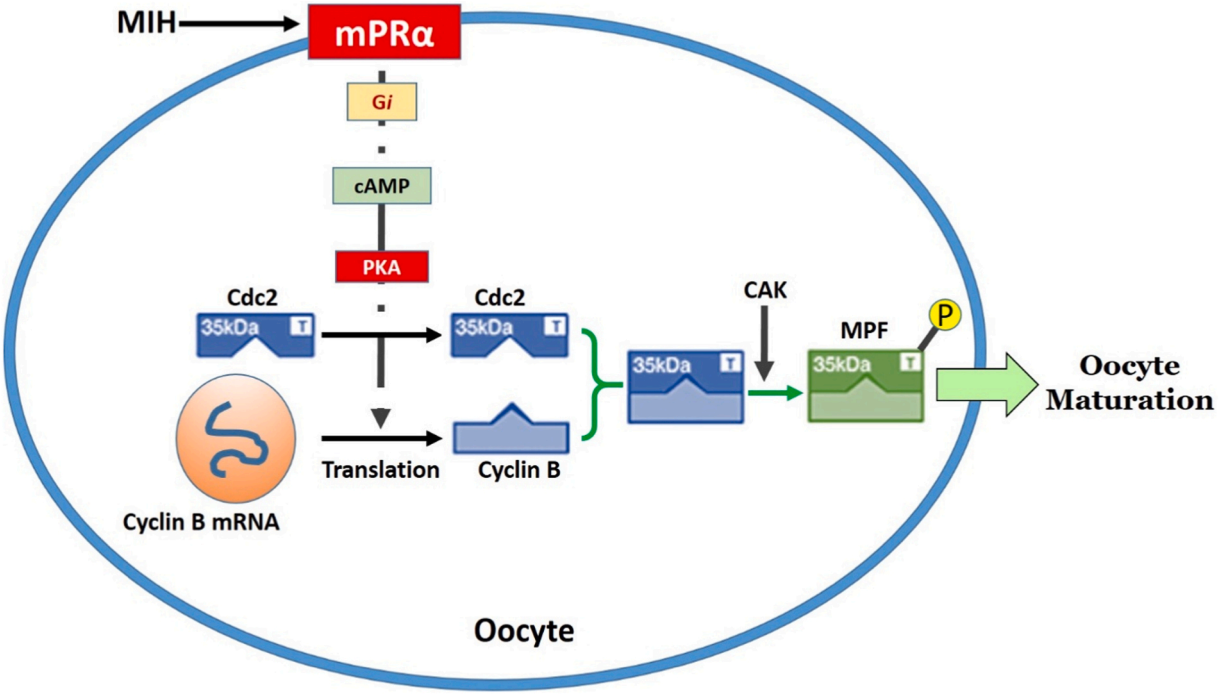

Fig. 5. Role of maturation inducing hormone (MIH) to produce maturation-promoting factor (MPF) and activation of oocyte maturation. The immature oocytes comprise of monomeric 35 kDa cdc2 but not cyclin B. Cyclin B is fashioned by translational activation of masked mRNA after signal transduction from the surface receptor mPRα to the oocyte cytoplasm through a pathway that sequentially includes inhibitory G-protein (Gi), cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA). After forming complex, the preexisting cdc2 and the de novo synthesized cyclin B, cdc2 is phosphorylated and activated on T161 (T), catalyzed by cdk-activating kinase (CAK). The activation of cdc2 is associated with its mobility shift from 35 to 34 kDa. (Reproduced from Senthilkumaran et al., 2004).

slashing intraoocyte cAMP levels and triggering the cAMP-PKA and cAMP-dependent PI3K/Akt pathways (Bhattacharya et al., 2022).

13. Initiators of OM in fish

When fish oocytes are ready to hatch, cyclin B acts as a catalyst. At the outset, the MIS initiates the process by activating the translation of cyclin B messenger RNA. The activation process is characterized by a shape change dependent on microfilaments. This change causes the mRNA to transition from a clustered state to a scattered state, most likely because the proteins covering it separate from it. MIS interferes with the masking protein complex and induces the translation of cyclin B mRNA by modifying the microfilament structure. This disruption propels the oocytes towards GVBD (Nagahama and Yamashita, 2008) (Fig. 6).

Substantial data indicates that the operational management of various carp, other cyprinids, catfish, and additional tropical and subtropical species is influenced by multiple environmental conditions. In rainbow trout (*Oncorhynchus mykiss*), photoperiod is the primary factor influencing OM, but water temperature exerts a moderate effect. Extended photoperiod facilitated a spawning progress of 3–4 months. Egg production remained normal at temperatures up to 15 °C but significantly declined following the temperature increase (Davies and Bromage, 1991; Pankhurst et al., 1996). Elevated temperatures suppressed ovulation in sturgeon, postponed oocyte maturation in Arctic charr, Atlantic salmon, and *Prochilodus argenteus*, and diminished egg production in Atlantic halibut (Jobling et al., 1995; Brown et al., 1995; Duncan et al., 1999; Arantes et al., 2011). Remarkably, sea bass commenced natural spawning in response to ambient temperature without hormonal intervention (Carrillo et al., 1989, 1991).

Decreased salinity inhibited ovarian development in striped mullet (Tamaru et al., 1994) and expedited ovulation in Atlantic salmon (Magwood et al., 1999), thereby being a permissive cue to photoperiod.

Reports indicate that a fish's size and nutritional status (food availability) are permissive in reproductive growth. One or more of these variables may interact with the hypothalamic-pituitary systems that eventually regulate puberty, ovulation, and subsequent spawning. This research indicates that photoperiod is the primary proximate cue in numerous fish species, entraining an endogenous rhythm regulating reproduction. This information is believed to be conveyed to the reproductive axis through diel and seasonal variations in melatonin. Temperature, nutritional state, and size, together with other variables, likely function permissively, potentially through gating mechanisms, to facilitate the progression of OM (Bromage et al., 2001).

In addition to the considerations mentioned above, endocrine-disrupting chemicals (EDC), prevalent in the environment, have been demonstrated to impact fish OM. These EDCs replicate the non-genomic effects of many steroid hormones and can interfere with the synthesis, metabolism, and release of endogenous hormones by binding to their membrane receptors. Di-isononyl phthalate (DiNP) has been demonstrated to facilitate ovarian maturation (OM) in zebrafish (Wang et al., 2015), but diindolylmethane (DIM) has been found

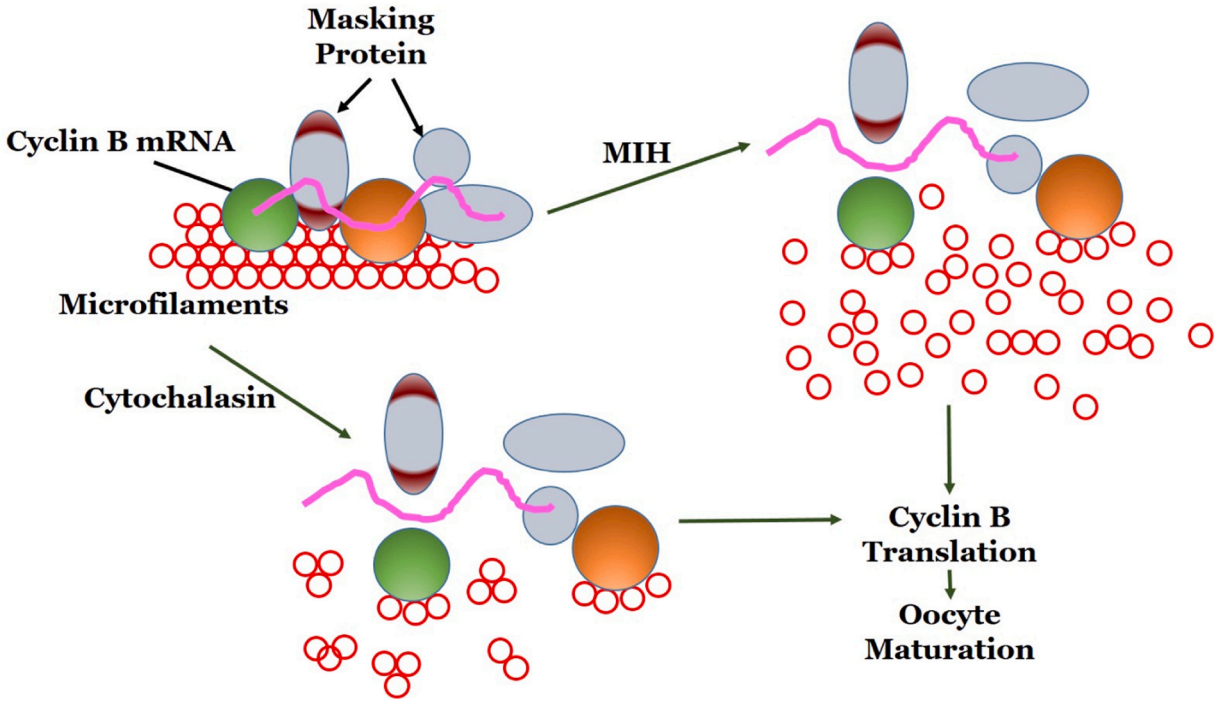

Fig. 6. Microfilament-dependent changes in cyclin B mRNA during fish oocyte maturation. Maturation-inducing hormone (MIH)-induced translational activation of cyclin B mRNA is associated with microfilament-dependent changes in the mRNA from the aggregated to dispersed form, representing the dissociation of masking proteins from the mRNA. MIH action is being mimicked by Cytochalasin B by inducing the dissociation of masking protein complex and the translational activation of cyclin B mRNA by destroying microfilament structure, compelling the oocytes to undergo breakdown of the germinal vesicle (GVBD) without MIH. (Reproduced from Nagahama and Yamashita, 2008).

to hinder OM in marine medaka (*Oryzias melastigma*) by obstructing the uptake of vitellogenin (Vtg) surge (Chen et al., 2017). In trout (*Salmo trutta fario*), Bisphenol A (BPA) has been demonstrated to postpone ovulation maturation through an alteration in ovulation timing (Lahnsteiner et al., 2005). BPA and three alkylphenols- tetrabromobisphenol A, 4-nonylphenol, and tetrachlorobisphenol A- have been demonstrated to impair ovarian maturation in zebrafish through a non-genomic mechanism that activates the Gper/-EGFR/MAPK 3/1 pathway (Fitzgerald et al., 2015).

14. Signaling events during hormonal stimulation of OM in fish

MPF orchestrates significant morphological transformations in maturing oocytes, such as GVBD, chromosomal abridgement, and spindle foundation, all in line with the progression of meiosis (Kotani and Yamashita, 2002). When oocytes are treated with MIS, it activates Gi, which reduces intracellular cAMP levels. This happens because the action of adenylate cyclase is suppressed. Many fish species have shown decreased cAMP levels following MIS stimulation (Jalabert and Finet, 1986; Finet et al., 1988; Haider and Chaube, 1995; Cerdà et al., 1998). In addition, studies have demonstrated that medications that increase the levels of oocyte cAMP, such as activators of adenylate cyclase and inhibitors of phosphodiesterase, can effectively decrease OM produced by MIS (DeManno and Goetz, 1987; Haider and Chaube, 1996; Haider, 2003). Therefore, it may be inferred that cAMP exerts a negative regulatory effect on initiating FOM.The cAMP/PKA pathway is often associated with a drop in PKA action caused by a fall in cAMP levels. Therefore, it is anticipated that PKA will have a substantial impact on the maturation of oocytes since its reduced activity will facilitate maturation. According to some workers (Haider and Baqri, 2002), blocking the action of PKA has been proven to effectively trigger OM in Indian catfish (*Clarius batrachus*).

The maintenance of meiotic seizure is achieved by continuous beckons that increase cAMP levels and inhibit maturation. The

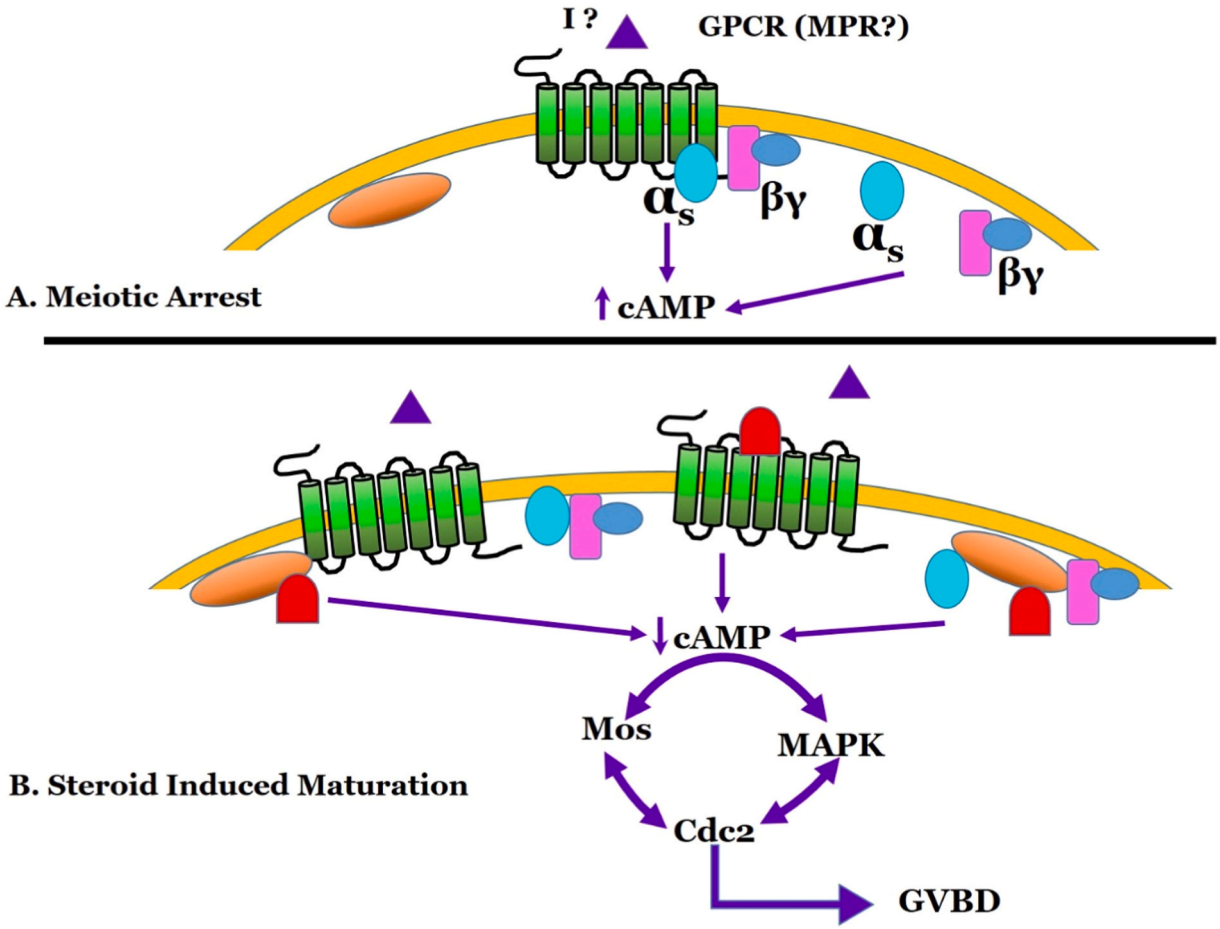

Fig. 7. Model for oocyte maturation. A. Meiotic arrest is conserved by constitutive signals which elevate cAMP and prevent maturation. These signals are endogenous and related to a G protein coupled receptor (GPCR). Sometimes, these signals are being regulated by an unknown ovarian inhibitor (I) activating a GPCR or some other receptor. B. Two of many possible mechanisms are either ligand-bound steroid receptor (SR) interrupts GPCR- (left) or free G protein-mediated (right) signaling or competitive binding of steroid directly to the GPCR. Once the inhibitory signals, which include cAMP, are withdrawn, secondary signals such as Mos, MAPK, and cdc2 are activated. These signals, by using a powerful positive-feedback loop, promote each other resulting in germinal vesicle breakdown (GVBD) and oocyte maturation. (Reproduced from Hammes, 2004).

oocyte produces internal signals such as Gαs and Gβγ, which can act independently or in reaction to a G protein-coupled receptor (GPCR), feasibly belonging to the family of mPR. Steroids counteract this inhibition, enabling the progression of meiosis. The presence of steroids bound to mPR can quickly trigger the activation of Gαi, reducing intracellular cAMP levels. mPR can potentially activate the PI3K or MAPK pathways. When steroids attach to the constantly active mPR, they can block the signaling process, reducing the amount of cAMP inside the cell. These deactivated receptors may potentially transition from Gαs to Gαi signaling, resulting in a further decrease in intracellular cAMP. Consequently, secondary signals such as Mos, MAPK, and cdc2 are activated, amplifying each other in a strong positive feedback loop, ultimately leading to GVBD and maturation (Fig. 7).

E2 sustains a heightened concentration of intracellular cAMP and PKA in immature oocytes via activating the G protein-coupled estrogen receptor (GPER), Gαs protein, and adenylyl cyclase. Activation of PKA in teleost oocytes inhibits the process of translational instigation and the MEK-MAPK cascade. MIS affects downregulating adenylyl cyclase and cAMP/PKA via mPR. In contrast, insulin/IGF stimulates the activation of PI3K/Akt/PDE3 through RTK to reduce PKA activity. The suppressive impact of E2 on the resumption of meiosis is negated by the synergistic influence of MIS and IGF1, as shown in the analysis conducted by Das et al. (2017).

Phosphatidylinositol 3-kinase (PI3K) is another signaling molecule activated in several species as oocytes mature. According to Sadler and Ruderman (1998), Weber and Sullivan (2001), and Ju et al. (2002), MIH-mediated OM in *Morone saxatilis*, starfish, and *Rana dybowskii* requires PI3K activation. Also, PI3K activation is necessary for OM in *Xenopus laevis*, *Morone saxatilis*, and *Cyprinus carpio* (Andersen et al., 1998; Weber and Sullivan, 2001; Paul et al., 2009) as well as for FSH- stimulated OM in mice (Hoshino et al., 2004). It is PI3K that is responsible for catalyzing the production of phosphatidylinositol-3,4,5-trisphosphate from the lipid phosphatidylinositol-4,5-bisphosphate found in the plasma membrane (Cantley, 2002). Class I PI3 kinases transition to heightened activity by direct interaction with phosphotyrosine residues found on active growth factor receptors. Their composition includes a regulatory p85 subunit and a catalytic p110α or 110β subunit. Stephens et al. (1997), Browaeys-Poly et al. (2000), and Weber and Sullivan (2001) discovered that this group of PI3Ks likely regulates the process of OM in *Xenopus laevis* and *Morone saxatilis*, which is stimulated by growth factors. Protein kinase Akt (PKB) and other signaling proteins with plexin homology domains are employed to the plasma membrane during PI3K activation and PIP3 production (Cantley, 2002). In order to stimulate OM in *Xenopus laevis*, starfish, and mice, Akt activation is required and adequate (Andersen et al., 1998; Okumura et al., 2002; Hoshino et al., 2004). Degradation and inactivation of cyclic AMP-containing enzymes, known as phosphodiesterase (PDEs), is one possible downriver focus of PI3K/Akt. When progesterone is absent, IGF persuades OM in *Xenopus laevis*, but PI3K/Akt activation of oocyte-specific PDE3 mediates this process.

The results from studying the ovaries of zebrafish suggest that the process of OM is affected by the activation or suppression of the nitric oxide/soluble guanylyl cyclase/cyclic guanosine monophosphate (cGMP) pathway, which eventually results in ovarian maturation. Nitric oxide (NO) and cGMP levels increase in follicular cells during OM, but NO levels remain consistent in oocytes while cGMP levels decrease (Li et al., 2018).The activation of MAPK is a common event during OM, though its necessity for GVBD remains undefined (Maller, 1998; Yamashita, 1998; Ferrell, 1999; Nebreda and Ferby, 2000). In *Xenopus laevis* oocytes, GVBD can be induced by hyperphrased of Mos and MAP kinase or by fundamentally active MAP kinase 1/3, even in various MAP kinase inhibitors (Gross et al., 2000). However, in *Carassius auratus*, MAP kinase activation is neither necessary nor provides enough support for OM (Yamashita, 1998; Kajiura-Kobayashi et al., 2000). Similarly, inhibition of MAP kinase 1/3 activity with PD98051 or U0216 in Atlantic croaker does not affect GVBD (Pace and Thomas, 2005).

A recent evaluation has determined that cAMP is the main second messenger accountable for conveying gonadotropin signals in the ovaries of teleost fish. FSH has been shown to promote the synthesis of E2 in developing follicles of teleost fish by activating cAMP signaling. On the other hand, LH has been seen to boost the production of a hormone that induces maturation in fully-grown follicles through cAMP signaling. Takahashi and Ogiwara (2023) have shown that cAMP signaling regulates follicle size, meiosis, and ovulation in teleosts.

15. Hormonal symphony in fish OM

OM refers to a series of complex cellular processes from meiosis resumption to the second metaphase arrest in most vertebrates. Fish morphological signs of this phenomenon are easier to observe and have been described since their in vivo development. Several hormones are involved in the fish ovary's complex and highly advanced hormonal regulation. The regulation of ovarian development, oocyte maturation, ovulation, and reproductive timing fundamentally relies on these hormones. The endocrine system, comprising the pituitary gland, gonads, and other endocrine organs, secretes and regulates these hormones.

GTHs, comprising LH and FSH, are glycoproteins synthesized by the pituitary gland and are essential for normal reproductive function and gonadal development in vertebrates. Their expression and release, integral to the hypothalamus-pituitary-gonad (HPG) axis, are primarily governed by hypothalamic GnRH. The effects on the gonads are differentiated: FSH promotes the development of ovarian follicles in females and spermatogenesis in males, whereas LH triggers ovulation in females and spermiogenesis in males. The distinct secretion pattern of each gonadotropin determines the reproductive condition of the organism and is essential for sustaining a healthy reproductive state (Hollander-Cohen et al., 2021).

In teleosts, two progestins, 17,20βP in most species and 20β-S in certain species, are recognized as MIH or MIS. These are generated in the preovulatory follicles following the ovulatory LH surge, facilitating OM and ovulation. The steroids promote OM by binding to a mPR on the oocyte's cell membrane. Progestin-activated mPR is thought to function through nongenomic mechanisms to facilitate OM. Conversely, progestins initiate a series of events linked to ovulation in follicle cells by binding to an nPR, which functions as a ligand-activated transcription factor. Progestin-activated nPR is essential for producing several factors and proteins necessary for ovulation via a chromosomal process (Takahashi et al., 2019).

The hormonal orchestration of OM has been well studied, mainly in teleost fish and, specifically, in zebrafish (*Danio rerio*). Several in vivo and in vitro works have been documented on Zebrafish OM, including knockout models. However, numerous cultivated species display reproductive dysfunctions in captivity, particularly those marked by the lack or irregularity of FOM and ovulation. Although research on the mechanisms governing FOM and ovulation in neotropical fish is sparse, comprehending and regulating these processes is essential for successful reproduction in captivity. Therefore, a study on the hormonal regulation of FOM is essential. Detailed information about the involvement of different hormones and their functional activities studied in different species has been summarized in Table 1.

16. The function of growth factors in controlling the FOM and ovarian steroidogenesis

16.1. Family of Insulin-like growth factors (IGFs) and insulin

Aside from pituitary gonadotropins, the involvement of insulin and IGFs in mammalian reproduction is widely recognized. Insulin and IGF-I are associated with growth, steroidogenesis, and maturational effects. Insulin and IGF-I wield biological effects via binding to

Table 1
Summary of hormones related to FOM in fish, their function in piscine groups.

Hormone	Function/Target	Group	Reference (s)
Pituitary GTHs			Mokhtar (2024)
E2	Initiation of OM and development of oocytes.	Salmonid	
17α,20β-DP	The interaction between granulosa and thecal cell layers produces E2 and 17α,20β-DP.	Sciaenid	
20β-S	Before OM, significant conversion from E2 to 17α,20β-DP occurs within the follicles.		
	The ovarian synthesis of steroidal regulators of oocyte development.		
MIH			El Mohajer et al., (2022); Mokhtar (2024)
Progestogens			
Progesterone (P4)	Progestogens are considered as the major MIHs in fish.	Teleost (Acanthuridae, Acipenseridae, Percidae, ichlidae)	
DHP	A higher level of progestogens was found in circulating plasma during the preovulatory period.		
THP			
Corticosteroids			El Mohajer et al., (2022); Mokhtar (2024)
11-deoxycortisol (11-DC)	Exhibit some MIH properties and induce OM in a dose-dependent manner.	Teleost, Catfish, Yellow Perch, Zebrafish, Pacific salmon	
11-deoxycorticosterone (DOC)	Corticosteroids are designated as credible MIHs in addition to progestogens.		
Cortisol			
Non-classical MIHs			Skoblina and Minin (2016); Kim and Baek, (2017); Takahashi et al., (2018).
Estrogens	Reported to boost oocyte development indirectly via other tissues.	Longchin gobby, Teleost, Eurasian perch	
	Reported to show an inhibitory effect within ovarian follicles.		
	To date, no data establish that it exerts a direct influence on OM.		
Testosterone	Induces FOM at higher concentration via GVBD induction.	Longchin gobby, Teleost, Eurasian perch	
Prostaglandin (PG)	Reported to display some MIH activities via DHP and THP induction.	Carp	
	PGF2 alpha and PGE2 have been documented to induce FOM.		
Pituitary peptides			Whittington and Wilson, (2013)
Growth hormone (GH)	Reported to impact on ovarian activity		
Prolactin (PRL)	PRL has been documented to contribute to reproductive development and associated functions.		
Other hormones			
Melatonin	Accelerates action of MIH for OM.		Chattoraj et al., (2005)
LH	Reported to act on follicular cells for MIH production.	In most fishes	Nagahama et al., (1993)
Thyroxine (T4)	Reported to affect indirectly ovarian development and function.		Deal and Volkoff, (2020)
Adrenocorticotropic hormone (ACTH)	Indirectly affects ovarian function.		Sousa et al., (2015)
Activin A and Inhibin A	Induced FOM in a dose-dependent manner.		Wu et al., (2000)
	Might act as local regulators mediating gonadotropin- and MIH-induced FOM.		
	Known as paracrine regulators of ovarian functions.		
Follistatin−288	Inhibits the effects of Activin A and Inhibin A.		
	Inhibits FOM induced by gonadotropin and MIH.		
Vasotocin	Stimulates OM, oocyte hydration, ovulation, and PG secretion via modulating steroidogenic shift via E2 inhibition and 17α,20β-DP stimulation.	Catfish	Joy and Chaube, (2015)

their respective insulin and IGF receptors. Insulin and IGF-I were initially identified in the ovary of mammals by Hammond et al. in 1982 and 1983. Subsequent research has shown that the ovary is a location where the synthesis of IGF is controlled by hormones (Hernandez et al., 1989; Yoshimura et al., 1994). Insulin and IGF-I have demonstrated the ability to promote cell growth and DNA replication in granulosa cells of cows, pigs, and sheep (Savion et al., 1981; Baranao and Hammond., 1984; Monniaux and Pisselet, 1992).

Considerable emphasis has been given to the role of insulin and IGF-I in regulating ovarian function in fish. Studies by Kagawa et al. (1995) and Duan et al. (1993) have shown the existence of IGF-I peptide and IGF-I messenger RNA expression in the fish ovary. Furthermore, carp and coho salmon ovaries have been demonstrated to have insulin and IGF-I receptors, together with their tyrosine kinase activity (Gutiérrez et al., 1993; Maestro et al., 1997a). The data presented in this study align with previous reports that have described the various consequences of insulin and IGF-I on the control of growth, steroidogenesis, vitellogenesis, and FOM in ovaries (Srivastava and Van Der Kraak, 1994; Maestro et al., 1997a; Tyler et al., 1987, Kagawa et al., 1994; Mukherjee et al., 2006; Paul et al., 2009). The findings recommend that insulin and IGFs may significantly impact ovarian physiology in fish by controlling steroidogenesis, growth, development, and cellular differentiation.

In their study, Maestro et al. (1997b) demonstrated that IGF-I stimulated the synthesis of E2 in the granulosa cell layer of Coho salmon. Studies have demonstrated that in common carp (*Cyprinus carpio*), there is a surge in the binding of insulin and IGF-I during vitellogenesis, but this binding decreases as maturation progresses. This shows that insulin and IGF-I portray a significant role in vitellogenesis in carp. Subsequent research has demonstrated that IGF-I and insulin stimulate ovarian steroidogenesis in *Cyprinus carpio* by activating PD and MAP kinase pathways (Paul et al., 2013). IGF-I-induced OM in the ovary of *Danio rerio* occurs through the EGF-like ligands/EGFR axis. The study investigated the impact of NVP-ADW742, a selective inhibitor of IGF-IR, on this process.

This work (Xie et al., 2016) explains the molecular process by which OM occurs via the action of IGF-I and the interaction between IGF-I and EGF in the zebrafish ovary. IGF-I and IGF-II have been shown to stimulate several phases of OM in southern flounder (*Paralichthys lethostigma*). Additionally, 20β-S has been identified as the primary MIS in this species. IGFs increased the expression of membrane progestin receptor alpha and stimulated the development of OM competence and meiosis in flounder oocytes (Picha et al., 2012). As ovarian development progressed, IGF-I and IGF-II mRNA expression rose. Immunoreactive IGF-I was seen in the theca cell layer during steroidogenesis and in granulosa cells at the tertiary yolk stage. Instead, immunoreactive IGF-II was only discovered in granulosa cells at the tertiary yolk stage (Higuchi et al., 2016). In the Neotropical characid fish, *Astyanax fasciatus*, the concentrations

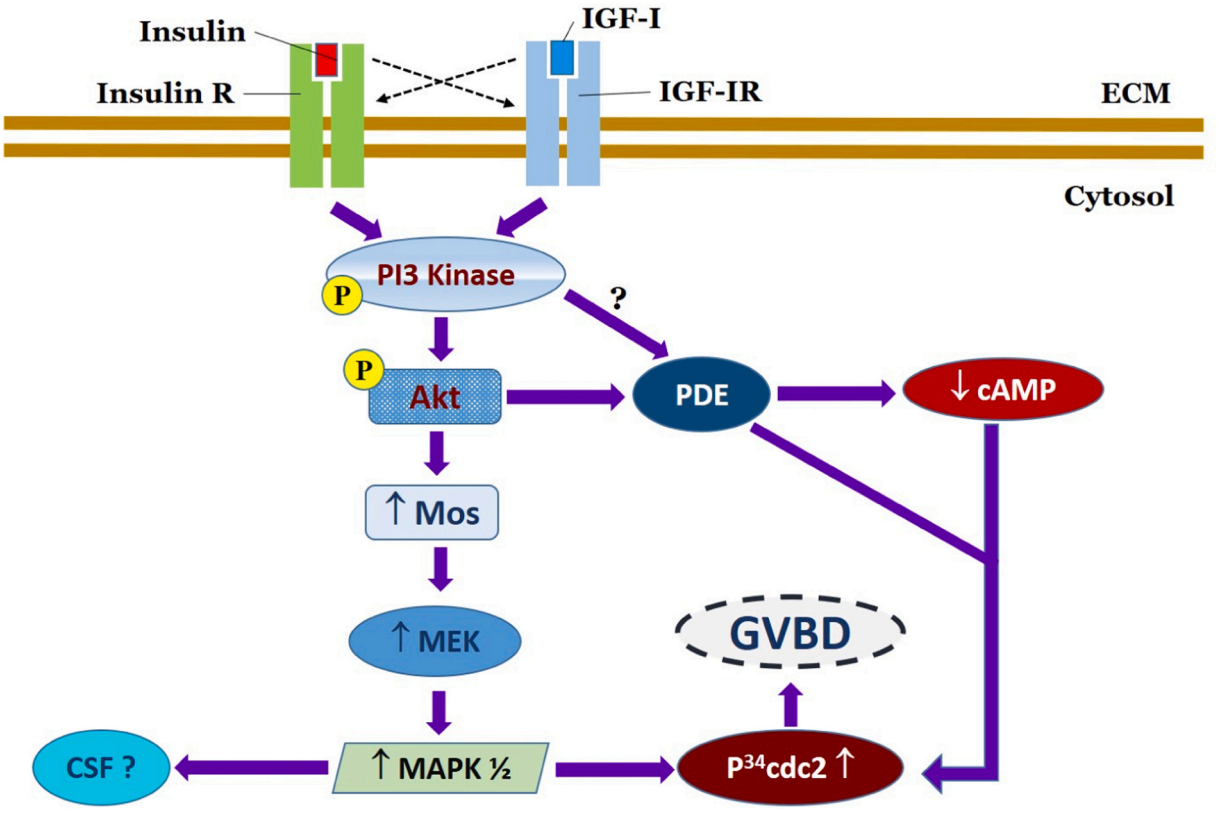

Fig. 8. Hypothetical model of IGF signaling on fish oocyte maturation. The intrinsic control of oocyte maturation was via insulin and IGF-I through insulin/ IGF-I receptor at the oocyte surface in fish and amphibia. Insulin/ IGF-I receptor-activated PI3kinase which phosphorylated Akt. Akt induced Mos and MEK kinase to activate MAPK ½ which in turn activated P34cdc2 to induce germinal vesicle breakdown (Reproduced from Mukherjee et al., 2014).

of both IGF-I and II in the female gonads play a crucial role in promoting gonadal maturation by controlling the growth and development of germ cells. Prado et al. (2019) state that IGF-I was most abundant in the ovaries when they were not actively producing eggs. However, during the stages of egg development and maturity, IGF-I was responsible for promoting the eggs' development and progress.

In the ovarian follicles of *Danio rario*, representation of IGF-III was stimulated by PKA activators. The cell survival, mediated by ovarian IGFs, was promoted by RhIGF-I, hCG, and forskolin. Interestingly, the ovarian IGF system has no role in producing 17α, 20β-P induced by hCG (Irwin and Van Der Kraak, 2012). In grey mullet, IGF-I, along with sex hormones, gonadotropins, insulin, and calcitonin, has been exhibited to induce OM via GVBD induction (Das et al., 2014). The intact follicles of the zebrafish defolliculated oocytes showed a surprising demonstration of IGF-I and IGF-III transcripts in vitro. This highly corresponded with increased phosphorylation of IGF-IR and Akt, mPRa immuno reactivity, PKA inhibition, and finally induced GVBD before ovulation (Fig. 8). The physiological relevance of MIS and IGF-I is believed to have a synergy in-between which helped in the resumption of meiotic OM which was inhibited by E2 earlier (Das et al., 2016). The zebrafish gene knockout model and commercially accessible species have shown that IGF-III plays a vital role in LH-induced OM. Additionally, the molecular mechanism of the signaling system involved in the meiotic restart in female reproduction has been clarified (Li et al., 2015). In another study conducted on *Danio rerio*, it was reported that messenger RNA and protein expression of IGF-III increased significantly during ovulation, directing the activation of several key components that are prerequisites for ovulation. Ovulation was directly stimulated by recombinant zebrafish IGF-III protein. It has also been observed that LH-induced IGF-IR activation during ovulation and inhibition of receptor-attenuated ovulation (Li et al., 2018). Using a potent, high-affinity insulin-like growth factor-I binding protein (IGFBP) inhibitor, it has been established for the first time that expression of IGFBPs is expressed in follicular cells and oocytes and inhibits OM. However, the inhibitor failed to exert its action on the denuded oocytes of zebrafish. The inhibitor was shown to increase the effect of IGF-III on zebrafish OM (Li et al., 2019). IGF-I and IGF-II enhance the synthesis of steroids by increasing the gene expression and the activity of the *cyp17a1* enzyme through the stimulation of PI3 kinase in the ovarian follicles of yellowtail (Higuchi et al., 2020). Das et al. (2020) discovered that in grey mullet ovarian follicles, human-insulin-like Growth Factor-I (h-IGF-I) or Bovine insulin (B-insulin) can stimulate OM through a steroid-independent mechanism. This process involves PI3 kinase signaling and a translational cascade (Das et al., 2020). In fish ovarian follicles, IGF-I, IGF-II, and IGF-III expression, regulation, and function are summarized in Table 2 (reproduced from Li et al., 2021). IGF-III presumably had a role in controlling the reproductive processes in orange-spotted grouper (*Epinephelus coioides*) by facilitating ovarian development and maturity. IGF-III promotes an upregulation of LHR1 expression, leading to an augmentation of LH binding to its corresponding receptor. This may have resulted in the decrease of Kit ligand A (*kitlga*) expression and the acceleration of OM in orange-spotted grouper (Jiao et al., 2023). Rainbow trout has recently been recognized as the first fish species in which IGF-I and -II did not stimulate oocyte maturation, and IGF-I did not produce OMC in follicles in vitro (Weber, 2023). Interestingly, IGF-III has been shown to induce ovarian maturation and steroidogenesis via induction of cdc2 and cyclinB mRNA expression in vitro in spotted steed (*Hemibarbus maculatus*) ovarian follicles (Liu et al., 2024). There exist two varieties of insulin-like growth factor (IGF) receptors. The type I receptor typically has a stronger affinity for IGF-I than IGF-II and demonstrates a weaker interaction with insulin. The type II receptor prefers IGF-II over IGF-I and does not bind insulin. The insulin and IGF-I receptors (IGFR) in fish are heterotetramers. They comprise two α subunits outside the cell with the ligand binding site and are connected to two β subunits inside the cell with the tyrosine kinase domain. This structure was described by Drakenberg et al. (1993), Lappova and Leibush (1995), and Maestro et al., 1997(a,b).

Insulin signaling mainly occurs via insulin receptors (IRs) and IGF-I through the IGF-1 receptor (IGFR-1). The activation of this receptor results in the phosphorylation of insulin receptor substrate (IRS), which in turn activates downstream signaling pathways, specifically PI3 kinase and MAP kinase (Mukherjee et al., 2017). The PI3 kinase serves as a primary element in the signal transduction pathway that precedes MAP kinase and MPF activation during IGF-I- and b-insulin-induced OM in common carp (Paul et al., 2009), as well as in carp ovarian steroidogenesis (Paul et al., 2013). Furthermore, the PI3K/Akt pathway activation is crucial for insulin-/IGF1-stimulated OM zebrafish (Andersen et al., 2003; Das et al., 2013).

In addition to the roles mentioned above, previtellogenic follicles in maturing sterlet females displayed elevated levels of IGF-I and IGFR-1 mRNA compared to age-matched non-maturing females, while females commencing vitellogenesis revealed an increase in ovarian IGF-I and IGFR-1 mRNA (Wuertz et al., 2007). Moreover, IGF-1 was identified in the granulosa and theca cells of coho salmon (Maestro et al., 1997a,b), as well as in the previtellogenic oocytes of gilthead seabream (Perrot et al., 2000) and sterlet (Wuertz et al., 2007), so underscoring the significance of provincial IGF-I.

Table 2
Summary regarding the expression, regulation and function exerted by IGF-I, IGF-II and IGF-III in fish.

	Expression	Regulation	Function
IGF-I	Initially expressed in the oocyte, but primarily in the granulosa or thecal cells after vitellogenesis.	By LH, GH and estrogen.	Follicular cell proliferation, follicle growth, oocyte maturational competence, oocyte maturation.
IGF-II	Initially expressed in the oocyte, but primarily in the granulosa or thecal cells after vitellogenesis.	By GH and estrogen.	Follicular cell proliferation, oocyte maturational competence, oocyte maturation.
IGF-III	Initially expressed in the oocyte, but primarily in the granulosa or thecal cells at later stages.	By gonadotropins and estrogen.	Follicular cell survival, germ cell proliferation, follicle activation, oocyte maturation and ovulation.

16.2. The Epidermal Growth Factor (EGF)

EGF is a growth factor that endorses cellular growth, replication, and specialization by attaching to its receptor EGFR. The peptide comprises 53 amino acids and has a solid mitogenic effect in several tissues (Carpenter, 1985). The discovery of EGF was initially made in the submaxillary gland of mice by Cohen and Elliott in 1963 (Cohen and Elliott 1963). Unlike most growth factors, mature EGF, which consists of 53 amino acids, is liberated from a substantial precursor attached to the plasma membrane (Scott et al., 1985; Gray et al., 1983). EGF functions by attaching to a particular EGF receptor (EGFR) on the cell's outer surface with a strong attraction (Carpenter, 1985). EGFR is a transmembrane protein that has undergone glycosylation (M.W. 170 kDa) and is considered the original affiliate of the receptor protein tyrosine kinase family (Boulougouris and Elder, 2001). The activation of tyrosine kinase triggers a series of cellular events called signal transduction cascades. This cascade leads to various biochemical alterations within the cell, such as an elevation in intracellular calcium levels, enhanced glycolysis, increased protein synthesis, and upregulation of specific genes, including the EGFR gene. Ultimately, these changes culminate in DNA synthesis and cell proliferation (Fallon et al., 1984).

EGF is crucial for promoting cell growth and specialization in several organs, including the ovary. The production of EGF has been seen in mammalian ovarian follicles (Maruo et al., 1993; Roy and Greenwald, 1990; Qu et al., 2000) and birds (Onagbesan et al., 1994), where it acts as a local paracrine/ autocrine regulator. The cloning of EGF and EGFR has been shown in the zebrafish ovary by Wang and Ge in 2004. EGF induces DNA synthesis in animals (Roy and Greenwald, 1991; Roy and Harris, 1994) and promotes the proliferation of granulosa cells in the ovarian follicles of pigs (Hammond and English, 1987). Additionally, it regulates the production of ovarian steroids and the differentiation of granulosa cells by enhancing progesterone synthesis and suppressing the production of estradiol caused by FSH. It also inhibits FSH and LH receptor expression in cultured granulosa cells (Bendell and Dorrington, 1990; Tilly et al., 1992; Feng et al., 1986). Furthermore, EGF promotes the process of OM in several mammalian species, as demonstrated by Ding and Foxcroft (1994) and Coskun and Lin (1995). EGF in chickens promotes the growth of granulose and theca interstitial cells while suppressing the synthesis of E2 and progesterone triggered by LH (Onagbesan et al., 1994, 1995; Li and Johnson, 1993). EGF stimulates the production of steroids in gonadal cells, such as Leydig cell lines (Manna et al., 2002; Ascoli and Segaloff, 1989), and perhaps in granulosa cells (Jezovà et al., 2001). EGFR controls the process of OM, as demonstrated by studies conducted by Park et al. in 2004 and Ashkenazi et al. in 2005. LH triggers the release of EGF molecules. These EGF molecules then communicate locally (in a paracrine manner) through EGFR to promote the enlargement of cumulus cells and the maturation of oocytes. Interestingly, EGF cannot directly initiate the development of oocytes that have been stripped of their surrounding cells. This implies that certain secondary messengers, activated by EGFR signaling in the cumulus cells, are necessary for OM (Jamnongjit et al., 2005). A substantial amount of information implicates EGFR signaling as a potential key mechanism that coordinates LH-mediated processes in the mammalian ovary. Jamnongjit and his colleagues documented that the activation of EGFR signaling is essential for the normal process

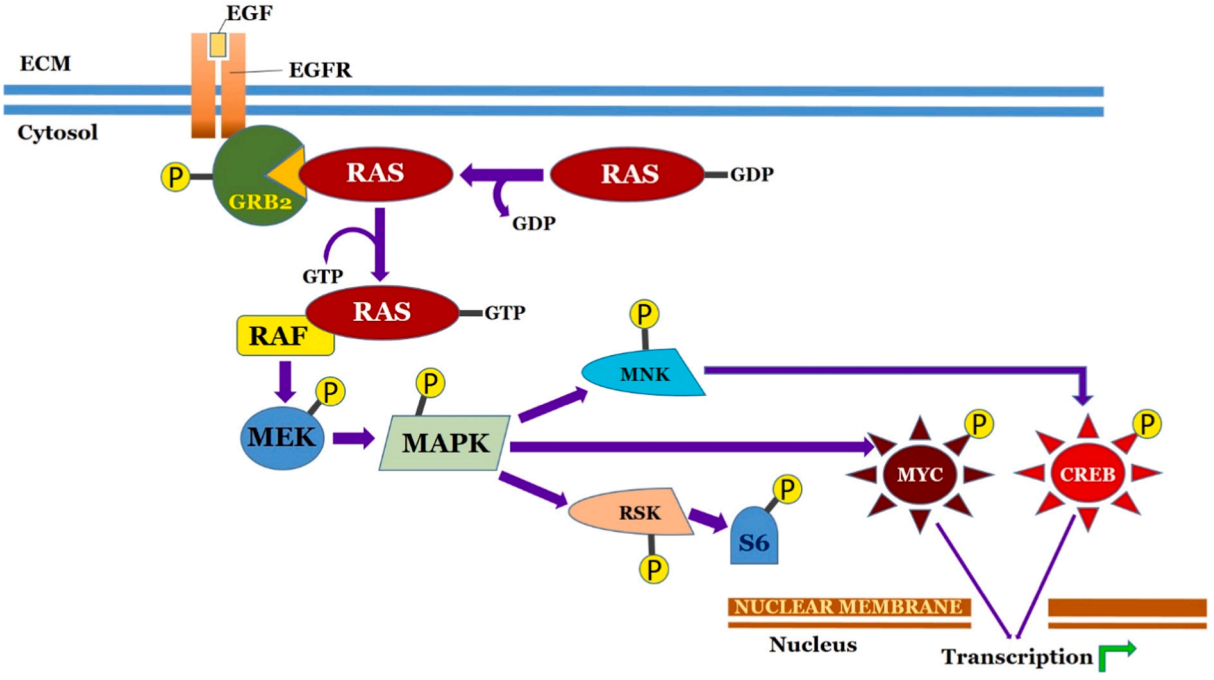

Fig. 9. EGF signaling on oocyte maturation. The dimer EGFR activates the protein tyrosine kinase by phosphorylation. A docking protein, GRB2 containing SH2 domains, binds to an activated site of EGFR and phosphorylates growth factor receptor binding protein-2- son of sevenless- Ras (Grb2-SOS-RAS) protein complex. After phosphorylation, RAS-GTP binds to RAF to activate mitogen activated protein kinase (MAPK) by phosphorylation. Activated MAPK phosphorylates MYC directly or CREB protein indirectly via MNK phosphorylation to induce transcription. The transcription of c-myc or c-fos regulates cell proliferation and oocyte maturation.

of OM and ovarian steroidogenesis in mice (Jamnongjit et al., 2005).

Research on EGF and its associated peptides in lower vertebrates, including teleosts, is restricted due to the absence of cloning the molecule in non-mammalian species. EGF was discovered to facilitate the effect of HCG on the synthesis of deoxyribonucleic acid in *Carassius auratus* vitellogenic follicles (Srivastava and Van Der Kraak, 1994) and inhibit apoptosis in preovulatory follicles of rainbow trout (Janz et al., 1997). The control of prostaglandin production during ovarian follicular development in goldfish may be influenced by EGF/TGFα, as MacDougall and Van Der Kraak suggested in 1998. Furthermore, it has been shown that both EGF and TGFα enhance the process of ultimate OM in goldfish, as demonstrated by Pati et al. in 1996. The cloning of EGF and EGFR from the zebrafish ovary was accomplished by Wang and Ge in 2004. Additionally, they documented that EGF functions as a possible paracrine element originating from the zebrafish oocyte to control the activin/ follistatin system (Fig. 9).

EGFR has been found to cause a dose-dependent and biphasic reduction in the expression of luteinizing hormone-chorionic gonadotropin receptor (LHCGR) in zebrafish follicular cells. The expression of FSHR was similarly reduced by the activity of EGFR, as documented by Liu and Ge in 2013. Additionally, they discovered that in the follicular cells of zebrafish, heparin-binding EGF-like growth factor (HBEGF), transforming growth factor α (TGFα), and betacellulin (BTC) significantly decreased the basal and E2-induced LHCGR expression through paracrine signaling. A recent study on zebrafish oocytes demonstrated a direct, non-genomic, estrogenic effect of an endocrine disruptor, Bisphenol A (BPA), known to be very toxic and disrupts the endocrine system. BPA, an eminent environmental estrogen, has been demonstrated to bind to the membrane estrogen receptor, G-protein-coupled estrogen receptor 1 (Gper), and then activate a Gper-dependent EGFR/ MAPK 3/1 pathway, so inhibiting meiosis restart (Fitzgerald et al., 2015).

Gonadotropins in the fish ovary stimulate the activation of EGFR, which is located in the cell membrane. This activation, in turn, triggers the activation of ERK ½, leading to the generation of steroids through GPCR. This process of trans-activation necessitates the liberation of EGF facilitated by matrix metalloproteinases (MMPs). This distinctive characteristic revealed the connections among cAMP, calmodulin, CaMKs, and MAP kinase pathways. IGF-I and insulin were discovered to stimulate fish ovarian steroidogenesis via activating MAP and PI3 kinase, as reported in a review by Mukherjee et al. in 2017.

17. Conclusion

In summary, the present review work indicates that while there has been substantial study on the control of fish ovarian steroidogenesis and OM by gonadotropins, there is a lack of research on the impact of growth factors, particularly the IGF family and EGF, in the ovaries. Insulin and IGF-I are responsible for regulating ovarian steroidogenesis and OM in fish, either by directly affecting these processes or by working along with gonadotropins. Research on the influence of EGF and EGFR on the control of ovarian function in the human species is expanding compared to fish. The review aimed to clarify the involvement of IGF, EGF, and their receptors in controlling the production of steroids in fish ovaries and the maturation of oocytes.

18. Future perspectives

Investigating IGF and EGF in gonadotropin-stimulated fish ovarian development and oocyte maturation has yielded a substantial understanding of the intricate hormonal and molecular mechanisms regulating reproductive functions in aquatic organisms. Nonetheless, akin to several domains of reproductive biology, many inquiries that necessitate additional investigation persist. Subsequent research may expand upon this study's findings to enhance our comprehension of these growth factors' specific functions in fish ovarian physiology and their use in aquaculture.

18.1. Elucidation of mechanisms of action

Although IGF and EGF are recognized for their significant roles in regulating ovarian growth and OM, the precise molecular routes by which they exert their actions are not fully elucidated. Future studies should focus on discovering and characterizing the intracellular signaling pathways IGF and EGF activate in fish ovarian cells. This may entail analyzing the activation of critical downstream signaling molecules, including PI3K/Akt, MAPK, and mTOR pathways, recognized for their roles in cell growth and differentiation. A comprehensive understanding of these molecular pathways may facilitate the identification of possible therapeutic targets for modulating fish reproduction that apply to aquaculture and conservation efforts.

18.2. Species-specific differences

IGF and EGF signaling may vary among fish species owing to differences in reproductive methods, life cycles, and environmental adaptations. Comparative analyses of teleost species exhibiting diverse reproductive traits- such as variations in spawning season duration or habitat (freshwater versus marine)- may elucidate the differential regulation and utilization of growth factors. Species-specific research may aid in identifying biomarkers for ovarian health and egg quality, hence enhancing management techniques in aquaculture.

18.3. Impact of environmental factors

Environmental stresses, including temperature fluctuations, water quality alterations, and the presence of endocrine-disrupting substances, can profoundly affect reproductive health in fish. Examining the influence of environmental conditions on the IGF and

EGF systems during gonadotropin-induced ovarian development is essential for comprehending the potential impacts of climate change and pollution on reproductive success in fish populations. This research may aid in formulating ways to alleviate the adverse effects of these stressors on reproductive success in both wild and aquaculture fish populations.

18.4. Functional genomics and biotechnology applications

Progress in genomic technologies, such as CRISPR-Cas9 gene editing, transcriptomics, and proteomics, offers considerable potential for improving our comprehension of IGF and EGF signaling in fish reproduction. Functional genomics methodologies may knock out or overexpress critical genes implicated in the IGF and EGF pathways to evaluate their contributions to ovarian development and oocyte maturation. Additionally, biotechnology interventions such as hormone supplementation or gene editing may be investigated to enhance reproductive efficiency in aquaculture species. Enhancing IGF and EGF activity may result in synchronized spawning, improved egg quality, or increased survival rates of fish larvae.

18.5. Interplay with additional hormonal systems

Although the functions of gonadotropins (e.g., FSH and LH) in ovarian development are extensively described, the interaction between IGF/EGF signaling and other reproductive hormones, including estrogens and progestins, is inadequately investigated in numerous species. Examining the molecular interactions of IGF and EGF with these hormones may uncover significant synergies or feedback processes that regulate ovarian maturation and oocyte development. This may result in a more comprehensive understanding of fish reproductive endocrinology.

18.6. Improvement of reproductive management in aquaculture

Enhancing reproductive success is essential for sustaining fish production in commercial aquaculture. Comprehending the functions of IGF and EGF in gonadotropin-mediated ovarian development may guide approaches to improving egg quality and quantity. Aquaculturists may enhance spawning rates and egg development by regulating the concentrations of IGF and EGF via nutritional supplementation, hormonal therapies, or environmental adjustments. Furthermore, investigating the management of these development elements may result in more economical and environmentally friendly methods in aquaculture projects.

18.7. Regulation of oocyte quality and fertility

The quality of eggs is a crucial factor in effective fish reproduction, with both IGF and EGF believed to affect processes such as oocyte growth, follicular development, and maturation. Future research should examine how these parameters govern oocyte quality at the molecular and cellular levels. Examining the correlation between IGF/EGF signaling and the expression of genes associated with egg yolk synthesis, oocyte viability, and fertilization potential may yield significant insights for enhancing reproductive outcomes in aquaculture and hatchery environments.

18.8. Conservation of endangered species

Numerous fish species confront the perils of overfishing, habitat degradation, and climate change, resulting in population decreases. Improving reproductive success in endangered species by advancing the understanding of IGF and EGF may serve as a crucial conservation strategy. By enhancing the hormonal and molecular circumstances essential for effective reproduction in controlled breeding operations, scientists may augment the reproductive output of endangered fish species, thus facilitating population recovery initiatives.

The future of research on the functions of IGF and EGF in fish ovarian development and egg maturation presents significant potential for both fundamental biological understanding and practical breakthroughs in aquaculture, conservation, and reproductive medicine. By resolving the inquiries mentioned above, researchers might elucidate the intricate relationships that regulate fish reproduction, facilitating more effective and sustainable aquaculture techniques while promoting biodiversity conservation in aquatic ecosystems.

CRediT authorship contribution statement

Sourav Kundu: Writing – review & editing, Writing – original draft, Validation, Software, Resources, Methodology, Data curation, Conceptualization. **Subhadeep Das Gupta:** Writing – review & editing, Validation, Resources, Formal analysis. **Basanta Kumar Das:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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