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Recent advances in meiotic maturation and ovulation: comparing mammals and pisces

Balasubramanian Senthilkumaran

Department of Animal Sciences, School of Life Sciences-Centre for Advanced Studies, University of Hyderabad, P. O. Central University, Hyderabad – 500 046, Andhra Pradesh, India

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1. ABSTRACT

Meiotic maturation is a complex process that involves resumption of meiosis in response to preovulatory luteinizing hormone (LH) surge just before ovulation. High levels of cAMP in oocytes maintain meiotic arrest at diplotene of prophase I in mammals and pisces. In mammals, the process by which LH induces recommencement of meiosis involves breakdown of oocyte-somatic cells communication, which is followed by a drop in intracellular cAMP levels that in turn causes exit from meiotic arrest. Maturation promoting factor (MPF) then accomplishes progression of oocytes to reach first metaphase followed by second metaphase after reinitiating meiosis. Pisces require precise completion of oocyte growth involving vitellogenesis before the entry of meiotic maturation. Then, both mammalian and fish oocytes enters resumption of meiosis involving germinal vesicle breakdown, chromosome condensation, assembly of meiotic spindle, and formation of first polar body. However, this process in pisces is regulated by three major mediators, LH, 17alpha,20beta-dihydroxy progesterone and MPF which are unique. The molecular mechanisms of meiotic maturation and ovulation by comparing mammalian and piscine research have been dealt in this review.

2. INTRODUCTION

Meiosis is an important cell division process dedicated exclusively to germ cells to propagate the progeny precisely with diploid number of chromosomes and it is the process by which the diploid germ cells, i.e. spermatogonia or oogonia reduce their number of chromosomes in half in preparation for uniting with a haploid cell of the opposite sex to engender a genetically new diploidic life form. Spermatogonia and oogonia show major differences to begin and culminate this major event. In the case of males, entry of germ cells into meiosis is an event associated with puberty and it happens without any intermittent arrest. Furthermore, the male germ cells complete the process of meiosis before their voyage to female reproductive tract to fertilize ova. In no way female germ cells follow this pattern. In females, meiosis occurs over a prolonged period of time where in the oogonia enter meiosis quickly, much before the puberty but become arrested at the diplotene stage of prophase I, which corresponds to the G2 phase of cell cycle (1). Resumption of meiosis, often termed as meiotic maturation or final oocyte maturation is evoked in response to preovulatory luteinizing hormone (LH) surge from the pituitary gland during the ovarian cycle shortly before ovulation wherein gonadotropin-releasing hormone (GnRH) secreted from hypothalamus have a pivotal role in LH surge and

ovulation. The process by which the oocyte completes first meiotic division along with other cytoplasmic changes and proceeds to meiotic prophase II is referred as final oocyte/meiotic maturation. Completion of meiotic maturation equips the oocyte with haploid set of chromosomes to ultimately await fertilization and then to begin the embryonic development. Interestingly, the mammalian oocyte gets arrested at second meiosis and awaits fertilization after the formation of first polar body. Fertilization marks the exit of second meiotic arrest and completion of meiosis to proceed for embryonic development. This review will highlight the pioneering studies examining how the oocyte maintains arrest, and will discuss potential mechanisms where by LH acts to stimulate meiotic resumption and ovulation. The main aim of this review is to focus up on the events of meiotic maturation and ovulation of mammals and pisces to emphasize the recent advances in this research field. However, occasional reviewing of the interesting observations made in starfish and *Xenopus* became necessary considering the pioneering work that even directed the studies pertaining to meiotic maturation in mammals and pisces.

3. MEIOTIC MATURATION AND OVULATION IN MAMMALS

3.1. Are follicular steroids indispensable for meiotic maturation?

Meiosis in mammalian oocyte have several 'stop' and 'proceed' signals which is essentially under the control of several factors associated with follicular layer. The process of meiosis in females is first initiated during embryonic development or around birth and later arrested after birth. Resumption of meiosis in graafian follicles is triggered by the preovulatory LH surge as explained earlier. However, the major debate in mammalian meiotic research is to understand how LH evokes its response on the oocytes to undergo maturation. Are the follicular steroids plays an indispensable signal-mediating role in meiotic maturation? This question became conspicuous as the defolliculated oocyte-cumulus complex underwent spontaneous resumption of maturation. In addition to this there are reports, which demonstrated tremendous increase in follicular steroid production, more specifically estrogens and progesterone after preovulatory LH surge. This perhaps led to several interesting observations, which tend to denote the mediation of follicular steroids to pass the signal of LH surge. Several *in vitro* studies using different mammalian models provided inconsistent results about the mediation of testosterone, dihydrotestosterone, estradiol-17beta and progesterone in the LH-induced resumption of meiosis (2-4). Recent analysis using knockout mice models provided altogether a different concept of steroidal involvement in final oocyte maturation. Mice knockout models lacking active steroid receptors for progesterone, estradiol and testosterone remain capable of resuming meiosis upon gonadotropin stimulation. Thus, in mammals ovarian/follicular steroids do not seem to serve as obligatory mediators for LH-induced stimulation of the final oocyte maturation. However, in some mammalian species wherein the time interval from gonadotropin stimulation to meiotic maturation is prolonged, the role of beneficial effects of follicular steroids cannot be ruled out. Steroids also play a vital role in the acquisition of meiotic and developmental competence of oocytes followed by cumulus expansion and rupture of follicle during ovulation in addition to their involvement in follicular development. Hence, steroidal involvement in meiotic maturation is a major puzzle in mammalian reproductive biology. Based on several studies, (2-4) elaborately speculated that the evolution of hierarchical growth of follicle and ovulation of one or more oocytes each ovarian cycle led to the abandonment of steroids as signals for the resumption of meiosis. The coexistence of follicles and oocytes at various stages of development and their cyclic exposure to relatively high levels of steroids presumably precludes the efficacy of steroids as an unambiguous signal for the resumption of meiosis in mammalian species. Such hierarchical follicle growth and high ovarian steroid levels might have bestowed to the evolution of more distinct paracrine mechanisms for regulating the meiotic resumption in mammals. On the contrary, it remains to be explained how the steroids selectively contribute for follicular growth and other maturational process in mammals. Why LH selectively develops paracrine mechanisms only for final oocyte maturation, after which how it is lost when the oocyte starting for additional maturational processes. These questions need to be answered to clarify the role of steroids or exclude steroidal involvement in LH-induced resumption of meiosis. Furthermore, follicle stimulating hormone (FSH) definitely requires steroidal mediation for oocyte development, (2, 5) which is the preparative step for resumption of meiosis during puberty. Since FSH also surges during ovulation, it remains to be seen whether FSH have any impact on follicular steroids around that time. Taken together, steroidal mediation in ovarian development and maturation is definitely a vast contentious topic in mammals. The next aspect of discussion is to understand the process of meiotic arrest and resumption. Though the mediation of follicular steroids in LH-induced resumption of meiosis is in stake, rapport of cAMP in this process is well established in several vertebrates.

3.2. Role of novel oocyte-specific A kinase anchoring protein and modulation of cAMP levels

Pioneering study in mammals revealed that the prophase I arrested oocytes removed from the ovary undergo spontaneous meiotic maturation in 1935 and also raised the idea that the follicular layer provides the oocyte with an inhibitory agent responsible for "meiotic arrest". Later on in 1978, it was the inventive work by Dekel and Beers (6, 7) identified that the cAMP is the "meiotic arrestor" and thereafter they characterized its inhibitory action in rat oocytes (8). Parallel studies in *Xenopus* (9) and teleosts revealed meiosis-associated reduction in cAMP levels (10), which has been attributed to the inhibition of adenylate cyclase activity. Interestingly in mammals, an alternative mechanism has been proposed rat oocytes where in phosphorylation of oocyte specific A kinase anchoring protein (AKAP) plays a crucial role in bringing down the cAMP levels. This protein was indeed a novel 140 kDa regulatory subunit II binding AKAP. Immunocytochemical

analysis of AKAP140 further confirmed that the regulatory subunits of protein kinase A underwent cellular translocation upon resumption of meiosis in rodent oocytes (11, 12). Earlier studies using synthetic peptide derived from thyroid anchoring protein convincingly demonstrated the role of AKAP in protein kinase A (PKA) regulation of meiosis (3, 13). Based on several studies and experimental evidences, following model has been proposed for meiotic arrest and resumption in mammals. Meiotic arrest is maintained by the relatively high intraoocyte concentration of cAMP (8) by enforcing its effect on the catalytic activity of PKA. This inhibitory effect of cAMP is not generated entirely by the oocyte rather transmitted from the follicular cells through gap junctions. This mode of supply of cAMP apparently generates a centripetal concentration gradient of the nucleotide within the oocytes. Under these conditions, targeting of PKA by AKAP to its site of action may aid its control of meiotic arrest. Alternatively, breakdown of cell-to-cell communication that terminates the flux of follicle cAMP to the oocyte, leads to dwindle the intraoocyte concentrations of cAMP. The plunge in cAMP within the oocytes, when combined with PKA translocation from its site of action may confer an efficient mechanism for down regulation of the catalytic activity of this enzyme. In more simple terms, LH-induced resumption of meiosis involves breakdown of the oocyte-somatic cells communication that is followed by a drop in intraoocyte concentrations of cAMP, which results in exit from meiotic arrest. Later the task is taken over by maturation promoting factor (MPF) to achieve progression of oocytes to reach first metaphase (MI) followed by second metaphase (MII) after reinitiating meiosis.

3.3. MPF regulates meiosis reinitiation

Cytological distinction of full-grown immature and immature oocytes is an essential requisite to understand the mechanisms of meiosis reinitiation. This became more obligatory for non-mammalian oocytes, which tends to accumulate yolk (vitellogenin) before entering the phase of maturational competence. Usually prophase I-arrested oocytes are characterized by a nuclear structure, known as germinal vesicle (GV). Resumption of meiosis will lead to GV breakdown (GVBD) followed by chromosomal condensation and formation of spindle that characterize the onset of MI. Meiosis I is completed upon segregation of homologous chromosomes between the oocyte and first polar body. This is immediately followed by the transition into the MII and then arrested until fertilization. MPF activation is necessary for the progression of prophase I arrested oocytes to MI. The protein components of MPF are the catalytic p34cdc2 kinase and the regulatory cyclin B1 (14, 15). The p34cdc2/cyclin B1 heterodimer is initially formed as an inactive pre-MPF and is activated by the dual specific Cdc25 phosphatase through dephosphorylation of Thr 14 and Tyr 15 of p34cdc2 (16). Another unique characteristic feature of MPF activation in mammals is its oscillatory pattern where in the kinase activity of MPF rises during resumption of meiosis reaching a maximum at MI followed by a decline during the formation of first polar body and then rises again before entry of second meiosis. MPF activation is conditioned to the reduction in intraoocyte cAMP (17). Elevation of cAMP inhibits MPF activation by the prevention of p34cdc2 dephosphorylation (18). An alternate mode execution of MPF activation by cAMP is through the repression of cyclin B1 synthesis thus depriving the availability of pre-MPF (17). Unlike fishes and amphibians, cdc25 is a multigene family in mammals, comprising three isoforms A, B and C. Impaired fertility in the mice that lack cdc25B demonstrated a role for cdc25B in G2/M transition in mammalian oocytes (19). This is further supported by the report (3) wherein the administration of cdc25B neutralizing antibodies blocked the ability of oocytes to undergo GVBD. Further studies on this line revealed the periodic expression pattern of both cdc25A and cdc25B that ultimately correlated well with the oscillatory pattern of MPF activation and meiotic progression (20). More in depth analysis of differential localization of cdc25B during meiosis progression further revealed a central role for cdc25B in the regulation of reinitiation of meiosis in mammalian oocytes in addition to cdc25A (3).

3.4. Inactivation and reactivation of MPF is a feature of mammalian oocytes and role of Mos

Though MPF activation and its elevated activity is necessary for meiosis reinitiation and progression to meiosis I, respectively, its inactivation and reactivation facilitates the transition of meiosis I and II. This is one of the key characteristic mechanisms in mammalian oocyte maturation. In fact the down regulation of MPF activity has not been achieved by rephosphorylation of p34cdc2, rather by the proteosomal degradation of cyclin B1 (18, 21). Indispensability of proteosomal degradation is well established for the exit of M phase in both second meiotic and mitotic cell cycles (3). However, it is not yet clear whether the segregation of homologous chromosomes in the first meiotic division is evoked by proteosomal action or degradation. On the other hand in the lower vertebrates, the dispensability of the proteosomal degradation machinery at the first meiotic division is well established (22, 23). However, in rat the essentiality of proteosomal-dependent degradation processes at the exit of meiosis I had been well proved (3, 21). As mentioned previously, MPF inactivation is transient and its reactivation is essential for the transition of second meiosis. Interestingly, the two rounds of meiosis in never interrupted by interphase as DNA replication never occurs after the formation of first polar body. The period between the two meiotic divisions is defined as interkinesis and MPF acts as a natural suppressor of interphase and it secure the oocyte for meiotic transition (3, 21). The studies on starfish oocytes (24) proved this phenomenon much earlier than the reports involving mammalian models (3). However, in lower vertebrates regulation of interkinesis is attributed to mitogen activated protein kinase (MAPK) family members that are obviously not the case in mammalian oocytes. Elaborate studies confirmed the involvement of extracellular-related kinases, members of MAPK family in the reinitiation of meiosis in mammals (25) and lower vertebrates. MPF activation stimulates polyadenylation of Mos mRNA and activation of MAPK (3). Interestingly, in *Xenopus* oocytes Mos is required for the activation of MAPK (26) and MPF for the suppression of DNA replication during interkinesis and also for the maintenance

of second meiotic arrest (3). Contrary to this MAPK-independent activation of MPF is also demonstrated in *Xenopus* (27) However, well executed studies from mammals using Mos knock out mice models categorically proved that Mos did not participate in the progression of first and second meiotic division, yet, mandatory for second meiotic arrest (17, 28-30). Taken together, prevention of resumption of meiosis can be attained via increased intraoocyte concentration of cAMP wherein MAPK is not activated (30). Taking into account that the upstream regulator of MAPK in the oocyte is Mos, it is conceivable that Mos could possibly mediate the effect of cAMP on the MAPK signaling cascade, which eventually proceeds for second meiotic arrest, which is required for the oocyte until fertilization. The next major event in mammalian oocyte development is ovulation which is the release of female germ cell, ovum.

3.5. Ovulation

Ovulation is a key episode in mammalian reproduction which involves the release of ovum by rupture of the follicle at the surface of the ovary. It is a complex process that is initiated by the LH surge and is controlled by the spatiotemporal expression of specific genes such as growth factors and estrogen receptors (31, 32). The prerequisite for ovulation is maturation of the preovulatory follicle by the combined actions of FSH, estradiol-17beta, and various growth factors, such as insulin like growth factor-1 (IGF-1; 33-36). The preovulatory follicle acquires specific functional characteristics and start expressing steroidogenic enzymes necessary for the synthesis of estrogens. The granulosa cells acquire the ability to produce estradiol-17beta which is required for oocyte growth. In mature follicles the thecal cells expressing the LH receptors respond to LH surge in order to terminate the transcription of genes (like IGF-1, FSH receptor, estrogen receptor beta, cyclin D2, etc…) that control folliculogenesis (33).

The three functional domains within the follicle (cumulus, theca and granulosa cells) are involved in various events that occur during ovulation. Preovulatory LH surge induces the specific genes such as growth factors and estrogen receptors that are required for the expansion of cumulus. Recent studies shown that ovulation is impaired in cyclooxygenase-2 (COX-2) deficient mice which are required for cumulus expansion (37, 38). The thecal layer has got a significant contribution in follicle rupture by expression variety of matrix metalloproteinases which digest the extracellular matrix. The granulosa cells of ovulating follicles in response to LH induces several transcription factors (39, 40) which include early growth regulatory factor-1 (Egr-1), CAAT enhancer binding protein beta (C/EBPbeta) and progesterone receptor (PR). All these factors are induced rapidly but expressed only transiently, with peak level approximately 4h after the LH surge. The other factors like c-Fos, c-Jun, Fra2, and JunD are induced rapidly and remain elevated during the postovulatory luteal phase (41). Egr-1 is an important transcription factor for several ovarian-expressed genes, such as Sgk and Cytochrome P450 side chain cleavage enzyme (P450scc), as well as MMP (42, 43) Efr-1 null mice are infertile, fail to ovulate and no corpora lutea is formed (44). C/EBPbeta is a member of a family of basic helix-loop-helix transcription factors which has a potential role in the regulation of COX-2 expression in granulosa cells (39). Mice null for C/EBPbeta display abnormal vascular morphology and hemorrhagic follicles resulting in impaired ovulation and luteinization (45, 46). PR is rapidly induced by LH in mural granulosa cells of preovulatory follicles. Mice null for PR fail to ovulate even when stimulated by exogenous hormones, but the expression of COX-2, cumulus expansion, and luteinization proceed normally (47). Thus PR appears to be a key regulator in controlling follicular rupture, rather than luteinization. Recently, two targets of PR action have been identified. These are the ADAMTS-1 (a disintegrin and metalloproteinase with thrombospondin like repeats) known as METH-1 in humans (48, 49) and cathepsin L (47). In the ovary, ADAMTS-1 is selectively induced by LH in granulosa and cumulus cells. ADAMTS-1 is a potent active protease involved in matrix degradation. Hence, ADAMTS-1 has a critical downstream role in mediating the PR-regulated rupture of a follicle.

The other LH-induced cellular signaling that may have impact on ovulation process are Wnt4 and Frizzled receptors. Wnt4 is expressed in primary follicles of immature and adult mice. It has a role in initial development of the female gonad (50). However, the specific functions of Wnt4 in the adult ovary are yet to be discovered. Wnt4 is expressed abundantly in corpora lutea following the LH surge. At the same time, Frizzled 4 receptor is also highly expressed. In addition, Frizzled 1 receptor is expressed at high levels in granulosa cells of ovulating follicles between 8–12 h after exposure to LH/hCG. This temporal pattern suggests that Frizzled 1 might control unknown events associated with ovulation or effect certain morphogenic changes that occur during the formation of the corpus luteum. In addition to the factors mentioned above, several other genes such as carbonyl reductase, 3alpha-hydroxysteroid dehydrogenase, 3beta-hydroxysteroid dehydrogenase (3beta-HSD), COX-2 and prostaglandins have also been implicated in the process of ovulation using hCG-induction strategy to initiate ovulation in mammals (51). Taken together, lot of in depth studies have been done, which implicated the involvement of several genes ranging from transcription factors to enzymes in mammalian ovulation. The events pertaining to mammalian meiotic maturation and ovulation have been summarized in Figure 1. Now the review will focus in understanding the process of meiotic maturation and ovulation in pisces.

4. MEIOTIC MATURATION AND OVULATION IN PISCES

One of the major differences between mammalian and fish oocyte maturation is the process in which the oocytes cope itself ready for maturation. Fish oocytes, like other non-mammalian vertebrates require precise completion of oocytes growth involving vitellogenesis before the entry of meiotic maturation. Once after the completion of oocytes growth, the oocytes enters

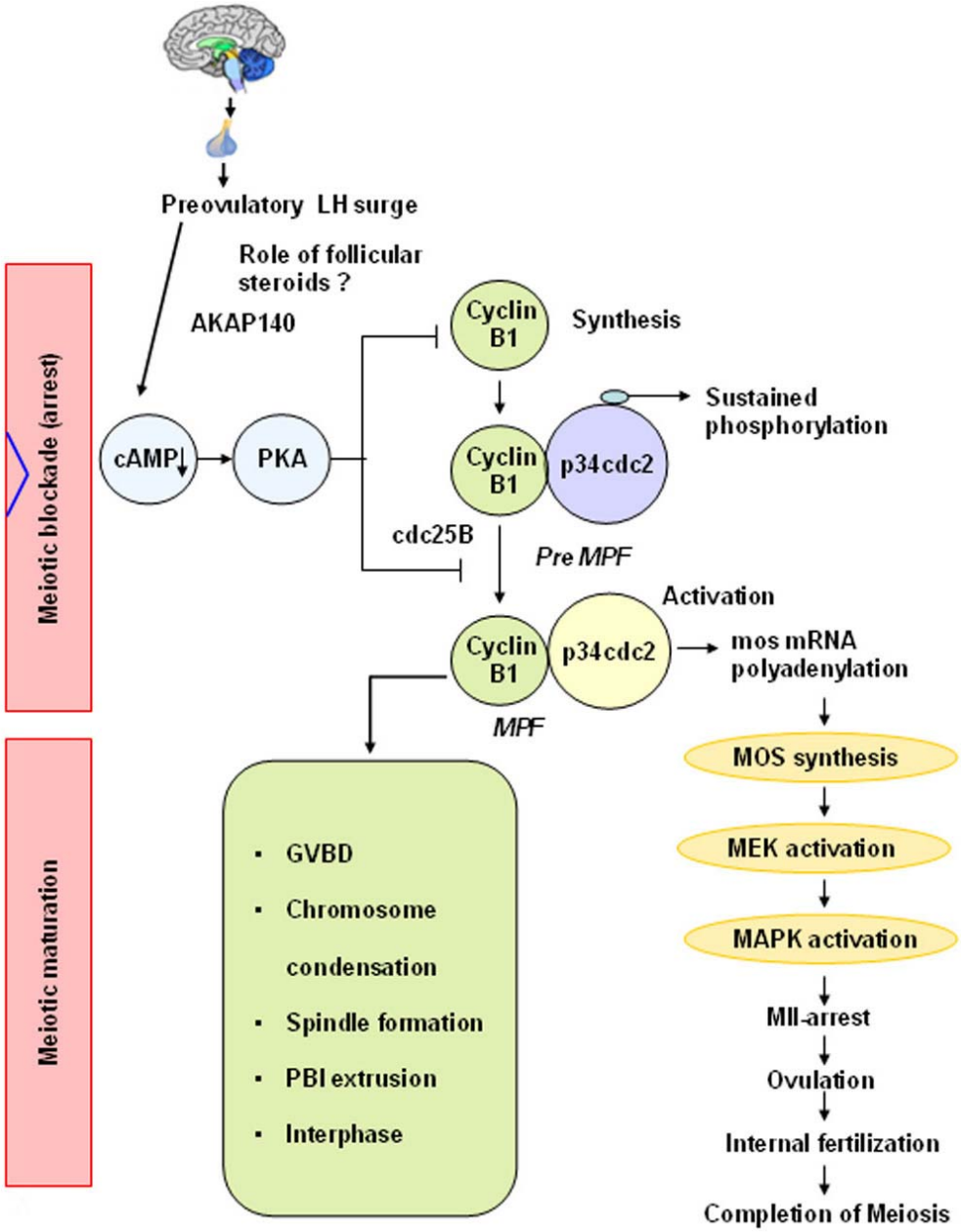

Figure 1. A schematic diagram explaining the mammalian meiotic arrest and resumption of meiosis.

for resumption of meiosis which involves GVBD, chromosome condensation, assembly of the meiotic spindle, and formation of the first polar body. Though oocytes maturation has been well studied in variety of vertebrates and invertebrates (10, 52-58), studies from fishes have highlighted the endocrine regulation of oocytes maturation most effectively (10, 55, 59, 60). In fact to emphasize further, studies using well-characterized *in vivo* and *in vitro* systems involving several fish models have revealed that oocyte maturation in teleosts is regulated by three major mediators, gonadotropin-II (LH), maturation-inducing hormone (MIH), and maturation promoting factor (MPF). This review will focus the involvement of these three mediators in meiotic maturation more explicitly.

4.1. Follicular steroids are indeed indispensable for meiotic maturation

Unlike mammalian oocytes, the follicular steroids are vital not only for oocyte growth but also for final oocyte maturation. The fish pituitary produces two types of gonadotropins that are homologous to mammalian FSH and LH (61-63). Like other vertebrates, pituitary gonadotropins, i.e. FSH and LH under the influence of GnRH regulate the ovarian growth, maturation and ovulation. Temporal pattern of gonadotropin gene expression (10, 64, 65) and

hormone levels (64, 66) clearly suggest that FSH regulates oocyte growth through the mediation of estradiol-17beta while LH involves in the final maturation of gametes partly through the stimulation of maturation-inducing hormone, 17alpha,20beta-dihydroxy progesterone (17alpha,20beta-DP). Extensive *in vitro* incubation studies were performed to examine the effects of various steroids that are naturally seen in follicular fluid or blood stream on the induction of oocyte maturation in variety of teleosts. Most of the C21 steroids such as 17alpha,20beta-DP, 17alpha,20beta,21-trihydroxy-4-pregnen-3-one (20beta-S), and 11-deoxycorticosterone have been shown to be potent steroid inducers of GVBD (67-71). Among them, 17alpha,20beta-DP is the most effective steroid in the induction of GVBD in the majority of teleosts examined to date (71). Testosterone, as well as other C19 steroids, was found to induce GVBD only at high concentrations (60). Estradiol-17beta and other C18 steroids are generally not effective inducer of oocyte maturation in fish. Interestingly in this category, diethylstilbesterol, a non-steroidal homologue of estradiol-17beta induces GVBD and other events pertaining to oocyte maturation (72). Furthermore, catecholestrogens, the metabolites of C18 steroid, estradiol-17beta were shown to induce GVBD and oocyte maturation (73, 74). Based on these studies it is possible to convincingly demonstrate that in fishes follicular steroids are indeed obligatory for meiotic maturation. Among the follicular steroids, 17alpha,20beta-DP is considered as MIH in several teleosts and hence, 17alpha,20beta-DP has been designated as MIH or maturation-inducing steroid. In fact the specific production of estradiol-17beta and 17alpha,20beta-DP is under the control of ovarian follicular layers. A two cell type model had been proposed in fishes to explain this phenomenon (10, 64). Ovarian follicles of teleosts, like those of other vertebrates, are composed of two cell layers, an outer theca and an inner granulosa, that are separated by a distinct basement membrane (75). The development of precise dissection methodology to separate the ovarian follicular layers from salmonid ovaries facilitate to propose that the thecal cell layer contributes for precursor steroids while the granulosa cell layer is responsible for the production of ovarian growth and maturation mediating steroids, estradiol-17beta and 17alpha, 20beta-DP, respectively (54, 59, 64, 76-78). The distinct production of these mediating steroids during the process of ovarian growth and maturation require a shift in steroidogenesis, which is an elite feature of the piscine ovary (59, 60).

4.2. Shift in steroidogenesis

A dramatic shift in the steroidogenic pathway from estradiol-17beta to 17alpha,20beta-DP or 20beta-S is occurring in fish ovarian follicles prior to meiotic maturation (Figure 2). This switch in the type of steroid produced during ovarian growth is likely to be primarily regulated by changes in the abundance of individual steroidogenic enzymes through changes in expression of genes encoding steroidogenesis related enzyme proteins in developing ovarian follicles. There are two important stages (Figure 2), the first being the shift in the synthesis of precursor steroids from testosterone to 17alpha-hydroxyprogesterone, while the second is the shift in the final steroidogenic enzymes from ovarian aromatase (CYP19A1, required for the production of estradiol-17beta) to 20beta-hydroxysteroid dehydrogenase (20beta-HSD; required for the production of 17alpha,20beta-DP or 20beta-S. Variety of teleosts such as salmonids, the medaka *Oryzias latipes* (daily breeder) and the Nile tilapia *Oreochromis niloticus* (fortnight breeder) were used to investigate the shift in steroidogenesis (79-82). Studies our laboratory had used seasonally reproducing annual breeder, catfish, *Clarias gariepinus* wherein we analyzed the expression of several steroidogenic enzyme genes. In addition for the first time our laboratory had reported (83, 84) changes in enzyme activity and protein content by employing highly specific methods such as radiometric assay and Western blot to precisely explain the molecular mechanisms of the steroidogenic shift. Our laboratory was the first to localize these steroidogenic enzymes in the follicular layer of catfish ovary using specific antisera (83, 84). Variety of teleosts serves as excellent animal models for studies on the hormonal regulation of ovarian cycles as they have varied pattern of reproductive phase and transcriptional regulation of genes that encode steroidogenic enzymes. This review will now highlight the importance of steroidogenic enzyme genes and its transcription factors in meiotic maturation.

4.3. Steroidogenic acute regulatory protein

Steroidogenic acute regulatory protein (StAR) is considered as a key rate-limiting factor and important target for acute steroidogenesis by tropic hormone which controls/mediates the transfer of cholesterol to mitochondria (85). Mammalian homologs of StAR have been cloned from various teleosts such as zebrafish, rainbow trout, eel, cod and stingray (86-90). In teleosts, besides its role in gonadal steroid production, very little is know about the dynamics of *StAR* transcripts during final oocyte maturation. In rainbow trout, *StAR* mRNA was increased during GVBD and it peaked just following ovulation. Later after 2 weeks its expression comes down in follicles during post-ovulation stages (87). More recently, results from our laboratory convincingly demonstrated elevation of *StAR* mRNA levels during hCG induced oocyte maturation, both *in vitro* and *in vivo* (91). In medaka also a significant increase in the expression of *StAR* was noticed in ovarian follicles undergoing oocyte maturation (60). Taken together, these results suggest that *StAR* might have an important role in final oocyte maturation.

4.4. Cytochrome P45017alpha-hydroxylase/c17-20 lyase

Cytochrome P45017alpha-hydroxylase/c17-20 lyase (P450c17) is a microsomal enzyme that has two distinct activities: the 17alpha-hydroxylase activity that converts pregnenolone or progesterone to 17alpha-hydroxypregnenolone or 17alpha-hydroxyprogesterone and c17-20 lyase activity that breaks the c17-20 bond of c21 steroids 17alpha-hydroxypregnenolone or 17alpha-OHP to produce dehydroepiandrosterone or androstenedione, respectively (92). The P450c17 enzyme is a key branch point in fish steroid hormone biosynthesis, as these two enzymatic activities distinguish between synthesis of C21 steroids and C18 and C19 steroids. During final oocyte maturation, a shift in steroidogenesis from estradiol-17beta

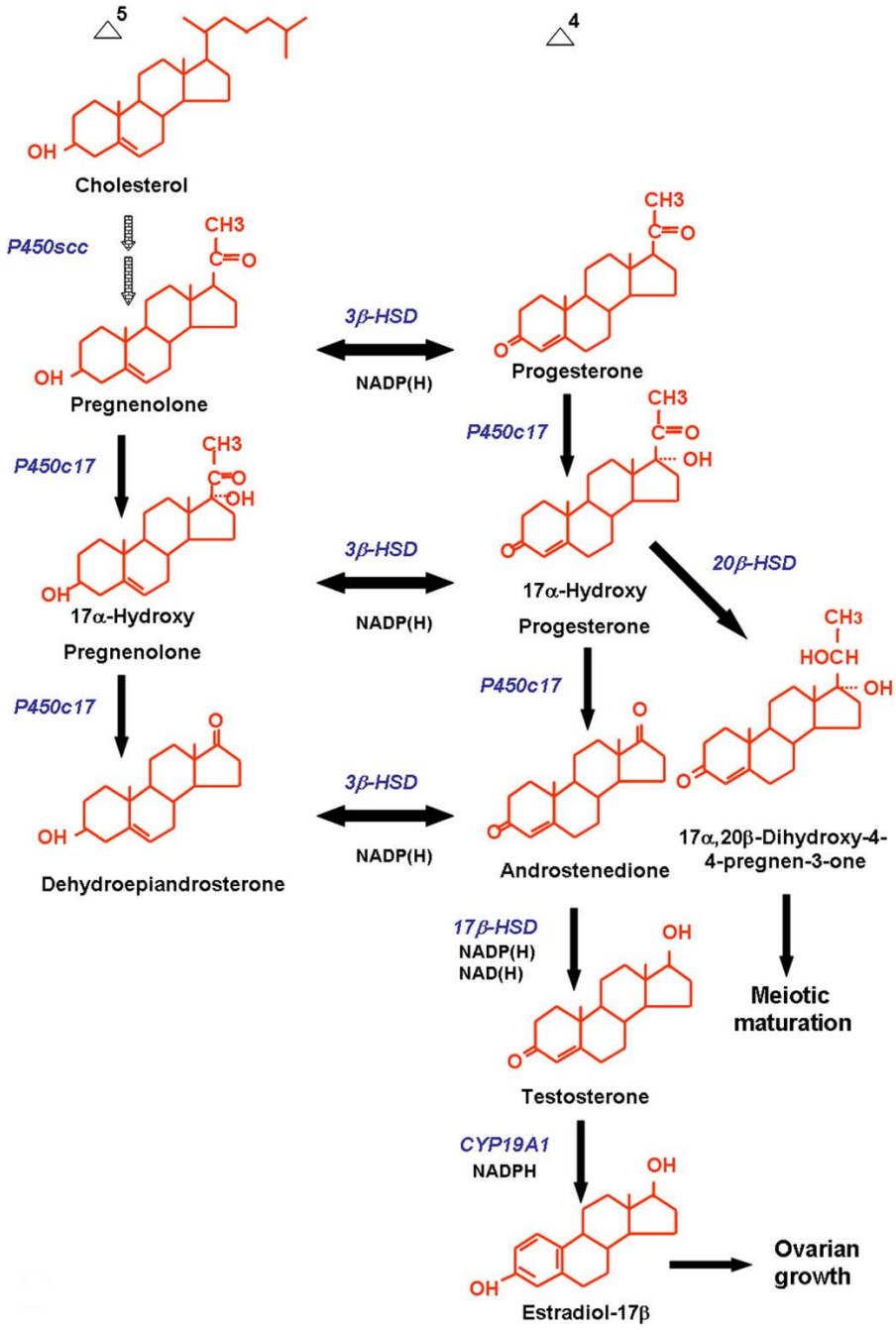

Figure 2. A shift in steroidogenesis occurring in ovarian follicles preceding to oocyte maturation.

to 17alpha,20beta-dihydroxy-4-pregnen-3-one is demonstrated for several teleost species (10, 66, 59). However, it is possible that P450c17 might play a crucial role in the shift in steroidogenesis by controlling the availability of precursor steroids. Though there are reports available on the cloning and expression of *P450c17* from different fish species (93-97), none of these reports neither recorded changes in expression pattern and protein level/activity during steroidogenic shift nor provided convincing claim of regulation of lyase activity. Recently, a novel form of P450c17 that lacks lyase activity has been cloned in the Nile tilapia (a fortnight breeder) and medaka (a daily breeder) whose differential expression pattern was proposed to be important during shift in steroidogenesis (98, 99). However this study too did not provide any data on enzyme activity, more particularly ratio of lyase/hydroxylase. We cloned a single form of *P450c17* that is homologous to *P450c17-I* from the ovarian follicles of catfish (83). Our report (83) was first of its kind to relate *P450c17* mRNA, protein and enzyme activity where in we

found higher levels of *P450c17* expression and activity during preparatory and prespawning phases of ovarian development in catfish. Furthermore, during hCG-induced oocyte maturation both *in vitro* and *in vivo*, neither protein level nor ratio of lyase/hydroxylase activity changed significantly although there was an increase in mRNA levels by 2 h after induction with hCG. Based on our findings and also from those of others, it seems that *P450c17* have the potential to exert an influence on the shift in steroidogenesis.

4.5. 3beta-Hydroxysteroid dehydrogenase

The sequential 3beta-hydroxysteroid dehydrogenation and delta^5-delta^4 isomerization of the delta^5 C21/C19 steroid precursors is essentially done by 3beta-HSD. Presence of multiple forms has been reported in human and rodents. Complimentary DNAs encoding *3beta-HSD* have been cloned from rainbow trout, zebrafish and eel (100-102). However, studies on systematic analysis of multiple forms of 3beta-HSDs and their differential expression pattern during ovarian recrudescence, more specifically during meiotic maturation are few in fishes. For the first time, we cloned two novel isoforms/variants of *3beta-HSD* from gonads of the Nile tilapia (103). Recently, we demonstrated differential expression of 3beta-HSDs in gonads during the reproductive cycle. Analysis of expression patterns of *3beta-HSD*s during gonadal recrudescence revealed that *3beta-HSD* type-I was stable in vitellogenic, full-grown immature and mature ovarian follicular stages while the expression of type-II variant 1 was high in vitellogenic and mature follicles. This shows that both forms of 3beta-HSD are important for ovarian steroidogenesis in tilapia while 3beta-HSD type-II variant 1 have a potential role in steroidogenic shift in turn final oocyte maturation (103). In accordance to the report in tilapia, in trout also a marked increase in the expression of *3beta-HSD* was observed in ovaries during maturation (104, 105). However, stable expression of *3beta-HSD* was noticed in ovaries throughout the development in channel catfish (106). Nevertheless, considering the experimental strategy and differential analysis, it is imperative that the 3beta-HSD have an important role in meiotic maturation (103-105).

4.6. 20beta-hydroxysteroid dehydrogenase-like carbonyl reductase

The steroidogenic enzyme, 20beta-HSD catalyzes NADPH dependent reduction of C20 carbonyl group of C21 steroids. *20beta-HSD* cDNA was first cloned and characterized from pig testis (107) and later from other teleosts fishes like rainbow trout (108), ayu (81), the Nile tilapia (80), zebrafish (109). In teleostean ovary, 20beta-HSD produces 17alpha,20beta-DP from the precursor 17alpha-hydroxyprogesterone. However, teleostean 20beta-HSD also have the property of carbonyl reductase (80, 81, 108) 17alpha,20beta-DP is known to promote meiotic maturation of prophase-I arrested oocytes in several teleost species. Though 20beta-HSD has been cloned from few fish species, its role in final oocyte maturation has been demonstrated explicitly only in the last decade (59, 60, 84). 20beta-HSD activity in some teleosts was found to be elevated in response to gonadotropins during final oocyte maturation (10). Subsequently, transcriptional and translational up-regulation of *20beta-HSD* leads to the elevation of its activity during final oocyte maturation (10, 80). In amago salmon, its activity was induced by LH in granulosa cells of post-vitellogenic follicles immediately prior to oocyte maturation (110). Several reports from teleosts revealed that *20beta-HSD* transcripts abundant in late/post-vitellogenic follicles and peaked in postovulatory follicles during oocyte maturation (80, 81, 84, 105). Further, hCG induced (*in vitro*) over expression of *20beta-HSD* in post-vitellogenic immature follicles of tilapia within 1-2 h, maturation of oocyte which clearly demonstrated its pivotal role in the meiotic maturation (80). Recent studies from our laboratory using catfish model confirmed the elevation of transcripts of *20beta-HSD* in turn protein levels and enzyme activity during final oocyte maturation. Our study also localized the 20beta-HSD in the follicular layer for the first time which affirms its pivotal role in meiotic maturation (84).

4.7. Transcription factors shift

Transcription factors such as Ad4BP/SF-1 and CREBs play an important role in the regulation of expression of CYP19A1 (ovarian form of aromatase) and 20beta-HSD during oocyte maturation. Gonadotropins (FSH and LH) regulate these transcription factors to induce the steroidogenic shift during the final oocyte maturation in teleosts (59). Studies on medaka and tilapia revealed that Ad4BP/SF-1 is the transcriptional regulator of the gene CYP19A1 (82, 111-113). Interestingly, the Ad4BP/SF-1 motifs of CYP19A1 gene of tilapia resemble those of goldfish and zebrafish CYP19A1 genes. In tilapia, CYP19A1 and Ad4BP/SF-1 transcripts increased significantly during vitellogenesis and declined during post-vitellogenesis. Interestingly, when the follicle entered the stage of meiotic maturation, the expression of both these genes became undetectable (82). In mammals, CRE integrates with Ad4BP/SF-1 to regulate *CYP19A1* gene expression (114). CRE elements were also identified in the teleosts *CYP19A1* gene however there is no clear confirmation about its role. On the other hand, Foxl2 is known to have a cofactor role in Ad4BP/SF-1 mediated regulation of CYP19A1 (115). Recent studies revealed that one of the CREBs shows a synergistic pattern of expression with CYP19A1 and Ad4BP/SF-1 while the other with 20beta-HSD during the spawning cycle (Unpublished data of Senthilkumaran *et al.*). Recently, transcription factors like CREB have been shown to be in the regulation *20beta-HSD* gene in post-vitellogenic follicles during oocyte maturation in the fish ovary (Unpublished data of Senthilkumaran *et al.*). Promoter analysis studies (Senthilkumaran *et al.*, 2001; In: Program of the 3rd IUBS symposium on Molecular aspect of fish Genomes and Development, Singapore, Abstract S37) revealed that the *20beta-HSD* promoter activity could be maintained in the presence of CRE but not Ad4 motif with a TATA box. Gel-shift assays showed that the CRE elements of the *20beta-HSD* gene bind specifically to follicular nuclear extracts. Taken together, the triggering of shift in steroidogenesis (Figures 2 and 3) to elevate 17alpha,20beta-DP (MIH) by gonadotropins in granulosa cells occurs through the subjugation of *Ad4BP/SF-1* in turn *CYP19A1* followed by

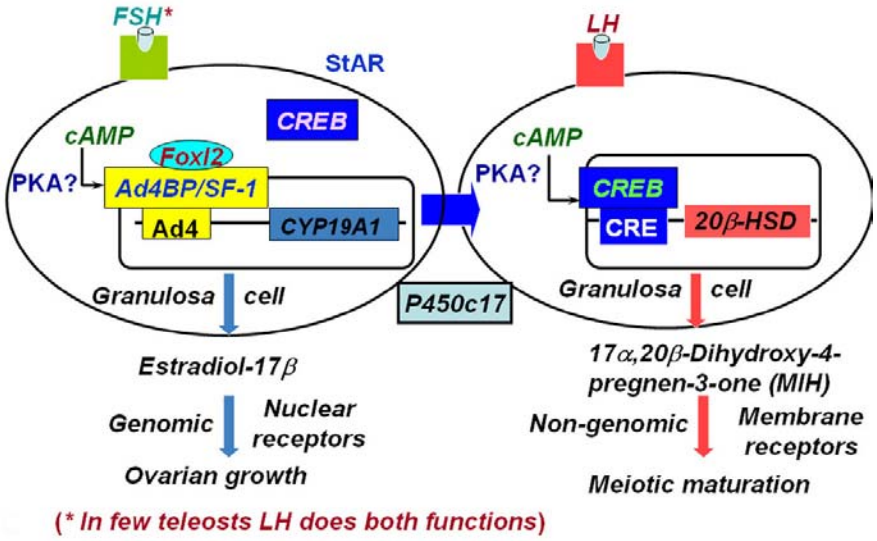

Figure 3. Transcription factor(s) swing to trigger a steroidogenic shift during final oocyte/meiotic maturation.

the over expression of *20beta-HSD* via *CREB*s (59, 60, 82, 84, 116). The potential action of 17alpha,20beta-DP is then to induce MPF for onward progression of meiotic maturation.

Interestingly, reports from our laboratory showed that *GnRH*, *vasa* and *sox9b* have been expressed abundantly during gonadal recrudescence and their levels drastically reaches nadir during final oocyte maturation (spawning phase) suggesting that they might have a role in oogenesis (117-119). Similarly, Pang and Ge (120) elaborated a potential role for activin in mediating LH-induced oocyte maturation in zebrafish. The exact mechanism by which these factors almost disappear when the oocyte reaches meiotic maturation is a fascinating area of research.

4.8. Maturation Promoting Factor

This is a key event during 17alpha,20beta-DP induced oocyte maturation wherein formation and/activation of MPF takes place in the cytoplasm of oocyte. In fact, the action of 17alpha,20beta-DP induces modulation of adenylate cyclase/phosphodiesterase activity there by reducing cAMP levels which results in the activation of MPF to induce progression of meiosis, in other words resumption of meiosis to reach first MI followed by MII (10, 60, 121-123). Though several evidences indicate the participation of protein kinase A to bring down cAMP levels, further studies are necessary to confirm this contention (60). Nevertheless, cAMP as 'meiosis arrester' is well accepted fact in fishes as well (10). Likewise in mammals, MPF is composed of two protein subunits in fishes. A protein having MPF kinase activity that is homologous to cdc2+ gene product of fission yeast referred to as p34cdc2 (cdc2) and a regulatory protein cyclin B (122). Two models concerning activation of MPF have been proposed and investigated extensively in several teleosts. First, a constant level of cdc2 is maintained during oocyte maturation and cyclin B protein is newly synthesized from its stored mRNA in oocyte after a signal from MIH (122). The newly synthesized cyclin B immediately forms a complex with pre-existing cdc2, rendering the CAK to phosphorylate cdc2 on Thr161 thus leading to the activation of MPF. The model proposed for goldfish is known to operate in several other fish species too including carp, catfish, and zebrafish, and also in lamprey giving the impression that absence of pre-MPF is common to fish (122). On the other hand, immature oocytes of *Xenopus* and starfish consists inactive MPF called pre-MPF (3, 9, 122). In support of this view, in fresh water perch (124) and trout (125) pre-MPF has been found in immature oocytes and the activation of MPF seems to be the key event to induce oocyte maturation in these species Further studies on this line clarifies the activation of MPF more explicitly (60). The downstream process that follows MPF activation is more or less similar to mammals. This aspect has been dealt extensively earlier under mammalian section and further reading can be done by referring the review of Nagahama and Yamashita (60).

4.9. Ovulation

Ovulation in fishes is defined as the release of mature ova from the surrounding follicular cells. Major differences between mammalian and piscine ovulation is the variation in the steroid feedback mechanisms. Negative feedback exerted by estradiol-17beta is a prerequisite for piscine preovulatory LH surge (64, 66), while the mammalian ovulation requires positive feedback to exert preovulatory LH surge (32). The ease of manipulating fish eggs as well as ovarian fragments (follicle) *in vitro* makes fish an excellent experimental model for investigating regulatory mechanisms of ovulation. Several studies pertaining to fish ovulation identified the involvement of arachidonic acid and its metabolites, including prostaglandins, are involved in ovulation in fish (126-128). Furthermore in depth analysis revealed that oocyte maturation is regulated by non-genomic action of MIH, while ovulation is regulated by genomic mechanisms such

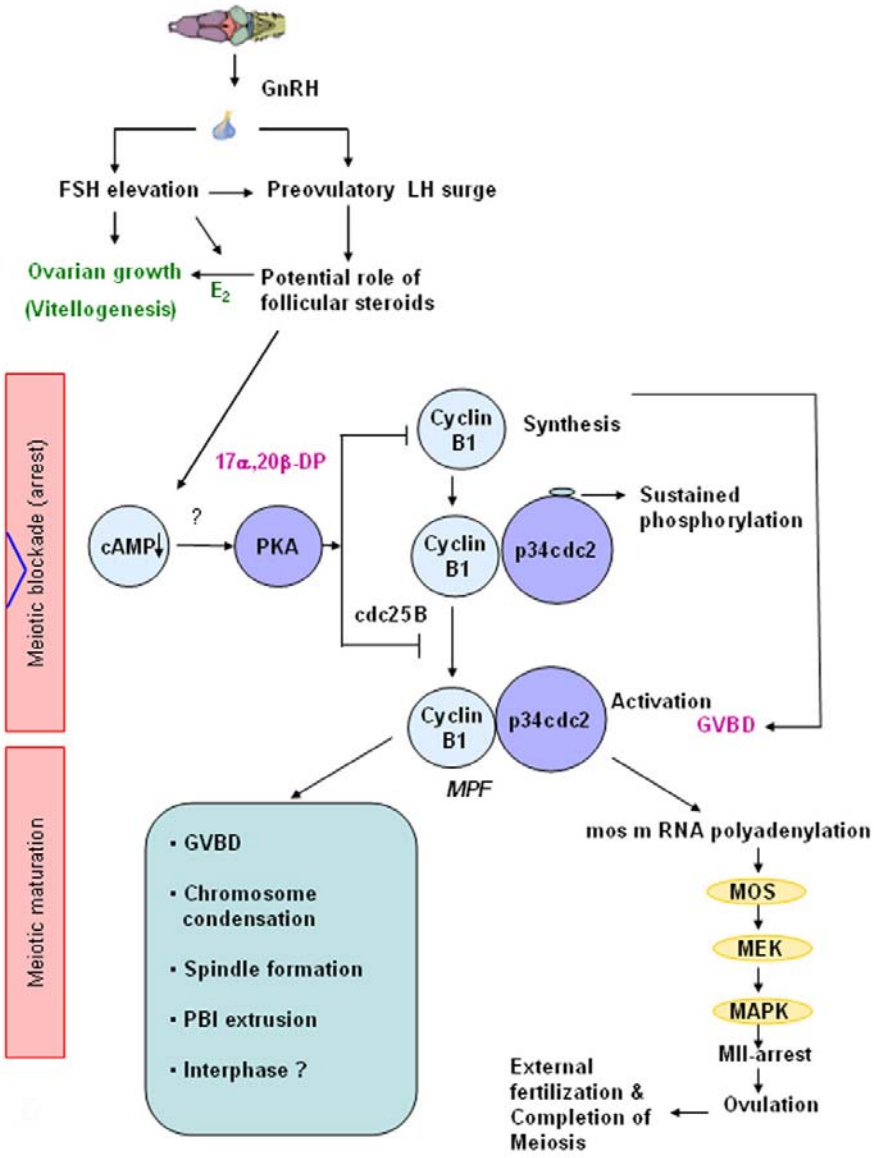

Figure 4. A schematic diagram explaining the piscine meiotic arrest and resumption of meiosis.

as transcriptional activity accompanied by new mRNA synthesis (129-131). One of the noteworthy points in piscine ovulation study was the identification of membrane receptor for progestins (132, 133), which paved way to identify the non-genomic action of steroids. Interestingly, studies using mammalian and other models have taken advantage of this pioneering research and identified similar mechanisms (132, 133). However the knowledge in the field of research pertaining to piscine ovulation is still limited. Further studies using advanced methods such as differential display, subtraction cDNA library and cDNA microarray may provide a way to identify new genes and factors that have pivotal role in piscine ovulation. Few comprehensive studies revealed important roles for hydrolytic enzymes and metalloproteinases in follicular rupture leading to ovulation (60, 134). Another important feature in the ovulation of marine teleosts is oocyte hydration. Kagawa *et al.* (135) have elucidated the mechanisms of oocytes hydration in the Japanese eel under *in vitro* and *in vivo* condition, where they have examined the morphological changes and hydration process occurring during final oocyte maturation and ovulation. The authors had indicated a pivotal role for aquaporins in this phenomenon in addition to yolk proteolysis. Interestingly, studies of this kind add a new dimension to piscine ovulation research based on the habitat that fishes live. All these findings warrant further research to add more perspectives to understand piscine ovulation when compared to the knowledge in mammalian ovulation. Nevertheless, with the knowledge gained from the studies of our laboratory and those of others a model explaining the process of meiotic maturation and ovulation in pisces has been presented in figure 4.

5. SEXUAL DIFFERENCE IN MEIOSIS EXECUTION

One of the interesting aspects in the process of meiosis execution is the sexual difference which is worth mentioning in this review. The process of meiotic maturation is more appropriate to describe as an exclusive event pertaining to final oocyte maturation of ova before attaining fertilizing ability, yet, maturational progression in males also require the action of several hormonal and other factors/genes to induce meiosis and spermatogenesis. In the case of sperm maturation, there is no meiotic arrest nor is the entry of male germ cells (spermatogonia) into meiosis quicker like that of female germ cells (oogonia). However, gene related hormonal trigger is required for the production of fertile spermatozoa. In addition, in the case of mammals, spermatozoa need to undergo capacitation in the female reproductive tract before the successful fertilizing the mature ova. One of key points is the presence of some comparable events pertaining to meiosis in male teleosts. Interestingly in male teleosts, 11-ketotestosterone induces meiosis and spermiogenesis while 17alpha,20beta-DP regulates sperm maturation through an increase in sperm duct pH, which in turn increases the cAMP content of sperm allowing the acquisition of motility (136, 137). However, the molecular mechanisms of these processes have been not elucidated in detail. Hence, it seems that the male teleosts may have a so called 'shift in steroidogenesis' during spermiation (138). Though this contention requires additional investigations by examining the steroidogenic enzymes genes and its transcription factors, it is an exciting area of research, which may impart new information to understand meiosis in males.

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Send correspondence to: Balasubramanian Senthilkumaran, Department of Animal Sciences, School of Life Sciences-Centre of Advanced Studies, University of Hyderabad, P. O. Central University, Hyderabad – 500 046, Andhra Pradesh, India, Tel: 91-40-23134562; Fax: 91-40-23010307, E-mail: bsksl@uohyd.ernet.in

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