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Oocyte Maturation as a Fascinating Research Problem

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Abstract

Proper development of oocytes is an essential step for successful fertilization. Formation of functional ova is far more complex than their male counterparts (i.e., sperms). The process of oogenesis gets interrupted at prophase I of meiosis and is reinitiated after suitable hormonal induction which leads to some molecular events. This resumption of prophase-arrested meiosis is called oocyte maturation. It is one of the central themes in endocrinology and reproduction of females. Oocyte maturation involves participation of Maturation Promoting Factor (MPF) and other molecules which also regulate the progression of cells through the stages of mitosis and have a pivotal role in cell cycle control. Since cancer is the result of uncontrolled cell division, it has an overlap with the regulatory mechanisms of oocyte maturation too. Many of the key molecules required in oocyte maturation also participate in signaling pathways involved in carcinogenesis. In this way the mechanism of oocyte maturation beautifully connects with not just female reproduction but cell cycle control and cancer. In this paper we take a closer look at this fascinating problem of oocyte maturation which has deep connections with diverse fields of biology enabling a researcher to make breakthroughs that may provide useful insights into many other interconnected problems.

Keywords: Oocyte maturation, Meiotic reinitiation, MPF, Oogenesis, MIS, Cell cycle, Cancer

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Introduction:

In human foetus, primordial germ cells originate in the dorsal endoderm of the yolk sac, close to the allantoic evagination. These cells migrate by 4th week through the hindgut to finally settle in the urogenital ridge. The number of oogonia reaches upto 7 million by the 25th week of gestation (Mandl & Zuckerman, 1951). At this stage, the primary oocyte gets surrounded by a single layer of flattened epithelial to form a primordial follicle. The process of meiosis I starts in the primordial follicle and it involves replication of DNA in S-phase of the cell cycle followed by meiotic arrest in the diplotene stage of prophase I.

The oocytes of vertebrates are surrounded by follicle cells and the whole structure is called a ovarian follicle. The release of oocyte from follicle cells is called ovulation which is the result of follicular growth and is an important step in oogenesis (Johnson et al., 2004). Oogenesis is the process of meiosis that produces haploid ova from diploid primary oocytes. Unlike spermatogenesis which is completed without any interruption, the formation of ova is arrested at two points during oogenesis (Masui & Clarke, 1979). Initially the oocytes are arrested at diplotene stage of prophase I and are arrested once again at metaphase II. Oocyte maturation refers to the reinitiation of prophase-arrest that allows oocytes to advance from prophase I to metaphase II of meiosis. This precisely regulated meiotic resumption is essential for normal ovulation and subsequent fertilization, and involves changes in the delicate balance between factors that promote meiotic arrest and others that stimulate maturation. There is a difference in the regulation of this event among vertebrates. While in lower vertebrates such as fishes and amphibians the oocyte maturation is a result of the activity of maturation inducing hormone (MIH), in mammals it is caused by the removal of maturation inhibiting factors. In both cases, the reinitiation of prophase-arrested meiosis is marked by the breaking of the nuclear envelope of oocyte in an event called germinal vesicle breakdown (GVBD) and subsequent release of

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the first polar body (Haider & Baqri, 2000a). In lower vertebrates, the molecule that triggers GVBD is an steroid which is progesterone in case of *Xenopus*, an amphibian and a progesterone derivative such as 17α,20β-dihydroxy-4-pregnen-3-one (17α,20β-DP) in case of *Clarias*, a fish (Nagahama et al., 1994). However, the MIH need not always be a steroid for 1-methyl adenine (1-MA) is the MIH in case of *Echinus*, the sea urchin. The action of MIH on oocytes results in a signaling cascade which leads to production of maturation promoting factor (MPF). Finally, MPF which is made up of p34cdc2-kinase and cyclin B triggers the resumption of meiosis arrested in prophase I (Balamurugan & Haider, 1998).

Oocyte Maturation vs Ovulation:

Ovulation is the appropriately timed release of a mature, developmentally competent oocyte from the ovary into the oviduct, where fertilization occurs. Importantly, ovulation is tightly linked with oocyte maturation, demonstrating the interdependence of these two parallel processes, both essential for female fertility.

Ovulation of an oocyte from the ovary into the oviduct is so regulated as to ensure the timely release of only high-quality oocytes at the appropriate time. Within the ovary, each oocyte, which is to be fertilized is said to first gain developmental competence. Once the oocyte is grown and competence acquired, it is released into the oviduct.

Interestingly, despite that the exposure of ovarian follicles to LH causes oocyte maturation, LH receptors were neither found in oocytes nor in surrounding cumulus granulosa cells. Although the ability of growth factors to promote cumulus cell expansion and subsequent oocyte maturation in follicle cultures has been known, their physiologic role in regulating meiosis and ovulation had been uncertain. In addition to promoting steroid production, LH triggers the release of growth factors from the theca and/or mural granulosa cells. These growth factors then act in a paracrine fashion to stimulate inner cumulus granulosa cell expansion, which is

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followed by disruption of oocyte-granulosa cell contacts, oocyte maturation, and eventual ovulation (Albertini et al., 2001). Prostaglandin E2 is of special significance in ovulation as it is involved in angiogenesis of human follicular endothelial cells along with vascular endothelial growth factor (Trau et al., 2016).

Oocyte Maturation & Female Infertility:

It can be seen that many cases of female infertility are attributed to errors in the process of oocyte maturation. This include follicular atresia in polycystic ovarian disease (PCOD) and anovulatory sterility. Polycystic ovarian disease is characterised by ovarian cysts, hypersecretion of luteinizing hormone (LH), elevated androgens, hyperinsulinemia due to insulin resistance and obesity. It is proposed that the complex process of folliculogenesis involves intrafollicular paracrine signaling between cumulus cells and oocyte (Tamba et al., 2010) and this is responsible for acquisition of developmental competence among the oocytes. In PCOD, the developmental competence of oocytes is severely comprised (Dumesic et al., 2006).

Steroids have been known to promote oocyte maturation in lower vertebrates such as fish and frogs for many decades. Interestingly, this steroid-mediated maturation occurs independent of transcription, and may be regulated by steroid receptors located at the plasma membrane of cells. Experiments aimed at determining the effects of steroids on mammalian oocyte maturation have been difficult to interpret. In addition to blocking steroidogenesis, several studies have directly examined steroid effects on the spontaneous maturation of isolated mammalian oocytes, finding that micromolar amounts of some steroids slowed maturation.

Whether or not androgens are physiologic mediators of oocyte maturation, their ability to trigger promeiotic signals in oocytes brings into question the consequences of excess androgens on oocyte development in diseases such as PCOD.

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Data suggest that excess androgen signaling in the ovary might be a major contributor to the unregulated folliculogenesis and infertility in diseases of androgen excess.

Furthermore, PCOD patients often have increased sensitivity to gonadotropins during in vitro fertilization protocols, suggesting that follicles and/or oocytes might be primed by the excess androgens. If the high androgen levels are indeed stimulating meiosis, then perhaps the aforementioned SARMs can be used specifically to regulate oocyte maturation and improve fertility in patients with androgen excess.

Endocrinology & Cell Signalling in Oocyte Maturation:

The control of the process of oocyte maturation involves sequential action of hormones of hypothalamo-hypophysial-gonadal (HHG) axis. It starts with the release of hypothalamic GnRH (gonadotropin releasing hormone) and subsequent induction of pituitary gonadotropins (FSH and LH) which in turn bind to their receptors on granulosa and theca cells of ovarian follicle. Both the gonadotropins initiate a signaling process involving stimulatory G-proteins ($G\alpha_s$) and use cyclic AMP as the second messenger. The FSH-induced signaling in granulosa cells results in the synthesis of Maturation Inducing Hormone (MIH) which stimulates the oocyte to reinitiate prophase-arrested meiosis. The study of hormone signaling during oocyte maturation has led to some novel insights. For example, in case of *Xenopus*, progesterone which is formed in granulosa cells and acts as the MIH was found to bind to membrane receptors on oocyte membrane (Baulieu et al., 1978). This behavior is contrary to the typical signaling mechanism of steroids which are known to bind to cytoplasmic and nuclear receptors. In fact, steroids are derived lipids and their permeability through the cell is attributed to lipoprotein nature of plasma membrane. Membrane localization of steroid receptors has been further confirmed by the binding of 17α,20β-DP to the oocyte membrane of *Clarias batrachus* where this steroid acts as the MIH. The steps subsequent to the binding of MIH to membrane

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receptors involve G-proteins and adenylate cyclase leading to a transient decrease of cAMP which is the trigger for oocyte maturation. In general, intracellular cAMP homeostasis is regulated by two distinct classes of enzymes: the adenylate cyclases (ACs), which form cAMP; and the phosphodiesterases (PDEs), which break cAMP into 5'-AMP. Most of the well-characterized ACs are induced by stimulatory G proteins ($G\alpha_s$) and inhibited by inhibitory G proteins ($G\alpha_i$). In contrast, the mechanisms controlling PDE activity are lesser known and may involve short-term activation in response to protein kinase A (PKA)-mediated phosphorylation, as well as long-term regulation that entails changes in mRNA and protein expression.

This fact is further established by the inhibition of oocyte maturation and GVBD in the presence of agents that elevate cAMP levels in the oocytes. These agents include adenylate cyclase activators (e.g., forskolin) and phosphodiesterase inhibitors such as isobutyl methyl xanthine (IBMX) and theophylline (Chaube and Haider, 1997). This is evidenced by induction of maturation in response to β-adrenoceptor antagonists like propranolol, alprenolol etc (Hader and Baqri, 2000b)

Further, the involvement of cAMP-dependent protein kinase (PKA) in the oocyte maturation of the catfish *Clarias batrachus* is also well documented (Haider & Baqri, 2001).

Similarly, most of the inhibitory mechanisms that prevent oocyte maturation in mammals appear to involve the upregulation of intracellular cAMP levels (Albertini and Carabatsos, 1998). These processes may include direct transport of the nucleotide into oocytes via gap junctions, G protein-mediated stimulation of adenylyl cyclase, and inhibition of intracellular phosphodiesterases. The maturation inhibiting hormone in mammalian oocytes has been the subject of much curiosity and hypoxanthine has been one of the earliest candidates to be considered for this role. Hypoxanthine is a purine that appears to be produced in the follicle, and inhibits in vitro meiosis of oocytes that are either denuded or encased in follicles.

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Thus, the investigation on the mechanism of action of hormones involved in oocyte maturation has led to unravelling of novel signal transduction mechanisms initiated by these chemical messengers.

Oocyte maturation, cell cycle control, and Cancer:

Cancer figures predominantly among the major health concerns of the world. It involves uncontrolled cell division due to failure of the molecular machinery which regulates cell division and dictates progression of cells through the stages of cell cycle. Cancer is considered an inevitable consequence of cellular physiology because of the possibility of spontaneous mutations in genes that regulate cell cycle. The spontaneous mutations may be caused by random errors in DNA replication, physical mutagens (e.g., UV, X, or γ-rays) and chemical mutagens. Altered regulation of expression of certain genes (oncogenes and tumour suppressor genes) may lead to carcinogenesis (i.e., tumour growth and metastasis).

It is important to note that MPF is the same molecule that induces G_2/M transition in the mitotic cell cycle where it is referred to as M-phase promoting factor indicating a convergence of regulatory pathways in mitosis and meiosis. Thus oocyte maturation is related to cell cycle and this links the two processes together. Similarly, developments in our understanding of oocyte maturation have applications in regulating induced breeding of fishes or in treating some forms of female infertility.

Conclusion:

The facts and figures presented above clearly suggest that oocyte maturation is a busy field of scientific exploration. What makes oocyte maturation a good research problem is that it can be studied in the context of several model organisms from diverse taxonomic groups. However, more importantly, oocyte maturation is a special problem because of its obvious connections with diverse fields such as fertility, cell signalling, cancer and apoptosis. Thus, it is a

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researcher's delight to be working on a problem which can have maximum impact simply because it has significant overlap with many other fields.

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