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Invited Article

Cyclic nucleotides regulate oocyte meiotic maturation and quality in mammals

Anumegha Gupta[1], Meenakshi Tiwari[1], Alka Sharma[1], Ashutosh N. Pandey[1], Pramod K. Yadav[1], Anil K. Yadav[1], Shilpa Prasad[2], Ajai K. Pandey[3], Tulsidas G. Shrivastav[4], Shail K. Chaube[1]

[1]Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, [2]Department of Biotechnology, Amity University, Ranchi, Jharkhand, [3]Department of Kayachikitsa, Banaras Hindu University, Varanasi, Uttar Pradesh, [4]Department of Reproductive Biomedicine, National Institute of Health and Family Welfare, New Delhi, India.

***Corresponding author:**
Shail K. Chaube,
Department of Zoology,
Institute of Science, Banaras
Hindu University, Varanasi,
Uttar Pradesh, India.

shailchaubey@gmail.com

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ABSTRACT

Oocyte meiosis is a prolong series of events that are comprised several intermittent channels in mammals. Oocyte meiosis starts during fetal life and then gets arrested at diplotene stage of first meiotic prophase in follicular oocyte. The continuous transfer of cyclic adenosine 3', 5'-monophosphate (cAMP) and cyclic guanosine 3', 5'-monophosphate (cGMP) from encircling granulosa cells to the oocyte through gap junctions helps in the maintenance of their high level required to achieve the long-lasting diplotene arrest so-called germinal vesicle stage. Phosphodiesterase inhibitors have been used to elevate intracellular level of both cyclic nucleotides and prevent spontaneous resumption of meiosis in oocytes under *in vitro* culture conditions. On the other hand, disruption of gap junction either by pituitary gonadotropin or by physical removal of encircling granulosa cells interrupts transfer of these nucleotides to the oocyte. As a result, intraoocyte cAMP as well as cGMP levels are decreased drastically that initiate downstream pathways to destabilize maturation-promoting factor (MPF). The destabilized MPF initiates meiotic resumption from diplotene arrest in mammalian oocytes. Oocyte meiosis further progresses from metaphase I to metaphase II stage and extrudes first polar body to get converted into haploid female gamete at the time of ovulation. Indeed, high level of cAMP as well as cGMP levels maintains diplotene arrest for a long time in follicular oocytes. On the other hand, transient decrease of their levels drives resumption from diplotene arrest, thereby meiotic maturation process, which enables oocyte to achieve developmental competency. Any defect in this process directly affects oocyte quality and thereby reproductive outcome in mammals including human.

Keywords: Cyclic nucleotides, Maturation-promoting factor, Oocyte meiotic maturation and quality, Mammals

INTRODUCTION

Mammalian oocytes are arrested at diplotene stage of first meiotic prophase for a long time in ovarian follicle.[1] The achievement of meiotic competency starts with resumption from diplotene arrest, passes through metaphase I (M-I) to metaphase II (M-II), and ends with the extrusion of first polar body (PB-I) at the time of ovulation.[2,3] Hence, progression of meiotic cell cycle from diplotene arrest to M-II stage and successful extrusion of PB-I enables oocyte to get converted into haploid female gamete needed for successful fertilization and early embryonic development.[4-6] Thus, the meiotic maturation of oocyte is an important event that determines its quality and directly affects reproductive outcome in mammals including human.[4-6]

The oocyte meiotic maturation is mainly regulated by cyclic adenosine 3', 5'-monophosphate (cAMP) and cyclic guanosine 3', 5'-monophosphate (cGMP). These nucleotides are either received

from encircling granulosa cells or generated by oocyte itself in mammals.[7-10] Synthesis of cAMP as well as cGMP is regulated by adenylyl cyclase (AC) as well as guanylyl cyclase (GC), while their degradation occur by cyclic nucleotide phosphodiesterases (PDEs) both in encircling somatic cells and oocyte within the follicular microenvironment.[10-12]

Pituitary gonadotropins regulate these enzymatic pathways in the granulosa cells and oocyte to reduce their levels in follicular oocyte.[8-12] The decrease of cAMP as well as cGMP levels initiates downstream signaling pathways to phosphorylation of cyclin-dependent kinase 1 (Cdk1) and synthesis/degradation of cyclin B1. Thus, changes in Cdk1 phosphorylation status and cyclin B1 level destabilize maturation-promoting factor (MPF) in the oocyte. MPF destabilization overcomes diplotene arrest and oocyte undergoes meiotic resumption, progression from M-I to M-II, and extrudes first PB-I to become female gamete just before ovulation in mammalian oocytes.[8-12]

cAMP SIGNALING AND REGULATION OF OOCYTE MEIOTIC MATURATION

The cAMP is an important regulator of meiotic maturation in mammalian oocytes. It is continuously generated in the encircling granulosa cells and gets transferred to the oocyte through gap junctions to maintain diplotene arrest within the follicular microenvironment [Figure 1].[5,12,13] Oocyte also generates cAMP sufficient enough to maintain meiotic arrest[1,7,10] suggesting that the sustained high level of cAMP is associated with the maintenance of meiotic arrest *in vivo*.

In mammalian oocyte, AC is responsible for conversion of adenosine triphosphate (ATP) into cAMP and results in the sustained high level of cAMP level within the oocyte.[7,10] A closely related nine transmembrane bound (AC 1–9) genes with sequence homology and structural similarities have recently been reviewed in the human genome.[10] Out of which, AC3 has been detected in both mouse and rat oocytes, which is widely expressed intracellular source of cAMP in mammal.[10] Further, AC activators such as forskolin increase intraoocyte cAMP level and inhibit spontaneous resumption from diplotene arrest in mice,[14] rats,[15] bovine,[16] and human[17] oocytes cultured *in vitro*.

It is well established that AC signaling pathway generates intrinsic cAMP in mammalian oocytes, cAMP-phosphodiesterase (cAMP-PDE) is required to be inactivated to prevent degradation of cAMP so that the elevated cAMP level could be maintained to maintain meiotic arrest in mammalian oocyte.[10] This notion is further strengthened by observations that PDE inhibitors increase intraoocyte cAMP level and maintains diplotene arrest in rat,[18] mouse,[19] bovine,[20] pig,[21] and human oocytes cultured *in vitro*.[17]

The cAMP as intraoocyte regulator of meiotic maturation is further strengthened by *in vitro* studies that membrane

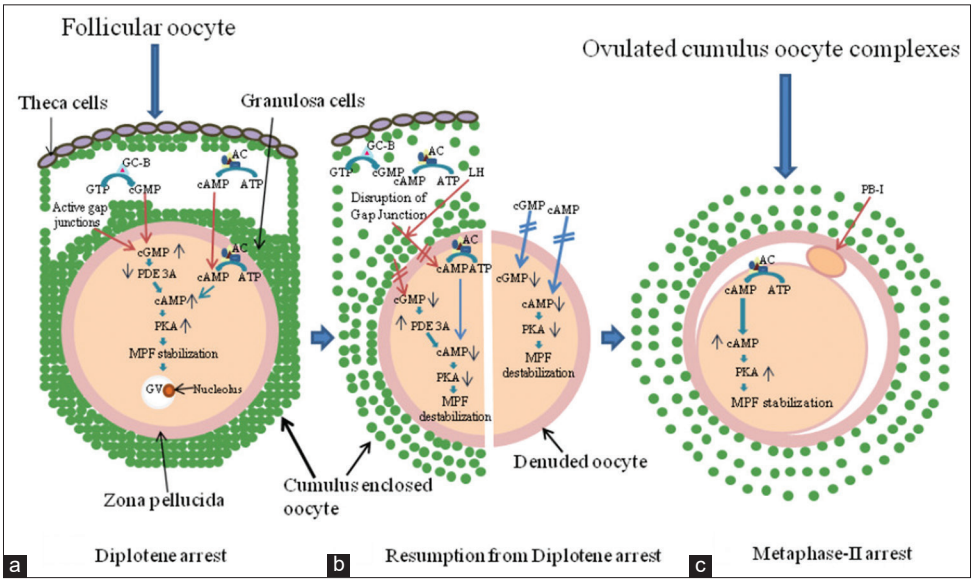

Figure 1: Schematic diagram showing the involvement of cyclic nucleotides (cyclic adenosine 3', 5'-monophosphate [cAMP] and cyclic guanosine 3', 5'-monophosphate [cGMP]) during the oocyte maturation in mammals. (a) Transfer of cAMP and cGMP from encircling granulosa cells and generation of cAMP with in the oocyte causes high sustained level of cyclic nucleotides that result in the maintenance of diplotene arrest for longer time within follicular microenvironment. (b) Disruption of gap junctions and interruption of cyclic nucleotides from encircling granulosa cells to the oocyte initiate downstream signaling pathways to destabilize maturation-promoting factor (MPF). Destabilized MPF induces meiotic resumption from diplotene arrest in mammalian oocytes *in vivo* as well as *in vitro*. (c) However, generation of cAMP through adenylate cyclase pathway is sufficient to maintain stabilize MPF and thereby M-II arrest in oocyte soon after ovulation.

permeable analogs such as db-cAMP or 8-bromo-cAMP increase intracellular cAMP and maintain diplotene arrest in rat, mouse,[22] rabbit,[23] goat,[24] and porcine oocytes.[25] Measurement of intracellular cAMP further suggests that high intraoocyte cAMP level maintains diplotene as well as M-II arrest, while transient decrease in its level induces meiotic resumption from diplotene as well as M-II arrest in rat oocytes cultured *in vitro*.[18,26]

Gonadotropin surge increases intracellular cAMP level in the encircling granulosa cells of preovulatory follicles through adenylate cyclase pathway.[27,28] through the activation of mainly G stimulatory protein-coupled cell surface receptors.[29] The increased cAMP level disrupts gap junctions among encircling somatic cells and between granulosa cells and oocyte that results in the interruption in the transfer of cAMP to the oocyte. In addition, hydrolysis through various cAMP-PDEs further reduces cAMP level leading to meiotic resumption from diplotene arrest in follicular oocytes.[7,29-31]

Physical removal of encircling granulosa cells disrupts gap junctions and culture of denuded oocytes in appropriate medium allows oocyte to undergo spontaneous resumption from diplotene arrest under *in vitro* culture conditions.[27-31] Thus, a transient decrease occurs in the oocyte that initiates downstream signaling pathway to induce resumption from diplotene arrest in mammalian oocytes. Taken together, these studies suggest that sustained high level of cAMP maintains diplotene arrest, while reduction in its level signals downstream pathway to induce meiotic resumption from diplotene arrest.[29,32] Indeed, cAMP is an intraoocyte regulator of meiotic maturation in mammalian oocytes.[33]

cGMP SIGNALING AND REGULATION OF OOCYTE MEIOTIC MATURATION

The cGMP is another important signal molecule produced by the membrane GC natriuretic peptide receptor 2 (NPR2, also called guanylyl cyclase-B or GC-B) in the granulosa cells of follicular oocytes.[34-36] The GC-B is expressed in mural as well as cumulus granulosa cells, while its expression was not reported in oocyte or theca cells of the follicle.[34-36] The mural granulosa cells produce C-type natriuretic peptide (CNP or natriuretic peptide C or NPPC) and activates NPR2.[34,35] Unlike cAMP, cGMP is generated in the granulosa cells only and transferred to the oocyte through gap junctions to regulate the meiotic cell cycle.[35]

The cGMP is hydrolyzed by specific PDEs that regulate cGMP level in the granulosa cells as well as in oocyte.[35,37] This possibility is further supported by *in vitro* studies that various PDE inhibitors increase intraoocyte cGMP level and responsible for diplotene arrest in rat,[35] mice,[37] and porcine oocytes cultured *in vitro*.[38] A decrease of intraoocyte cGMP increases PDE3A activity that results in the decrease of cAMP level. The decrease of cGMP triggers resumption from diplotene arrest in rat oocytes cultured *in vitro*.[39] In addition, pituitary gonadotropins decrease cGMP level and induce meiotic exit from diplotene arrest in mouse[40-42] and pig oocytes,[43] while high level of cGMP maintains diplotene as well as M-II arrest in rat oocytes cultured *in vitro*.[8,11,33] Taken together, these observations suggest that increase of cGMP prevents spontaneous exit from diplotene arrest, while reduction in its level initiates downstream pathway to induce exit from diplotene arrest in mammalian oocytes. Indeed after cAMP, cGMP is another intraoocyte regulator of oocyte meiotic maturation in mammals.

CYCLIC NUCLEOTIDES REGULATE MPF

Changes in cAMP as well as cGMP levels regulate oocyte meiotic competency either by changing the activity of MPF or regulating its destabilization/stabilization process. Increase of cAMP level results in the activation of protein kinase A (PKA), which, in turn, phosphorylates several proteins and stabilizes MPF to maintain meiotic arrest.[13,16] The cGMP from granulosa cell origin inhibits the activity of PDE 3A, which is responsible for the hydrolysis of cAMP and elevates intraoocyte cAMP level in the oocyte [Figure 1].[36] Increased level of cAMP promotes the phosphorylation of Cdk1 at threonine-161 and stabilizes MPF.[42,44] Thus, meiotic arrest in diplotene as well as M-II stage is maintained by sustained high level of stabilized MPF in oocytes.[33] Indeed, high level of cAMP as well as cGMP maintains stabilized MPF and thereby meiotic arrest at diplotene as well as M-II stage *in vivo* as well as *in vitro*.[8,11] The non-specific as well as specific PDE inhibitors prevent spontaneous exit from diplotene arrest under in vitro culture conditions probably by increasing cAMP and cGMP level. PDE inhibitors reduce fertilization rate, blastocyst formation and also induce pregnancy loss without disturbing reproductive cyclicity and ovulation process in mammals.[45]

The decreased level of cGMP relieves inhibition of PDE3A in the oocyte[40,41] and active enzyme reduces intraoocyte cAMP level. Hence, reduced intraoocyte cAMP level results in the inactivation of PKA and thereby MPF destabilization and triggers meiotic exit from diplotene and M-II arrest.[33,44] Further, denudation process by physical removal of encircling granulosa cells interrupts transfer of cAMP as well as cGMP from the granulosa cells to the oocyte and spontaneous hydrolysis by PDEs results in the transient decrease of their levels in the oocyte.[8,9] The decrease of these cyclic nucleotides drives downstream signaling pathways to induce meiotic exit from diplotene arrest *in vitro*.[4] Similarly, pituitary gonadotropins surge disrupt gap junctions among encircling granulosa cells and between encircling cumulus granulosa cells to the oocyte.[46] Disruption of gap junctions affects the transfer of cAMP as well as cGMP from granulosa

cells to the oocyte,[11,14,15] thus causing a transient decrease of their levels in the oocyte.[36] The reduced intraoocyte cAMP level modulates phosphorylation status of Cdk1 and triggers cyclin B1 degradation that destabilizes MPF and/or increases Cdk1 activity.[9,12] The meiotic competency is initiated due to destabilized MPF and/or increased Cdk1 activity that leads to meiotic exit from diplotene arrest in pre-ovulatory follicles of several mammalian species.[3]

CLINICAL AND COMMERCIAL USE OF CYCLIC NUCLEOTIDES

The *in vitro* maturation (IVM) is clinically attractive reproductive technology, wherein immature germinal vesicle stage oocytes are collected and cultured for IVM until it reaches M-II stage possessing PB-I.[47-49] The artificial elevation of cAMP in under *in vitro* culture conditions has shown potential to improve pregnancy rates.[7] To increase cellular cAMP, COCs are exposed to AC activators and PDE inhibitors have been used during pre-IVM phase.[50-54] This type of cAMP modulating system has been shown to increase cAMP level in COC substantially that mimics to some extent the *in vivo* spike of cAMP caused by gonadotropin surge.[55] Studies suggest that artificial modulating system of cAMP significantly improves oocyte quality, thereby blastocyst development, blastocyst quality, and pregnancy rates.[56-58] Thus, cAMP modulating system during pre-IVM stage could be a potential approach to bridge gap between IVM and IVF and has clinical as well as commercial relevance.

CONCLUSION

The cAMP as well as cGMP are produced in encircling granulosa cells and transferred to follicular oocyte through gap junction. Oocyte is also capable of generating cAMP good enough to maintain meiotic arrest at diplotene as well as M-II stages. Thus, high sustained levels of these cyclic nucleotides do not permit oocyte to complete meiotic maturation and affect oocyte quality. On the other hand, gonadotropin surge or removal of granulosa cells disrupts the transfer of these two cyclic nucleotides to the oocyte. As a result, intraoocyte cAMP as well as cGMP levels decrease that further increase their hydrolysis by oocyte-specific PDEs. Thus, a transient decrease of cyclic nucleotides triggers downstream pathway to destabilize MPF and/or its activity. The MPF destabilization drives spontaneous exit from diplotene arrest and oocyte achieve meiotic competency by reaching at M-II stage and extruding PB-I. The M-II arrested oocytes with PB-I are the right choice for successful fertilization and various assisted reproductive technology (ART) programs to optimize the reproductive outcome in several mammalian species including human. Indeed, cyclic nucleotides play an important role in the regulation of oocyte meiotic maturation and quality that could be used to improve ART outcome in several mammalian species including human.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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