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Nitric oxide signaling during meiotic cell cycle regulation in mammalian oocytes

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1. ABSTRACT

Nitric oxide (NO) acts as a major signal molecules and modulate physiology of mammalian oocytes. Ovarian follicles generate large amount of NO through nitric oxide synthase (NOS) pathway to maintain diplotene arrest in preovulatory oocytes. Removal of oocytes from follicular microenvironment or follicular rupture during ovulation disrupt the flow of NO from granulosa cells to the oocyte that results a transient decrease of oocyte cytoplasmic NO level. Decreased NO level reduces cyclic nucleotides level by inactivating guanylyl cyclases directly or indirectly. The reduced cyclic nucleotides level modulate specific phosphorylation status of cyclin-dependent kinase 1 (Cdk1) and triggers cyclin B1 degradation. These changes result in maturation promoting factor (MPF) destabilization that finally triggers meiotic resumption from diplotene as well as metaphase-II (M-II) arrest in most of the mammalian species.

2. INTRODUCTION

Meiotic cell cycle in mammalian oocyte involves several stop/go channels (1–3). Follicular oocytes are arrested for the first time at diplotene stage and remain arrested at this stage in the ovary from birth to puberty (2, 4–9). The diplotene arrest for such a long period is mainly due to continuous transfer of several signal molecules from encircling granulosa cells to the oocyte via gap junctions (5, 10–12). Pituitary gonadotropins surge disrupt gap junction and cumulus-oocyte communication, which interrupt supply of several signal molecules to the oocyte leading to meiotic resumption from diplotene arrest (13–17). Further, physical removal of encircling granulosa cells disrupt transfer of signal molecules to denuded oocyte resulting in spontaneous resumption from diplotene arrest under *in vitro* culture conditions (3, 12, 18–20).

Meiotic cell cycle in follicular oocyte progresses from diplotene arrest to metaphase-I (M-I) stage (5) and further gets arrested at metaphase-II (M-II) stage by extruding first polar body (PB-I) at the time of ovulation in most of the mammalian species (2, 8, 9, 21, 22). These freshly ovulated oocytes remain arrested at M-II stage until fertilization (2, 3, 12, 20–25). However, if fertilization does not occur, postovulatory aging mediates spontaneous exit from M-II arrest by triggering the initiation of extrusion of second polar body (PB-II) in oocytes of several mammalian species (22, 26, 27). However, PB-II does not get completely extruded and oocytes are further arrested at metaphase-III (M-III) like stage (20–24, 28, 29).

Several signal molecules are involved in meiotic cell cycle regulation of mammalian oocytes. These signal molecules are generated either by encircling granulosa cells or oocyte itself (2, 3, 13–17). Changes in levels of these signal molecules decide whether meiotic cell cycle has to be resumed or remain arrested at diplotene stage or M-II stage (12, 13, 16, 20, 30). The adenosine 3',5'-cyclic monophosphate (cAMP), guanosine 3',5'-cyclic monophosphate (cGMP), hydrogen peroxide (H_2O_2), calcium (Ca^{2+}) and nitric oxide (NO) are major signal molecules involved in the modulation of meiotic cell cycle in mammalian oocytes (2, 3, 5, 20).

It is accepted that NO is one of the major signal molecules that alters oocyte physiology (31–33). It is generated through enzymatic as well as non-enzymatic pathways in various cell types including follicles of mammalian ovary (5, 34). The enzymatic pathway includes nitric oxide synthases (NOS) that are responsible for NO generation in mammalian ovary. These enzymes convert L-arginine to L-citrulline to generate NO in various cell types (35). NO is also generated through non-enzymatic pathway from nitrite at low-pH under reducing conditions involving H_2O_2 and D- or L-arginine (36–39). The NO generated through non-enzymatic pathway may also play a similar role as NO generated enzymatically (40).

The NOS genes are expressed in ovary, oocyte, follicles and granulosa cells suggesting their roles during folliculogenesis, oocyte growth development and meiotic maturation (33, 41–48). All three NOS isoforms, neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) are expressed at various stages of folliculogenesis in mouse, rat, porcine and bovine ovaries (49–53). The eNOS and iNOS levels increase in theca and granulosa cells during follicular development in porcine ovary (54). In addition, eNOS mRNA has been detected in rat ovary and porcine oocytes cultured *in vitro* (49, 55). Recent studies show the involvement of NOS/NO system in the control of meiotic maturation of cumulus-oocyte complexes (COCs) (35–48).

The involvement of NO in the regulation of oocyte meiotic cell cycle has been reported in several mammalian species. However, a discrepancy exists between the level of NO and meiotic cell cycle resumption/arrest. Few studies suggest that increase in the level of NO derived from both eNOS and iNOS induce meiotic resumption from diplotene arrest (34, 41–43, 54, 56–59) as well as M-II arrest (26). However, other reports advocate a transient decrease of NO level during meiotic resumption from diplotene arrest (19, 60–64) as well as M-II arrest (65). A reduced level of NO reduces guanylyl cyclase (GC) activity, reduces cAMP level by decreasing adenylyl cyclase (AC) activity in oocyte cytoplasm (5, 60, 66, 67). The reduced cyclic nucleotides level signals downstream pathways to destabilize maturation promoting factor (MPF) that finally triggers meiotic resumption from diplotene arrest as well as M-II arrest in several mammalian species (3, 11, 12, 68).

This review mainly focuses on NO signaling during meiotic cell cycle resumption from diplotene stage, progression via M-I to M-II stage, a period when oocyte achieve meiotic competency. Further, we have attempted to update the involvement of NO during meiotic exit from M-II stage, a first step towards spontaneous egg activation that limits assisted reproductive outcome (ART) in mammals.

3. NO AND MEIOTIC RESUMPTION FROM DIPLOTENE ARREST

Follicular oocytes are arrested at diplotene stage of meiotic cell cycle for a long time in several mammalian species (5, 10, 16, 17). These diplotene arrested oocytes are morphologically characterized by the presence of germinal vesicle (GV: Figure 1A) in the cytoplasm and nucleolus within the GV (3, 5, 11, 12, 69). The diplotene arrest in follicular oocyte for a long time might be due to synthesis and secretion of various reactive nitrogen species (RNS) such as NO through NOS-mediated pathway either from follicular cells or from oocyte itself or both (5, 15). Resumption of meiosis from diplotene arrest, which is morphologically characterized by germinal vesicle breakdown (GVBD: Figure 1B) occurs due to disruption of gap junctions by pituitary gonadotropins surge at the time of puberty (3, 14). Disruption of gap junctions interrupts intercellular communication within the follicle (18). As a result, transfer of several signal molecules from encircling granulosa cells to the oocyte is disrupted (13, 15).

Pituitary gonadotropins modulate expressions of various NOS isoforms (70). Both pregnant mare's serum gonadotropin (PMSG) and human chorionic gonadotropin (hCG) have been shown to influence eNOS and iNOS expressions in rat ovary (34). The presence of various NOS isoforms has been reported in mouse (45), rat (57), porcine (42) and bovine oocytes (44, 46). The NO generated either by follicular somatic cells or by oocyte itself is involved in the maintenance of meiotic arrest at diplotene stage for a long time, while its reduced level triggers resumption of meiosis from diplotene arrest (19). This possibility is strengthened by observations that a decreased level of NO through iNOS-mediated pathway is involved during luteinizing hormone (LH)/hCG-induced meiotic resumption from diplotene arrest in mouse oocytes (70, 71). Similarly, hCG reduced iNOS expression in granulosa cells and thereby NO levels in follicular fluid, which triggers meiotic resumption from diplotene arrest in rat oocytes (31, 72, 73). However, NO donor inhibits LH-induced disruption of gap junctions, cumulus cells expansion, mitogen-activated protein kinase (MAPK) activity, resumption of meiosis from diplotene arrest and increases cGMP production in rat ovary (74).

Follicular oocytes are capable of generating NO sufficient to modulate oocyte physiology (74). This is supported by the observations that eNOS expression increases during acquisition of meiotic competency in porcine follicular oocytes (52, 55, 75, 76). The increased level of eNOS has been reported in rat oocytes (34). Further, an increased iNOS expression has been observed in mouse (56, 76) and

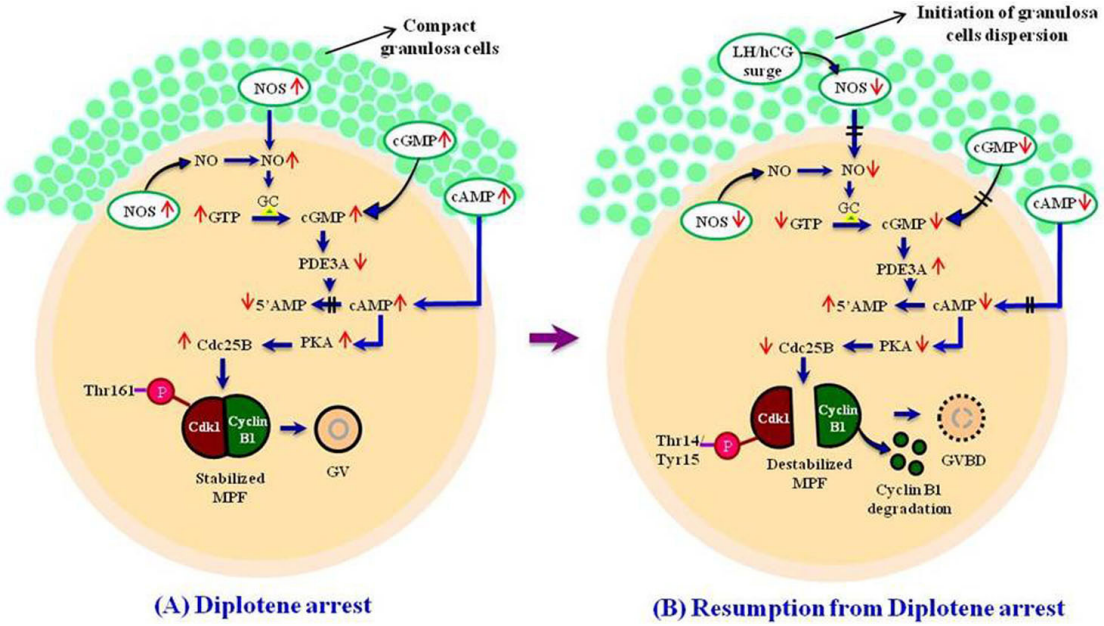

Figure 1. A. Schematic diagram showing a proposed model for the involvement of nitric oxide (NO) signaling during meiotic resumption from diplotene arrest in mammalian oocytes. The synthesis and transfer of NO from encircling granulosa cells to the oocyte and from oocyte itself maintains high level of NO in diplotene arrest. The increased level of NO elevates guanosine 3',5'-cyclic monophosphate (cGMP), adenosine 3',5'-cyclic monophosphate (cAMP), protein kinase A (PKA) and Cdc25B, which maintains stabilized maturation promoting factor (MPF) and thereby diplotene arrest in follicular oocytes. B. Luteinizing Hormone (LH) surge disrupts gap junction, intercellular communication and reduces nitric oxide synthases (NOS) expression in granulosa cells as well as in oocyte. The reduced NOS expression decreases total NO level in oocyte. The decrease in NO level reduces cGMP, cAMP, PKA and Cdc25B levels that trigger MPF destabilization. The destabilized MPF finally induces meiotic resumption from diplotene arrest in mammalian oocytes.

rat diplotene-arrested oocytes (19) during final stages of folliculogenesis. These studies suggest that oocytes are capable of generating NO through NOS-mediated pathway sufficient enough to maintain meiotic arrest at diplotene stage inside the follicular microenvironment from birth to puberty (19, 56, 63).

Role of NO during meiotic resumption from diplotene arrest in follicular oocytes remain controversial. Few studies suggest that an increase of NO level induces meiotic resumption from diplotene arrest in mouse (56, 59), rat (57), porcine (42, 43, 54) and murine oocytes (58). However, other studies suggest that reduced level of NO associates with meiotic resumption from diplotene arrest in mouse (60), rat (19, 63) and cattle oocytes (61, 62, 64) The biphasic role of NO has also been documented. Few studies indicates that lower concentration (0.0.1 mM) of NO donor such as sodium nitroprusside (SNP) induces meiotic resumption, while higher concentrations (0.5. mM) inhibit meiotic resumption from diplotene arrest in bovine oocytes cultured *in vitro* (77). The NO donor has been used to prevent meiotic resumption from diplotene arrest in mouse (78, 79), rat (19, 31), cattle (64), canine (80), bovine (77) and porcine oocytes (54). Studies suggest that iNOS inhibitor such as aminoguanidine (AG) induces meiotic resumption from diplotene arrest in rat (19, 31) and mouse (59) cumulus-enclosed oocytes cultured *in vitro*. Based on these studies, we propose that reduced level of NO through iNOS-mediated pathway could play an important role during meiotic exit from diplotene arrest in mammalian preovulatory oocytes. The dual actions of NO (stimulation or inhibition; depending on its concentration) have been reported during meiotic resumption from diplotene arrest in mouse oocytes cultured *in vitro* (60). A possibility exists that the differential actions of NO in meiotic cell cycle resumption/arrest might be due to geographical, species or follicular stage variations in mammals. However, more studies are required to elucidate the molecular mechanism(s) by which NO regulates meiotic cell cycle in mammalian oocytes.

The decrease of intraoocyte NO level may induce meiotic resumption from diplotene arrest in follicular oocytes. The removal of diplotene-arrested oocytes from preovulatory follicle probably deprive the supply of NO from follicular cells to the oocyte resulting into decrease of intraoocyte NO level that might be associated with spontaneous resumption of meiosis under *in vitro* culture conditions (19, 63, 81). This reduced NO level in follicular fluid during ovarian stimulation provides some beneficial effect to oocyte quality in human (82). These findings suggest that reduced NOS activity in response to LH/hCG surge or removal of oocyte from its follicular microenvironment result in the decrease of intraoocyte NO level that could

be associated with meiotic resumption from diplotene arrest in mammalian oocytes.

The downstream pathway(s) by which reduced NO level triggers meiotic resumption from diplotene arrest remains to be elucidated. Few studies indicate that iNOS-derived NO increases guanylyl cyclase and thereby cGMP level to maintain meiotic arrest at diplotene stage. On the other hand, decrease of NO level and thereby reduced cGMP level may facilitate meiotic resumption (31, 59, 70, 71, 77, 83, 84). The reduced cGMP level activates cAMP-phosphodiesterase 3A (PDE3A) and reduces intraoocyte cAMP level (17, 83, 85). A reduction of intraoocyte cAMP inactivates protein kinase A (PKA) since high cAMP level and PKA activation play a critical role in the maintenance of meiotic arrest (70, 86). The inactive PKA inactivates Cdc25B phosphatase in rat oocytes (83, 87–89). If the Cdc25B is inactive the phosphorylation of Thr14/Tyr15 of cyclin-dependent kinase 1(Cdk1), a catalytic subunit of MPF is increased resulting in MPF destabilization and meiotic resumption from diplotene arrest (86, 90, 91). Thus, reduced intraoocyte NO level possibly through cGMP/PDE/Cdc25B/MPF-mediated pathway may induce meiotic resumption from diplotene arrest in mammalian oocytes (17, 19, 31).

The reduced Cdc25B expression level induces an accumulation of Thr14/Tyr15 phosphorylated Cdk1 level (86, 92). However, Thr161 phosphorylated Cdk1 as well as cyclin B1 levels decrease during meiotic resumption from diplotene arrest. Although MPF destabilization does not solely depends on cyclin B1 degradation (93), phosphorylation at Thr14/Tyr15 and dephosphorylation at Thr161 residues of Cdk1 destabilizes MPF (92–95). On the other hand, dephosphorylation at Thr14/Tyr15 and phosphorylation at Thr161 residues stabilizes MPF (68). The involvement of NO in the regulation of specific phosphorylation/dephosphorylation of Cdk1 such as Thr14/Tyr15 and Thr161 and cyclin B1 degradation shows the NO-mediated regulation of MPF activity in rat oocytes. Studies from our laboratory suggest that high levels of Thr161 phosphorylated Cdk1 as well as cyclin B1 level and low levels of Thr14/Tyr15 phosphorylated Cdk1 and cyclin B1 are associated with the maintenance of diplotene arrest via Cdc25B-mediated pathway (19, 63).

4. NITRIC OXIDE AND MEIOTIC RESUMPTION FROM METAPHASE-II ARREST

Meiotic cell cycle progresses from diplotene stage to M-I in response to pituitary gonadotropin just prior to ovulation (2). M-I arrest occurs for a very short period and oocyte achieves M-II stage at the time of ovulation in most of the mammalian species (2, 3, 25). Freshly ovulated oocytes are physiologically arrested at M-II stage (Figure 2A) of meiotic cell cycle and morphologically characterized by the presence of PB-I in mammals (2, 3, 25). These freshly ovulated oocytes await for fertilizing spermatozoa in the ampulla of fallopian tube for certain period of time. If the fertilization does not occur within the window period, these oocytes undergo postovulatory aging-mediated spontaneous exit from M-II arrest (20–24, 28). The spontaneous exit from M-II arrest is morphologically characterized by the initiation of extrusion of PB-II that never gets completely extruded (23, 24, 28). Due to scattered chromosomes in the cytoplasm, these oocytes are unable to complete meiosis and are further arrested at M-III like stage (Figure 2B) (21). This is a pathological condition observed in various mammalian species including human that affects oocyte quality, fertilization rate and reproductive outcome (22, 65, 96). A growing body of evidences suggests the involvement of various signal molecules such as cAMP, cGMP, H_2O_2, Ca^{2+} and NO in regulation of meiotic cell cycle at M-II stage in rat oocytes (3, 20, 25–29).

The role of NO during regulation of meiotic cell cycle at M-II arrest remains ill understood. Recent studies from our laboratory suggest that NO modulates meiotic cell cycle in ovulated oocytes (26, 97). The biphasic role of NO during meiotic cell cycle regulation at M-II stage has also been reported in mammalian oocytes (60, 65). A NO donor such as *S*-nitroso, *N*-acetyl penicillamine (SNAP) prevents meiotic exit from M-II arrest in mouse and rat aged oocytes (65, 97). A possibility exist that a certain amount of NO is required to maintain egg quality, fertilization ability and embryonic development (65). This is further supported by the observations that low concentration of NO induces meiotic resumption, while high concentration maintained meiotic arrest in bovine, mouse and rat oocytes (60, 77, 97).

NO donor has been used to prevent spontaneous exit from M-II arrest in mouse and rat oocytes (65, 97). Our recent study suggests that SNAP prevented spontaneous exit from M-II in a concentration-dependent manner. The SNAP (1 mM) was sufficient to prevent spontaneous exit from M-II in majority of oocytes (~ 90%) that otherwise resume meiosis under *in vitro* culture conditions without showing any degenerative features (97). NO has been reported to delay oocyte aging, maintain egg quality and developmental potential and prevent chromosomal abnormalities (65). Exposure of freshly ovulated oocytes to NO donor has been reported to prevent reduction in microtubule dynamics, zona pellucida dissolution time; spontaneous cortical granule loss and rate of spindle abnormalities (65, 96).

A possible mechanism(s) by which NO delays oocyte aging and prevent postovulatory aging-mediated spontaneous exit from M-II arrest remain

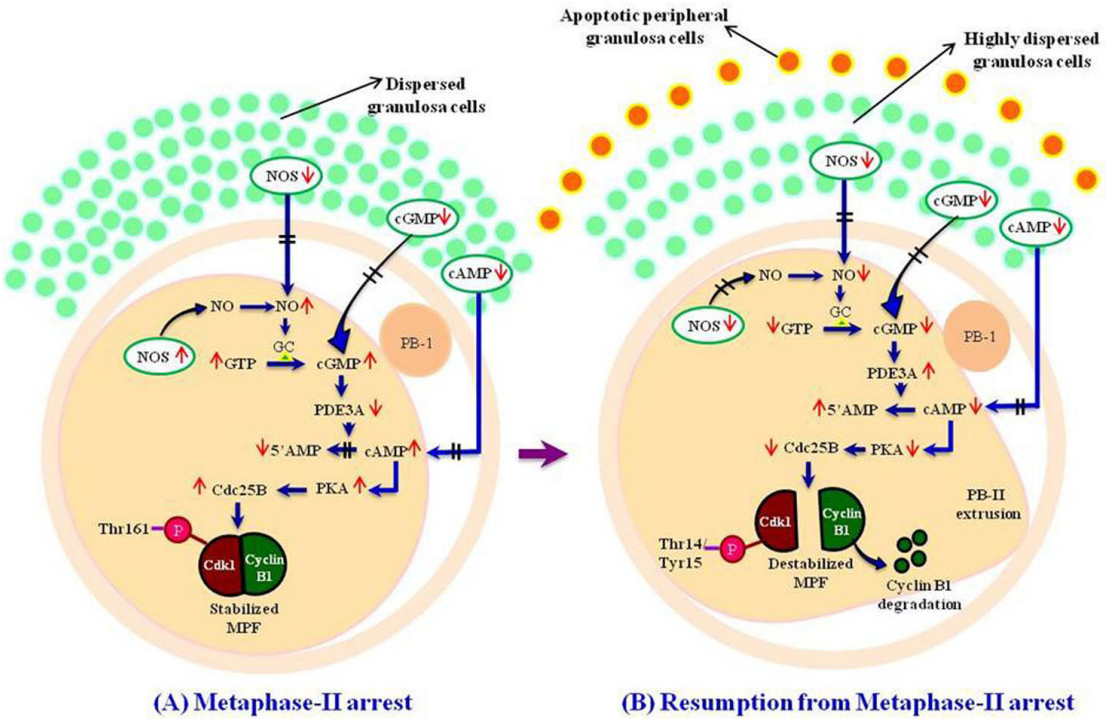

Figure 2. A. Schematic diagram showing a proposed model for the involvement of NO during meiotic resumption from metaphase-II (M-II) arrest in mammalian oocytes. Although disruption of gap junctions interrupts the transfer of NO, cGMP, cAMP in oocytes after ovulation, oocyte is capable of generating NO sufficient to maintain M-II arrest by preventing MPF destabilization through cGMP/cAMP/PKA/Cdc25B-mediated pathway. B. Post ovulatory aging downregulates NOS expression in the oocyte that results reduced NO level in oocyte after ovulation. The decreased NO level destabilizes MPF through cGMP/cAMP/PKA/Cdc25B-mediated pathway. The destabilized MPF finally results in meiotic resumption from M-II arrest in mammalian oocytes.

to be elucidated in mammals. However, few studies suggest that NO prevents cortical granule exocytosis possibly by inhibiting increase in cytosolic free Ca^{2+} (65). Increased cytosolic free Ca^{2+} has been reported to induce postovulatory aging-mediated spontaneous exit from M-II arrest by inducing MPF destabilization in rat and mouse oocytes (20, 22, 28, 92). Reports suggest that NO may act as an antioxidant that could reduce reactive oxygen species (ROS) and peroxyl lipid radicals in oocytes (65, 96). Artificial increase of NO helps in restoring the balance between NO available biologically and excess production of free radicals that contributes to aging (65). Another possible mechanism by which NO could participate in preventing postovulatory aging mediated spontaneous exit from M-II arrest is by activating guanylate cyclase that leads to an increased production of cGMP (65, 96, 98, 99). Study from our laboratory suggests that NO donor prevented postovulatory aging-mediated spontaneous exit from M-II arrest by maintaining stabilized form of MPF (97). NO donor prevented decrease of Thr161 phosphorylated Cdk1 and cyclin B1 levels thereby maintaining M-II arrest in rat oocytes cultured *in vitro* (97). Further, NO donor prevented the increase of Thr14/Tyr15 phosphorylated Cdk1 level and inhibited Cdk1 activity thereby maintaining M-II arrest in rat oocytes cultured *in vitro* (97). These studies suggest that NO modulates specific phosphorylation of Cdk1 and its activity resulting in the accumulation of stabilized MPF that is responsible for the maintenance of M-II arrest in rat oocytes (97). Based on our laboratory investigations and other findings, we propose that the follicular rupture results in disruption of the ovarian support to the ovulated COCs. Disruption of gap junctions, dispersion of granulosa cells and peripheral granulosa cell apoptosis results in the interruption of transfer of various signal molecules such as cAMP, cGMP and NO. Postovulatory egg aging further declines synthesis and secretion of these signal molecules from the oocyte itself (22, 100). Under these conditions, oocytes are unable to retain the sufficient level of these signal molecules required for M-II arrest. Thus, net reduction of NO, cGMP and cAMP destabilizes MPF and mediates spontaneous meiotic resumption from M-II arrest. Hence, supplementation of NO from extracellular sources would be beneficial to prevent postovulatory egg aging mediated spontaneous exit from M-II arrest as well as deterioration of egg quality (65, 97).

5. CONCLUSION

NO acts as a signal molecule and modulate meiotic cell cycle in mammalian oocytes. The high level

of NO maintains meiotic arrest within the follicle and even after ovulation under *in vitro* culture conditions. On the other hand, decrease of intraoocyte NO level associates with reduction of intraoocyte cGMP as well as level Cdc25B levels. The increased Cdc25B level and Thr161 phosphorylated Cdk1 as well as cyclin B1 levels stabilize MPF and maintain diplotene as well as M-II arrest. On the other hand, reduced Cdc25B level intern induced an accumulation of Thr14/Tyr15 phosphorylated Cdk1 level and decreased Thr161 phosphorylated Cdk1 as well as cyclin B1 levels thereby destabilizing MPF. The MPF destabilization triggers spontaneous resumption of meiosis from diplotene as well as M-II arrest in oocytes. Although, role of NO during meiotic cell cycle regulation remain controversial, based on existing literature we propose that reduced level of NO triggers meiotic resumption from diplotene as well as M-II arrest possibly through cGMP pathway in most of the mammalian species.

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Abbreviations: AC, adenylyl cyclases; AG, Aminoguanidine; ART, assisted reproductive outcome; Ca^{2+}, calcium; cAMP, adenosine 3',5'-cyclic monophosphate; Cdk1, cyclin-dependent kinase 1; cGMP, 3',5'-cyclic monophosphate; COCs, cumulus-oocyte complexes; eNOS, endothelial nitric oxide synthase; GC, guanylyl cyclases; GV, germinal vesicle; GVBD, germinal vesicle breakdown; H_2O_2, hydrogen peroxide, hCG, human chorionic gonadotropin; iNOS, inducible nitric oxide synthase; LH, luteinizing hormone; MAPK, mitogen-activated protein kinase; M-I, Metaphase-I; M-II, Metaphase-II; M-III, Metaphase-III; MPF, maturation promoting factor; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthases; PB-I, first polar body; PB-II, second polar body; PDE3A, phosphodiesterase 3A; PKA, protein kinase A; PMSG, pregnant mare's serum gonadotropin; RNS, reactive nitrogen species; ROS, reactive oxygen species; SNAP, *S*-nitroso, *N*-acetyl penicillamine; SNP, sodium nitroprusside.

Key Words: Nitric oxide, Oocyte physiology, Cyclic nucleotides, MPF, Meiotic cell cycle, Review

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