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Rat: An Interesting Model to Study Oocyte Meiosis in Mammals

Shail K Chaube*, Shilpa Prasad, Meenakshi Tiwari and Anumegha Gupta

Cell Physiology Laboratory, Biochemistry Unit, Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Editorial

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***For Correspondence**

Shail K Chaube, Cell Physiology Laboratory, Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi-221 005, Uttar Pradesh, India, Tel: +9154226702516, Fax: +915422368174.

E-mail: shailchaube@bhu.ac.in

In most of the mammalian species, oocyte meiosis takes very long time and passes through several stop/go channels to generate female gamete [1-3]. Within the ovarian follicles, oocytes are normally arrested at diplotene stage of first meiotic prophase for a long time. Meiotic resumption from diplotene stage in follicular oocytes takes place after pituitary gonadotropins surge. Oocytes then progress through metaphase-I (M-I stage) to metaphase-II (M-II stage) just prior to ovulation in several mammalian species. Meiotic resumption from diplotene arrest to M-II arrest is a very important period because follicular oocyte achieves meiotic competency during this period. The M-II arrest is a physiological arrest in preovulatory oocytes and exit from M-II arrest normally occurs due to sperm triggering at the time of fertilization in most of the mammalian species including human. Studies carried out in last two decades suggest that the rat is an interesting and peculiar animal model among mammals to analyse meiotic cell cycle regulation in oocytes within the ovarian follicle and even after ovulation [3,4].

Meiotic cell cycle in rat oocyte starts during foetal life and gets arrested for the first time at diplotene stage of prophase-I, which can be identified by the presence of germinal vesicle (GV) within the follicular oocytes [1,4,5]. The diplotene arrest is a longest phase in rat oocyte and may last for few months to several years in follicular microenvironment [6-9]. At the time of puberty, pituitary gonadotropins surge triggers resumption of meiosis from diplotene arrest, which is morphologically characterized by germinal vesicle breakdown (GVBD) [1]. These oocytes are further arrested at M-I stage for a short time (few hours) [1]. The organization of spindle during M-I stage in oocytes leads to the formation of metaphase plate that initiate extrusion of first polar body (PB-I) [3,10,11]. The complete release of PB-I leads to conversion of diploid oocyte into haploid egg just prior to ovulation. The freshly ovulated eggs are arrested at M-II stage of meiotic cell cycle possessing PB-I [3,10-16]. These M-II arrested eggs are the right choice for successful fertilization *in vivo* as well as *in vitro* in several mammalian species including human [17].

Rat is an interesting animal model to study meiotic cell cycle in oocytes because of two peculiarities [3]. The first peculiar reason is that the diplotene-arrested oocytes undergo spontaneous resumption of meiosis if isolated from ovarian follicles and are cultured under *in vitro* conditions for extended period [1,3,4] but they are unable to extrude PB-I and remain arrested at M-I stage of meiotic cell cycle under *in vitro* culture conditions [1,3,6,18]. The second peculiar reason involves the unique feature of spontaneous exit from M-II arrest in ovulated eggs [3,10,11,13-16,19-24]. Recent studies suggest that the ovulated M-II arrested rat eggs do not wait for fertilization and initiation of extrusion of second polar body (PB-II) has been observed *in vivo* as well as under *in vitro* culture conditions. This is an atypical conditions and even freshly ovulated eggs undergo spontaneous exit from M-II arrest, so called abortive spontaneous egg activation (SEA) [3,13-15,21,22,25]. Although initiation of extrusion of PB-II occurs but it never gets completely extruded [3,13-15,22,25]. Meiotic status of these eggs suggest that the chromosomes are scattered throughout the cytoplasm, unable to form metaphase plate and further arrested at metaphase-III (M-III) like stage without forming pronuclei [13,14,22]. These eggs are of deteriorated quality and cannot be used for fertilization *in vivo* or during several assisted reproductive technologies (ARTs) programs *in vitro* [17]. Due to depletion of adenosine triphosphate (ATP), these eggs undergo apoptosis resulting in compromised reproductive outcome under *in vivo* as well as *in vitro.* Due to abortive SEA, it is very challenging to clone a rat following somatic cell nuclear transfer protocol [2,10].

Studies from our laboratory using rat as an experimental model explored the possible reasons behind spontaneous exit from diplotene as well as M-II arrests. Reports suggest that when diplotene arrested oocytes are removed from ovary and cultured under *in vitro* conditions, they encounter decrease in the level of cyclic 3', 5' –adenosine monophosphate (cAMP) and generation of reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) that results in oxidative stress (OS) in oocytes [26-30]. The OS modulates mitochondrial membrane potential (MMP), increases cytosolic free calcium (Ca^{2+}) level, triggers maturation promoting factor (MPF) destabilization, which results in spontaneous resumption of meiosis from diplotene arrest [3,30-33]. These oocytes although resume meiosis from diplotene stage but never extrude PB-I under *in vitro* culture conditions. They remain arrested at M-I stage and due to depletion of energy resources leads to the generation of OS that induces oocyte apoptosis [10].

The M-I arrest has not been reported in rat under *in vivo* conditions and oocytes are converted into egg by releasing PB-II. However, studies suggest that freshly ovulated eggs immediately experiences postovulatory aging under both *in vivo* as well as *in vitro* conditions that causes spontaneous resumption of meiosis [13,14,22]. Postovulatory aging *in vivo* as well as *in vitro* conditions cause molecular changes such as generation of ROS leading to OS in aged eggs. The OS modulate MMP thereby increasing Ca^{2+} level [32,34,35]. These changes trigger destabilization of MPF resulting in spontaneous exit from M-II arrest and further deteriorates egg quality by inducing apoptosis [2-4,13-16,32].

Hence, rat can be treated as interesting model due to M-I arrest under *in vitro* culture conditions and abortive SEA *in vivo* as well as *in vitro*. These peculiar features results in poor quality oocytes/eggs that are not suitable for *in vivo* fertilization as well as for various ARTs programs. These peculiarities make rat oocytes/eggs as interesting cell model to study meiotic cell cycle progression from diplotene arrest to M-II arrest, a period that decides the achievement of meiotic competency required for successful fertilization, early embryonic development and expected reproductive outcome. Further studies are required to explore the underlying causes that could be responsible for these peculiarities in oocyte meiosis in rat.

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