Chapter 2
The Control of Oocyte Survival by Intrinsic and Extrinsic Factors

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Capsule Mechanisms that control the survival of oocytes and, by extension, the duration of ovarian function have been identified. However, it is still not clear whether oocyte "quality" is related to survival, nor is the role of the granulosa cells of follicles in follicle survival entirely understood. Here, we consider oocyte-intrinsic and oocyte-extrinsic mechanisms of oocyte loss and argue that developing a better understanding of such physiological events is needed to protect fertility, fecundity, and ovarian function in women.

Abstract The duration that ovaries function is, as is intuitive, controlled by the number of remaining oocytes within follicles. Once the number of follicles drops beneath a threshold number, ovarian function ceases. Thus, understanding mechanisms that control oocyte survival is paramount as we consider strategies to protect or prolong ovarian function in women. It is often assumed that physiological oocyte survival is entirely controlled by "oocyte- intrinsic" factors, such as poor genetic quality or accumulated damage to the oocyte itself. Oocytes that have poor genetic quality due to development or accumulated damage would then die sooner than

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those of higher "quality." Indeed, new data suggest that oocyte-intrinsic genetic quality as determined by the ability to repair double-stranded DNA breaks is a significant contributor to oocyte survival and the duration of ovarian function. However, the nature of the follicle, where the oocyte and surrounding granulosa cells exist in intimate contact and rely upon each other for survival signals and metabolic function, makes it unlikely that oocyte-intrinsic factors entirely control oocyte survival. We and others are assessing the role of adjacent somatic (granulosa) cells in follicle survival, determining the relative importance of "oocyte-extrinsic" factors.

Keywords Oocyte • Ovary • Function • Follicle • Granulosa

2.1 Introduction

2.1.1 CSO: Crime Scene Ovary

The follicles of the mammalian ovary consist of an oocyte and granulosa cell layers, bounded by a basement membrane and theca cells. Although there are many thousands of follicles present during the reproductive years, only one follicle per menstrual cycle will survive to ovulate and be made available for conception. The fate of the vast majority of follicles is instead death (referred to as atresia), and it is the rate of follicle death that determines the duration of ovarian function—the timing of the onset of menopause. Along with the numerical decline of follicles, the ability of human eggs to give rise to offspring declines precipitously around age 35 (Conway 1997; Hunt and Hassold 2008). This decline has been shown to correlate with age-related changes in oocyte meiotic spindle morphology and chromosome alignment (Hunt and Hassold 2008). This means that many oocytes survive for long periods of time that do not have the "quality" to give rise to offspring (below).

While a great deal has been revealed about the nature of follicle death, a precise understanding of the causes and timing of events that activate atresia is lacking. If we could perform an "autopsy" on individual follicles, we could pinpoint the ultimate cause of death. Did the subject die of "natural" causes, the aforementioned physiological atresia that is the fate of the majority of follicles? Certain factors need to be ruled out at the time of autopsy. We would like to use "forensic" techniques to reveal whether the oocyte died first, the granulosa cells, or, perhaps both died at the same time. In a population of follicles, why did one follicle die while its neighbor lived? Could it have been… foul play?

2.1.2 Foul Play: Poisoning and Murder

For ovarian follicles, external sources of foul play are well known. Poisons can be to blame, perhaps heavy metal (Banu et al. 2011) or toxic chemical (Hoyer et al. 2001) exposure. Radiotherapy (Oktay and Sonmezer 2008) and certain chemotherapeutic

agents (Beard et al. 1984; Jurisicova et al. 2006; Mazaud et al. 2002; Oktem and Oktay 2007; Sklar 2005) are remarkable in terms of how potently they damage the different cells of the follicle (Bar-Joseph et al. 2010; Roti Roti et al. 2012) and induce atresia. Or was it perhaps the insidious effects of long-term cigarette smoking? (Matikainen et al. 2001). Determining that the cause of follicle death was due to such exposures has led to major advances in protecting ovarian function from damage due to extra-physiological factors like these. The use of some of these stimuli in experimental models has also generated information about the massive loss of follicles that occurs physiologically over time.

Without evidence of foul play, a challenging question emerges in the autopsy: was there perhaps a hidden defect? Was there a previously hidden defect, akin to a heart anomaly in a human, that resulted in the subject's early demise? Are some oocytes less "fit" than others and thus sentenced to die early without warning? Here, we consider whether the cause of death was absolutely oocyte-intrinsic (Thomson et al. 2010). Was the oocyte itself less fit (or damaged such that it was less fit), and this was the ultimate cause of its demise? If we knew that the oocyte died first while the granulosa cell layers were intact (in the absence of an external toxic influence), we would favor this explanation. Alternatively, was there an oocyte-extrinsic cause of follicle death? Was the development of the granulosa cell layers abnormal, or, did granulosa cells begin to die first, and the oocyte died as indirect consequence of the loss of its supporting granulosa cells? In both cases, there could be genetic underpinnings of the compromise. Below, we will consider some evidence that certain alleles of genes involved in DNA repair can accelerate follicle death due to fostering oocyte or granulosa cell dysfunction.

Last, in insects, we have identified a particularly striking ovarian crime. We have shown that a unique oocyte-extrinsic mechanism exists where the surrounding somatic cells can be stimulated to destroy a perfectly intact oocyte (Thomson and Johnson 2010; Thomson et al. 2012). Data in Fig. 2.1 show that inhibition of the TOR pathway by feeding Drosophila fruit flies the specific inhibitor Rapamycin (RAP) results in a loss of oocyte (and, when mated, embryo) production. In those studies, we showed that this was a result of the somatic cells around the oocyte collapsing and phagocytosing the germ cell(s) before there were any signs of oocyte damage (Thomson and Johnson 2010). If embryos laid by these mothers are moved to food lacking RAP, the embryos essentially all hatch and develop to adulthood. This outcome supports an oocyte-extrinsic mode of oocyte death, the "killing" of the oocyte by a former partner and ally (Sect. 2 2, below). Using the same model, flies were instead treated with the chemotherapeutic agent Cyclophosphamide (CP) (Becker and Schoneich 1982; Hansmann 1974). Here, embryo production was unaffected. However, when embryos laid by flies treated with CP were moved to fresh food lacking drug, significantly fewer numbers of embryos survive even to hatch as larvae. We interpreted this as being the result of damage to the oocyte inside the mother(s), evidence of oocyte-intrinsic damage that did not result in follicle involution and clearance.

Could an equivalent process be activated in mammalian ovarian follicles? Can granulosa cells be activated such that they destroy intact oocytes? We have shown that the same stimulus, RAP treatment, results in the destruction of mouse oocyte within follicles cultured in vitro (Thomson and Johnson 2010). Whether these

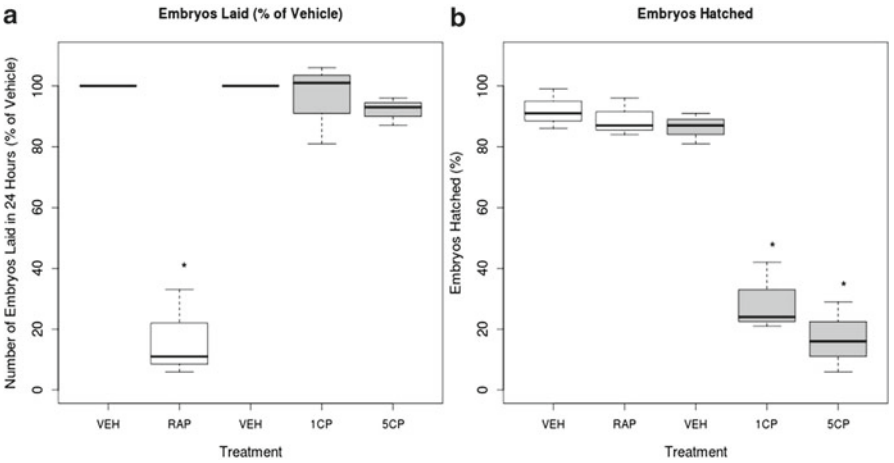


Fig. 2.1 Somatic versus germ line control of oocyte survival. Drosophila fruit flies were housed on food containing 10 mM RAP, 1 or 5 mM Cyclophosphamide (CP), or the respective vehicles for the two drugs. Embryos were moved to fresh food lacking any treatment hourly. As seen previously (Thomson and Johnson 2010), RAP treatment resulted in significantly reduced embryo laying (**a**). However, the embryos laid by RAP-treated mothers hatched and survived to adulthood at normal rates (**b**, *white boxes*). In contrast, CP treatment did not significantly affect embryo laying (and therefore, oocyte development). However, CP treatment did result in a dose-dependent decrease in embryo hatching, suggestive of oocyte damage

oocytes were similarly undamaged by the drug—as seen in the fly—before being destroyed by their surrounding granulosa cells remains unclear.

In this chapter, we consider the data about follicle death so that we might one day identify better strategies to protect the ovarian reserve of follicles. We first provide a more detailed discussion of follicle development, and consider how tightly intertwined oocytes' fate is with their attached granulosa cells. This is followed by a reconsideration of the concept of "oocyte quality," and finally, the forensic examination of factors that result in ovarian follicle atresia.

2.2 The Victims: Oocytes and Granulosa Cells Have a Dependent Relationship

During postnatal life, most oocytes exist in dormant primordial follicles within a single layer of a few "flat" squamous, non-proliferating granulosa cells. Upon growth activation, the granulosa cells switch to a cuboidal morphology and begin to proliferate while the oocyte initiates a growth phase. Follicle development consists of continued proliferation and differentiation of the granulosa layers, acquisition of an additional cell layer outside the basement membrane termed the theca, and continued oocyte growth. Eventually, a fluid-filled cavity forms within the granulosa layers termed the antrum, giving the follicle an asymmetrical character.

By this time, the granulosa cells in closest association with the oocyte are physically separate from those that make up the follicle wall; the granulosa cells in these locations are a separate functional lineage, the steroidogenic mural population (in the wall) and the cumulus population (surrounding the oocyte) (Chaffin et al. 2012; Johnson et al. 2001). Should the follicle survive to finish the journey of growth and maturation, the egg within its cumulus layers is expelled from the surface of the ovary during ovulation.

During the early stages of follicle growth, specialized gap junctions form between the oocyte and granulosa cells (Albertini and Rider 1994; Moor et al. 1981; Simon et al. 2006). These gap junctions are referred to as transzonal processes due to their crossing the zona pellucida. Proteins (Cieniewicz and Woodruff 2010; Curran and Woodruff 2007) and other critical macromolecules like cyclic AMP (Kalma et al. 2004; Sela-Abramovich et al. 2006) can transit these processes. Metabolic processes can be shared, or can be compartmentalized into the oocyte, or, granulosa cells (Eppig et al. 2005; Sugiura et al. 2005) meaning that they truly cannot develop without one another. Specifically, oocytes regulate glucose metabolism and the TCA cycle in granulosa cells by regulating the expression of glycolytic enzymes. A further example of this is the regulation of oocyte pH by granulosa cells (FitzHarris et al. 2007); immature oocytes lack pH-regulatory HCO(3)(−)/Cl(−) exchange factors and thus rely on the granulosa cells to maintain their physiological pH for normal function and development, and possibly survival.

We highlight the tight developmental interdependence of the oocyte and its attached granulosa cells to emphasize the difficulty of identifying the cause of death at the time of "autopsy." When considering the fate of the follicles in the ovary and the rate at which they die, it's important to know who to try to protect. Establishing that so much critical metabolic function (e.g., glycolysis and the TCA cycle) has been assigned to the granulosa cells, though, also means that granulosa cells, and not the oocyte, are the major source of metabolites that can cause oxidative stress during early follicle development. Does this also mean that reducing the amount of reactive oxygen species produced by granulosa cells will prevent damage from occurring in the oocyte? The accumulation of damage, including DNA breaks, due to oxidative stress over time has long been hypothesized to be a cause of ovarian aging and oocyte loss. A very recent paper provides both model-based basic information and clinical data from patients suggesting that it is the ability to repair DNA damage that declines with age.

2.3 Autopsy Results: Evaluation of Compromised DNA Repair Reveals an Oocyte-Intrinsic Mechanism

Accumulating damage with age is an attractive model for accelerating oocyte loss. Primordial follicles are thought to be present for the postnatal lifetime of most female mammals, and if this is true, the enclosed oocytes must experience a lifetime of potential oxidative "hits." DNA double-stranded breaks (DSBs) are one consequence of oxidative stress, arising due to interactions between the DNA and reactive oxygen species that result from normal metabolism. Titus et al. (2013), (see Johnson

and Keefe 2013, for a commentary) evaluated the role of genes known to be involved in the repair of DSBs, hypothesizing that reduced BRCA gene function would correspond to accelerated oocyte loss. The BRCA1 and 2 proteins function in the well-characterized general ATM (ataxia telangiectasia mutated) DNA repair complex (Gage et al. 2012; Kitagawa and Kastan 2005). DNA DSBs attract a complex of BRCA1, Rad50, Mre11, and ATM proteins, which in turn attract BRCA2 and Rad51 in order to elicit repair. If the lesion cannot be repaired, or, if the number of lesions overwhelms the available repair machinery, apoptotic cell death can be activated in a p53-dependent fashion.

Titus et al.'s data can be briefly summarized as follows. First, aged oocytes and follicles were found to have more histone H2A.X-positive lesions (marking DSBs) than their respective controls. The expression of Brca1 and Brca2 were each found to decrease with age. Heterozygous Brca1 mutant mice were found to have significantly reduced numbers of follicles at all stages of development, and increased H2A.X-positive lesions. This was paralleled by the finding that the indirect measure of the number of immature follicles, Anti-Müllerian hormone (AMH) levels, was significantly reduced in women harboring BRCA1 mutations, while women with BRCA2 mutations had a slight, but nonsignificant reduction in AMH levels. The data were bolstered by a direct look at the consequences of dysregulating DNA repair, by the delivery of siRNA targeted to individual molecules of the ATM repair complex into mouse oocytes. Knockdown of any of Brca1, Mre11, Rad51, or Atm resulted in significantly increased numbers of DSBs, an induction of the apoptosis marker active caspase 3, and decreased oocyte survival. In sum, these data reveal the potent role(s) for ATM-mediated DNA repair in oocyte survival, and also how that role changes during aging.

We can make several inferences from these data. We can infer that death susceptibility due to DNA DSBs begins with follicle growth activation (e.g., when primordial follicles begin to grow). This is because meiotic entry itself consists of the programmed generation of DNA DSBs. Progression past prophase did not appear to be affected by the level of DNA damage (Marangos and Carroll 2012). Further, it seems that this effect may be specific to DNA double-stranded breaks as at least one other type of lesion does not prevent progress through meiosis (Yuen et al. 2012). Last, we can infer that an oocyte's "quality" may also be highly dependent upon the capabilities of its DNA repair pathway, as summarized in the following model.

The cartoon in Fig. 2.2 uses stoplight colors to denote thresholds for oocyte survival and offspring-competence. After attempting to repair damage, oocytes that both survive and achieve the ability to give rise to offspring reach the green threshold on the graph. A separate pool of oocytes survives, but does not reach the threshold for being able to give rise to an offspring (yellow). Last, oocytes that inefficiently repair DSBs or other types of damage do not reach the survival threshold and follicle atresia is activated. In the case of BRCA mutations, the lack of efficient DNA repair reduces the number of oocytes that can efficiently achieve the threshold of repair required for survival, and perhaps the threshold for offspring production. Extremely exciting questions for the field to address are (1) is this truly an

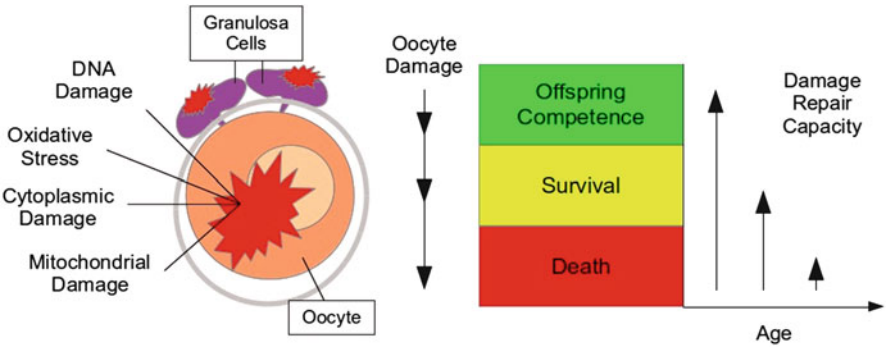


Fig. 2.2 Oocyte-intrinsic versus -extrinsic mechanisms of oocyte loss and thresholds of oocyte repair. The cartoon shows the two cell types considered as targets responsible for oocyte loss. Either the oocyte or a threshold number of granulosa cells is damaged (*red bursts*, *down arrows*), activating damage repair mechanisms. A model is supported, most strongly in the case of double-stranded DNA breaks (Titus et al. 2013), where the capacity to repair damage decreases with age (*graph at right*). Interestingly, oocytes can be repaired to the point that they survive (*yellow*), but cannot support the development of healthy offspring (*green*). The acceleration of oocyte loss with age then occurs when the ability to repair damage cannot reach the survival threshold. It remains unclear whether damage to granulosa cells (*purple*) in the absence of damage to the oocyte can result in follicle death by itself

oocyte-intrinsic outcome, where oocyte loss can occur in the absence of granulosa cell damage? (2) How are these theoretical threshold levels of DNA damage set? Are there specific numbers of DNA DSBs that can be tolerated? Last, (3) do the thresholds for survival and offspring competence depend on a woman's genetic background? Since these factors appear to change with age, do the age-related changes arise solely from declining DNA repair complex expression and activity? The deceptively simple concept of oocyte "quality" is at the heart of these critical forensic questions.

In our view, the jargon terms oocyte "quality" or "health" refer to "…the intrinsic genetic, epigenetic and cytoplasmic characteristics required for the completion of development and capability of producing a normal offspring." (Thomson et al. 2010). If a mechanism is present that ensures the selection and survival to ovulation of high-quality oocytes at the expense of those that cannot give rise to offspring, how might it work? If a quality control mechanism is present that selects for the eggs of highest quality, it must be that in young mammals, the threshold for survival is very stringent, with only few eggs incapable of producing offspring escaping the mechanism. The threshold must become less stringent with age, because the fraction of incompetent eggs that survive to ovulation increases. The identification of the role of DNA repair in the duration of ovarian function provides a basis for investigating these forensic questions and clarifying these concepts more precisely.

2.4 Recreating the Crime Scene: Models Used Dissect the Control of Oocyte Survival

Both in vitro and in vivo models have been used to address the questions of oocyte quality and the factors involved in oocyte death. Most of the time, these models are evaluated in terms of their ability to support follicle survival. In our case, however, we are interested in why, how, and at what rate follicles die.

In 1994, Spears et al. reported the generation of live pups after the two-dimensional culture of primary (small preantral) follicles to maturity, in vitro fertilization, and transfer of embryos to pseudopregnant females (Spears et al. 1994). Starting with these follicles, the group found that without EGF supplementation, 47 % of follicles survived ($n=240$) for 5 days in culture, and none of those produced eggs capable of early embryogenesis after fertilization. With EGF supplementation, nearly 70 % of follicles survived ($n=60$), but only 9 % of fertilized eggs from this group developed into 2-cell embryos. Additional serum supplementation increased the percentage of oocytes that could develop into 2-cell embryos to 41 % ($n=60$), and all of those developed into blastocysts. It is interesting that in the best case of follicles cultured identically, about 30 % of follicles died in culture, and under the best circumstances, approximately 60 % could not develop into even 2-cell embryos. These attrition rates are informative when considering the situation in vivo where only fractions of eggs would be selected to survive to ovulation.

In an attempt to generate mature eggs from primordial follicles, Eppig and O'Brien (1996) started by culturing the ovaries of newborn mice that would have contained many thousands of primordial follicles. After 8 days of culture, oocytes were isolated and cultured further. 192 two-cell embryos were generated after fertilizing the hundreds of mature eggs produced. Of those 192 embryos, only a single live pup was generated after transfer into mothers. A short time later, an improved culture method was provided by the same group (O'Brien et al. 2003). Here, again beginning with many thousands of primordial follicles, thousands of oocytes were produced in vitro that gave rise to 1,160 two-cell embryos; from those, 59 pups were produced after transfer. Pup survival was slightly lower than a control group using mature eggs that developed in vivo, but the survivors themselves were reported to be normal. More recent work has shown that offspring-competent oocytes can be generated from follicles that were cryopreserved and thawed (dela Pena et al. 2002; Kagawa et al. 2007; Liu et al. 2002).

The reason that these models are relevant to the questions of oocyte survival and competence to produce offspring, is that there is a high level of attrition at every step, in what appear to be equivalent follicles. What is killing off these thousands of follicles? Is it possible, that as seen through the course of reproductive life, that some follicles are doomed to atresia, and this cannot be corrected with ideal culture systems under any circumstances? This is highly reminiscent of the clinical situation, where a fraction of oocytes retrieved after gonadotropic stimulation seems always incapable of supporting blastocyst development and the generation of healthy babies (Patrizio et al. 2007). Accordingly, in vitro culture results in a high level of follicle attrition by atresia.

In our hands using a two-step culture method developed in the laboratory of Dr. Evelyn Telfer (McLaughlin and Telfer 2010; Smitz et al. 2010; Telfer et al. 2008), the attrition of human follicles occurred similarly (McLaughlin et al. 2011). Not only did about one-third of follicles die and disappear from strips of human ovarian cortex in the 6 days of culture, the addition of RAP again resulted in increased follicle attrition, such that about two-thirds of follicles went missing. What is the difference between those follicles that died and those that survived? We hypothesize, consistent with Titus et al.'s data, that individual follicles have differential abilities to repair damage induced during handling and culture. Some were able to repair this damage above the survival threshold, and some were not. The remaining question is whether anything can be done about this attrition, within the functioning ovary, or in in vitro models perhaps most relevant to fertility preservation strategies (see Johnson and Patrizio 2011, for a review).

2.5 Using Postmortem Examinations to Reduce Deaths in the Future

It is important to remember that the threshold of follicle survival does not always—and does not always need to—meet the threshold of offspring production. Supporting ovarian function, and potentially extending it so that menopause is delayed, can be considered as a powerful way to increase health and wellness parameters in aging women. In terms of developing techniques to offset DNA damage, one must contrast the situation with that seen in cancer patients. In cancer, many chemotherapeutic agents rely on their genotoxicity (e.g., induction of DNA double-stranded breaks) for their deleterious action upon rapidly dividing cancer cells. There, we seek in increase DNA double-stranded breaks and decrease the cells' ability to repair them. In the case of oocytes and follicles, however, we must decrease those breaks and foster DNA repair, a challenge that is beginning to be addressed.

So how might we reduce the rate of oocyte loss during the aging process? As seen with more general parameters like total lifespan, and global metabolic function, ovarian function has been extended in mouse trials of caloric restriction (Selesniemi et al. 2011), and treatment with different dietary agents. For example, resveratrol (Bentov et al. 2010; Kong et al. 2011; Liu et al. 2013) and dietary omega-3 fatty acids supplementation (Nehra et al. 2012) each increase the duration of ovarian function and extend the window of fertility in mice beyond the limits of controls. The common theme seems to be the ability to offset oxidative damage that would otherwise accumulate. This would seem to be the same target as that of therapies that target mitochondria (Barritt et al. 2001). Overall, dietary and/or pharmacological interventions are in development that could have similar effects upon the thresholds for oocyte survival and offspring competence (Fig. 2.2) in women. The more crime scenes we analyze, and the more basic and clinical forensic data that we generate, the more we will be able to protect follicles and potentially help them "cheat death."

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