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The Interconnections Between Somatic and Ovarian Aging in Murine Models

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Abstract

The mammalian female is born with a limited ovarian reserve of primordial follicles. These primordial follicles are slowly activated throughout the reproductive lifecycle, thereby determining lifecycle length. Once primordial follicles are exhausted, women undergo menopause, which is associated with several metabolic perturbations and a higher mortality risk. Long before exhaustion of the reserve, females experience severe declines in fertility and health. As such, significant efforts have been made to unravel the mechanisms that promote ovarian aging and insufficiency. In this review, we explain how long-living murine models can provide insights in the regulation of ovarian aging. There is now overwhelming evidence that most life-span–extending strategies, and long-living mutant models simultaneously delay ovarian aging. Therefore, it appears that the same mechanisms that regulate somatic aging may also be modulating ovarian aging and germ cell exhaustion. We explore several potential contributing mechanisms including insulin resistance, inflammation, and DNA damage—all of which are hallmarks of cellular aging throughout the body including the ovary. These findings are in alignment with the *disposable soma theory of aging*, which dictates a trade-off between growth, reproduction, and DNA repair. Therefore, delaying ovarian aging will not only increase the fertility window of middle age females, but may also actively prevent menopausal-related decline in systemic health parameters, compressing the period of morbidity in mid-to-late life in females.

Keywords: Calorie restriction, Fertility, Follicle, IGF, Menopause

Aging is the progressive decline of cellular and molecular functions throughout the body thereby impeding the maintenance of homeostasis. These declines promote the onset of several chronic diseases in parallel leading to multimorbidity and frailty (1). In the female, aging is also associated with the decline of ovarian function, which will be the main focus of the current review. This decline in ovarian function is linked to reduced fertility and increased incidence of chronic diseases in older women. The field of Geroscience aims to understand the molecular pathways that promote aging so that therapeutic approaches that target these pathways can be developed. Several interventional strategies have successfully extended life span in rodents. Among these, calorie restriction (CR) is the most commonly studied. Several studies have demonstrated that subjecting mice to 20%–40% CR slows the aging process, resulting in increased life span and healthspan compared as to littermate controls (2). Treatment with rapamycin

(3), metformin (4), and nicotinamide adenine dinucleotide (NAD^+) (5) has also been found to increase life span. Additionally, a reduction in growth hormone (GH) production and/or signaling have also been shown to significantly attenuate biological aging and extend life span (6,7).

Interestingly, several trials have revealed that the rate of aging and responsiveness to a myriad of interventional strategies differs between sexes, although the mechanisms responsible remain unclear (8). Therefore, there is a clear need to unravel the mechanisms that promote these sexually divergent outcomes so that its implication on gonadal aging can be elucidated. In the female, aging is associated with the decrease of the ovarian follicular reserve. Females are born with a lifelong supply of oocytes, therefore, the term "ovarian reserve" reflects the number of oocytes enclosed in the ovarian tissue and, therefore, the functional reproductive potential of the ovary (9). The ovarian reserve is represented mainly by the primordial follicles, an oocyte surrounded by a single layer of granulosa cells, which are in a quiescent state (10). Once activated, the primordial follicles start developing in an irreversible process and may undergo ovulation or become atretic. The exhaustion of the ovarian reserve will result in diminished ovarian activity, characterized by reduction of estradiol output and cessation of ovarian cycles, also known as menopause in humans (9). Menopause is associated with metabolic declines that increase susceptibility to chronic diseases (11). Furthermore, increased age at menopause is linked to reduced mortality and increased life span in women (12), thereby confirming the importance of the ovary in regulating aging. Therefore, this review will focus on pathways that are affected by life-span–extending therapies and what role they play in the ovarian life span.

Ovarian Reserve Exhaustion and Activation of Primordial Follicles

The number of primordial follicles gradually decreases as females age. In C57BL/6 mice, the ovarian reserve is reduced to half at 10 months of age and at 18 months of age the reserve is reduced approximately 10 times (13). Additionally, female C57BL/6 mice will stop producing pups at around 18 months of age, while significant fertility reduction is already observed at 10 months of age (14). These data indicate that, although a clear menopausal transition is not observed in mice, there is a severe reduction in the ovarian reserve followed by reduced fertility and reduced fidelity of reproductive cycles, similar to what is observed in humans (9). Therefore, mice serve as a relevant model for testing therapies that may prolong the reproductive life span and impact overall longevity and healthy aging.

Activation of the primordial follicles from the ovarian reserve represents a tightly regulated process. Activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway and the phosphorylation of forkhead box protein O 3a (FoxO3a) are essential steps in the activation of the primordial follicles in ovaries (15). Hyperphosphorylation of FOXO3a in oocytes results in its nuclear exclusion, culminating in the global activation of primordial follicles and premature ovarian failure (15). Therefore, the presence of FOXO3a in its non-phosphorylated form is crucial to maintaining the primordial follicles in their quiescent state. Interestingly, this process depends on the regulation of pathways in granulosa cells and oocytes. Activation of dormant oocytes through the PI3K/Akt/FOXO3a signaling in oocytes depends on granulosa KIT ligand production (16). One of the regulators of granulosa cell KIT ligand (KITL) production is the mechanistic target of rapamycin complex 1 (mTORC1) (16). Therefore, granulosa cells mTORC1 activation promotes KITL production, which in the oocyte activates KIT and PI3K/Akt signaling and FOXO3a phosphorylation, activating the primordial follicle irreversibly (16). Knockout of tuberous sclerosis 1 (TSC1), an inhibitor of mTORC1 signaling, in primordial follicles granulosa cells resulted in global follicular activation and premature ovarian failure (16). Similarly, FOXO3a knockout results in primordial follicle hyperactivation and premature exhaustion of the ovarian reserve (15). Therefore, it becomes clear that mTOR and FOXO3a pathways act in concert as main regulators of primordial follicle activation and ovarian aging.

The Aging/Reproduction Trade-off

The Reproductive Cell Cycle Theory of Aging states that the hormones that regulate reproduction act in an antagonistic pleiotropic manner to control aging via cell cycle signaling (17). Therefore, this theory proposes that promoting growth and development early in life to achieve reproduction results in increased senescence and age-related diseases later in life. Reproduction is critical for the survival of the species, therefore reproductive cell cycle signaling factors will also regulate growth, development, fertility, and senescence, ultimately regulating the rate of aging and life span. Many pathways can be implicated in this trade-off. However, existing evidence indicates that FOXO3a and mTOR are central to this trade-off. The role of FOXO3a and mTOR in the regulation of the ovarian reserve is critical as explained in the previous section. In the same way, these pathways are critical regulators of overall body growth and aging (18).

The FOXO3a protein is regulated by the insulin/PI3K/Akt signaling pathway (19). FOXO members are linked to multiple physiological and pathological processes by inducing transcription of target genes involved in apoptosis, proliferation, cell cycle progression, survival, and DNA damage (18). FOXO3a signaling is associated with longevity in several species (18). Similarly, the mTOR pathways is a central regulator of complex biological functions, including cell growth, proliferation, and survival in response to nutrients and hormones (20). Downstream effectors of mTOR include mTORC1 and mTORC2 (21). mTORC1 disruption increased longevity in mice (22), as well as pharmacological inhibition of mTORC1 by rapamycin decreases body weight gain and increases longevity in mice (23). Therefore, both mTOR and FOXO3a are regulated by nutrient-sensing pathways and can result in reduced cell growth and increased longevity. At the same time, overactivation of these pathways will result in premature exhaustion of the ovarian reserve and inability to reproduce in adulthood (15,16).

To exemplify this trade-off, lower GH/IGF levels correlate with increased life span and delayed sexual maturation in different strains of mice, which indicates the existence of a trade-off between growth rate, sexual maturation, and longevity (24). GH-deficient Ames dwarf mice (df/df) live longer than normal littermates, are smaller, have delayed puberty, and have a prolonged reproductive life span (25,26). This model clearly displays the trade-off between longevity and reproduction. It is important to emphasize that while reproducing for a longer period, mice receiving life-extending interventions have reduced number of offspring, as observed for CR mice (14). This further reflects the evolutionary trade-off that diverges energy from reproductive efficiency to prioritize self-preservation.

The Effect of Life-Extending Interventions on Reproductive Life Span

Caloric Restriction and Mimetics

Caloric restriction is one of the first and most studied life-extending therapies. It can be defined as a reduction in caloric intake (27), usually between 20% and 40% (without malnutrition), compared to ad libitum controls (28). CR can increase longevity by up to 50% in different species (2). Mice subjected to CR have a significant increase in insulin sensitivity, decrease in body fat, and reduced systemic inflammation (29). CR reduces liver IGF-I secretion (30), therefore several beneficial actions of CR are also observed in GH (31) and GH receptor (GHR) (32) deficient mice. At the cellular level, the life-extending effects of CR are dependent on FOXO3 and decrease mTOR activation (33,34). Nevertheless, it is believed that the collective effects of CR in several pathways, including inflammation and oxidative stress-related pathways, exerts positive effects on longevity (35).

Due to limitations in the use of CR for an extended period to increase longevity, the search for CR mimetics that benefit longevity through similar pathways has been pursued (29). In this sense, rapamycin is an immunosuppressive drug (21), used in clinical practice for organ transplant recipients. Rapamycin is recognized as a promising mimetic of CR (3). When provided continuously, it promotes an increase in longevity similar to that observed for CR mice (36). Rapamycin has also been shown to have wide-spread anti-inflammatory effects (37), even in the ovary (38). Long-term rapamycin treatment resulted in reduced body weight and body fat despite an increase in insulin resistance (23). Although CR and rapamycin produce similar effects in longevity, the specific mechanisms of action may diverge between the 2, especially regarding insulin sensitivity (36).

In a previous study by our group, we found that young female mice exposed to CR (30%) and rapamycin (4 mg/kg of weight) for a 3-month period maintained twice as many primordial follicles in the ovarian reserve compared to control mice (39). In contrast to primordial follicles, the number of primary follicles was reduced, although there was no difference in the number of total follicles, suggesting that the transition from primordial to primary follicles was reduced (39). In this study, both CR and rapamycin had similar effects on ovarian function, but dissimilar systemic effects. CR promoted reduced body weight and fat, and increased insulin sensitivity, while rapamycin treatment did not influence body weight or fat content and promoted insulin resistance. This suggests a mechanism of action that is independent of insulin signaling and most likely dependent on mTORC1. Our results indicate that mice subjected to CR and rapamycin exhibit higher ovarian expression of FOXO3a in primordial follicles compared to control females (39).

The beneficial effect of CR on ovarian reserve preservation is well established in the literature. In young mice and rats submitted to CR (30%–40%), the number of quiescent primordial follicles increased 2-fold, compared to ad libitum controls (14,40). Interestingly, CR mice remained fertile for longer and had a higher pregnancy rate and litter size compared to age-matched control mice receiving an ad libitum diet (40). Similarly, young and old female mice and rats treated with rapamycin at 2–5 mg/kg maintained twice the number of primordial follicles compared to controls, and produced twice as many pups (38). Additionally, chemotherapy can result in primordial follicle activation and premature ovarian failure (41). In this sense, both CR and rapamycin protected ovaries of mice submitted to chemotherapy from premature follicle exhaustion (42,43). Furthermore, the simultaneous use of mTOR and Akt activators promote follicle growth and exhaustion of the follicular reserve (44).

As mentioned before, activation of the mTORC1 in granulosa cells promotes FOXO3a phosphorylation in oocytes to stimulate the awakening of primordial follicles (16). However, there is still much to be studied about this interaction. The complex mechanisms by which rapamycin and CR act beneficially in the ovary are not yet fully understood. The evidence presented here suggest that the mTORC1 pathway may be an important mediator of the beneficial effects of CR and rapamycin at the ovarian level.

Growth Hormone

The GH/IGF-I axis is crucial to determine longevity in mice. GH-deficient df/df mice are known for living 35%–75% longer than normal littermates due to their recessive homeobox protein prophet of Pit-1(Prop1) loss-of-function mutation that results in deficient GH, thyroid-stimulating hormone, and prolactin secretion (6). In addition, GHRKO mice are long-lived and share several metabolic phenotypes with df/df mice which are likely responsible for their extended longevity (7). In contrast, transgenic mice overexpressing bovine GH (bGH), have high plasma GH levels, increased serum IGF-I levels, and a life span about 50% shorter than normal mice (45). Interestingly, submitting GHRKO mice to 30% CR does not benefit insulin sensitivity and longevity, suggesting similar mechanisms of action (32). Importantly, treatment with GH in early life shortens the life span of long-living df/df mice (46). This suggests that GH exposure affects developmental programming of aging producing persistent changes through adult life. Conversely, GHR disruption in adult mice did not improve median life span, with only a modest increase in maximal life span of females (47).

It is well established in reproductive biology studies that the GH/IGF-I axis is important for normal ovary function, especially the later stages of follicle development before ovulation (48). df/df mice are unable to maintain pregnancy without prolactin treatment, while GHRKO mice have decreased pregnancy rate and number of pups/litter (49). However, several studies from our group showed that GH can also modulate the initial stages of follicle development and, therefore, ovarian aging. Long-lived df/df mice have almost 4 times more primordial follicles at 6 months (50), 3 times more at 12 months (51), and twice as many at 18 months of age compared to normal littermates (26). This suggests that the difference in the ovarian primordial reserve between df/df and normal mice counterparts is larger at the beginning of life and decreases with age, as the reserve gradually becomes smaller in both genotypes. In addition, the treatment with exogenous GH for a short period increased primordial follicle activation and reduced the ovarian reserve in df/df and normal mice (26). Similar to df/df mice, GHRKO mice have a larger ovarian reserve than normal mice (52,53) and the treatment of GHRKO mice with IGF-I decreased the primordial follicle reserve (53). bGH mice, otherwise, had accelerated ovarian aging and a decreased ovarian primordial follicle reserve (26). Overall, this indicates that the size of the ovarian primordial follicle reserve can be a direct reflection of the circulating levels of GH/IGF-I, indicating a central role of the GH/IGF-I axis to regulate primordial follicle recruitment and ovarian aging. More importantly, these findings indicate strong association between GH/IGF-I, ovarian reserve, and life span. In the clinical setting, the use of GH adjunct therapy in women is controversial. Although it increases the number of oocytes retrieved in poor responders, it did not improve the number of live births (54).

The expression of FOXO3a mRNA was 10-fold higher in the ovaries of 20-month-old df/df mice when comparing to normal littermates (55). At the protein level, FOXO3a is also increased in oocytes from primordial follicles of df/df mice compared to normal littermates (26). GH treatment reduced the FOXO3a protein level, while it increased its phosphorylated form in primordial follicles oocytes (26). Oocytes from primordial/primary follicles of df/df mice also had a lower level of p-FOXO3 protein compared to normal littermates (55). Therefore, suggesting that higher FOXO3a levels can help maintain follicles in the primordial stage. In the ovaries of young GHRKO mice, we also observed a tendency for increased expression of FOXO3a (56). In contrast with df/df and GHRKO models, bGH mice had higher level of pFOXO3a protein in primary follicle oocytes compared to normal littermates, which could be related to the higher rate of primordial follicle activation observed in bGH mice (26). Therefore, this suggests that GH/IGF-I dependent FOXO3a activation could be a key pathway for primordial follicle activation. This suggests that this pathway can have a central role in the regulation of the trade-off between somatic and reproductive aging.

We previously discussed that GH-deficient long-lived mice maintain a larger ovarian reserve, even at older ages. Besides quantity, several factors can influence oocyte quality during aging. Mammalian oocytes enclosed in primordial follicles remain arrested in prophase I of meiosis up to several decades in women (57,58). This long dormancy period increases the chances of accumulating DNA damage, as shown in mice and humans, where DNA double-strand breaks accumulate in primordial follicle oocytes with aging (59). At 6 months of age, df/df mice had less DNA damage in oocytes and granulosa cells of primordial and primary follicles compared to normal littermates (50). The GH deficiency not only preserves the quantity, but also the quality of the remaining follicles and oocytes in the reserve. Therefore, along with FOXO3a activation, reduced DNA double-strand breaks in primordial follicle oocytes can be a mechanism of increased preservation of the ovarian reserve in long-living GH-deficient mice. Overall, these important observations confirm that the delayed aging phenotype in these unique long-living mice is strongly associated with the beneficial characteristics of longevity in the female reproductive organs.

Other Life-Extending Therapies

Although CR and GH deficiency are the most studied life-extending therapies, several other therapies have been successfully tested. Among these, another drug that effectively increases life span is metformin (4,60). In humans, clinical trials regarding antiaging effects of metformin in healthy individuals are being developed. A decrease in the mortality rate of diabetic patients treated with metformin was showed, regardless of the effects on diabetes control (61). Metformin's mechanisms of action are similar to those of CR, such as decreased insulin and IGF-I levels (60), and therefore it is mainly used for the treatment of type 2 diabetes mellitus (62). Metformin promotes reduction of blood glucose concentrations by decreasing intestinal glucose absorption, improving peripheral glucose uptake, lowering fasting plasma insulin levels, and increasing insulin sensitivity (63). It also inhibits the mTOR pathway (64), and reduces the production of reactive oxygen species (65), thereby reducing DNA damage (60). As the mechanism of action is similar to CR, similar effects on the ovarian reserve should be expected. In fact, this has recently been proved true. Metformin administration decreased primordial follicle activation in mice (66). Also, metformin has been reported to improve estrous cycle and hormonal profile in rodents, specially by decreasing testosterone and FSH/LH ratio (67). Even though it did not influence estradiol serum levels, metformin suppressed irregular estrous cycles, usually observed with aging (68). Metformin is also used in the treatment of polycystic ovary syndrome (PCOS), restoring ovulation and decreasing androgenesis (67,69). Overall, decades worth of studies in animals and humans showed that metformin has a significant impact on female reproductive organs. In addition to treating PCOS and improving insulin resistance in type 2 diabetes patients, metformin also delayed reproductive senescence, improved fertility rate, and increased longevity in animal studies.

Another pharmacological intervention able to increase life span that has been intensively studied is the enhancement of the NAD^+, through supplementation with its metabolic precursor nicotinamide mononucleotide (NMN). NAD^+ is an important redox cofactor and enzyme substrate, involved on the maintenance of epigenetic homeostasis, since it serves as a required substrate for the deacetylase activity of sirtuin (70). Increased NAD^+ levels lead to increased activation of sirtuins, thereby decreasing the aging process (5). NAD^+ levels naturally decrease with age in somatic tissues, including the ovary (71). Recently, it was demonstrated that NAD^+ levels in ovulated oocytes also decrease with age, and supplementation with NMN restored these levels in oocytes of aged mice. Oocytes from NAD^+ supplemented females also, had better rates of *in vitro* maturation and embryo production, and greater pregnancy and birth rates in aged animals (72). However, although these data suggest a positive impact of NMN on the ovarian reserve, no direct measurement of the effects of NMN supplementation on primordial follicles has been performed.

17α-Estradiol (17αE2) is another drug that has been shown to increase life span of male mice (73). 17α-E2 is considered a non-feminizing estrogen due to its minimal activation of classical estrogen receptors (74). Treatment with 17α-E2 reduces energy intake due to activation of hypothalamic anorexigenic pathways (75), resulting in reduced body mass, visceral adiposity, and ectopic lipid deposition (76), similarly to CR. However, these effects are stronger in males, while in females, 17α-E2 has little or no effect (75). As discussed throughout this review, most drugs that contribute to a longer life span also result in a slower exhaustion of ovarian reserve. Interestingly, 17α-E2 appears to have no effect on the ovarian reserve of normal mice, while in the long-lived GHRKO mice, it decreased the number of primordial follicles (52). These results are interesting and show that drugs proven to be more effective in males, have no effect in the ovarian aging of females. This also demonstrates that in females, the positive effects of many life-span–extending therapies are closely linked with the preservation of the ovarian reserve.

Other Determinants of the Ovarian Reserve

Obesity/High-Fat Diets and Aging

As mentioned previously, CR results in extended longevity. In contrast, obesity reduces life span among human populations (77). Leptin deficiency, due to a mutation in the ob gene, results in severe obese phenotype (78). The ob/ob mice have severe obesity and insulin resistance, among other comorbidities (79). The life span of ob mice is also compromised, averaging 18 months for obese mice and 27 months for normal lean littermates (80). While life-prolonging therapies such as CR (29), rapamycin (37), and GH deficiency (6,7) lead to a diminished inflammatory state, the obese phenotype is

associated with a greater secretion of proinflammatory cytokines (81). These proinflammatory cytokines are elevated in adipose tissue and in systemic circulation during obesity (82).

The ob mice are infertile and have a lower gonadal weight in both males and females (83). This condition is mainly associated with the lack of leptin action at the hypothalamic level, decreasing the release of gonadotropins (84) and impairing final follicle growth (84) and ovulation (85). As a consequence, ob mice have a reduced number of corpora luteum and increased follicular atresia (86). However, fertility can be restored when exogenous leptin is supplemented (84) or when females are transplanted with adipose tissue from normal littermates (87). Although gonadotropin independent, the early stages of follicle development are also impaired in the ob mice. Studies have shown a decreased number of primordial and total follicles in ob mice (83) and that exogenous leptin treatment rescued the number of primordial follicles (84). This suggests that leptin is involved in the survival of primordial follicles, as ob mice have an increased rate of granulosa cell apoptosis in preantral follicles (83). Interestingly, prolonged exposure to a high-fat diet in young mice also caused a significant reduction in the total number of primordial follicles, even though these mice did not develop obesity (88). These effects seem to be mediated trough increased activation of the mTOR pathway and suppression of sirtuin signaling (89). Additionally, the high-fat diet was associated with increased systemic proinflammatory cytokines and macrophage infiltration in the ovary, resulting in impaired fertility (88).

In addition to impaired ovulation and reduced ovarian reserve, deformed oocytes with irregular granulosa cell layers are observed in preantral and antral follicles from ob mice (90). Increased oxidative stress is observed in ob mice and impairs mitochondrial function and distribution in oocytes, resulting in apoptosis (91). Obesity, induced by a high-fat diets or ob gene mutation, is also associated with oocyte epigenetic modification, disruption of meiotic spindle formation, and reduced oocyte polarity, resulting in reduced oocyte maturation and germinal vesicle breakdown (91). Exposure of mice to a high-fat diet for 4 weeks results in increased lipid accumulation in oocytes and in cumulus cells (92), and a 6-week exposure had irreversible effects on oocyte quality (93). Overall, this evidence indicates that obesity in mice accelerates several negative aspects of ovarian aging, presenting effects opposite to those observed in CR and GH-deficient mice.

Intrauterine Origins of the Ovarian Reserve

The primordial ovarian reserve is formed in utero in rodents. Primordial germ cells colonize the gonads at around 10 days of gestation in mice, forming cysts that cease mitosis and enter meiosis I around day 14 of gestation (94). Just after birth, the cysts break down and form the primordial follicle pool (94). Transcription factors play crucial roles in this process, such as *factor in the germline alpha* (FIGLA), which is responsible for coordinating the expression of oocyte-specific zona pellucida genes (94) and the *newborn ovary homeobox* (NOBOX), essential for the survival of the oocyte and assembly of the primordial follicle (94). Increased expression of FIGLA was correlated with loss of primordial follicles and premature ovarian failure in women (95).

Exposure to a stimulus or stress during the prenatal period can result in long-term adaptations of the physiological functions of the offspring, a process called fetal programming (96). In addition, protein-caloric malnutrition during pregnancy can result in delayed fetal development and obesity in adult rats and mouse offspring

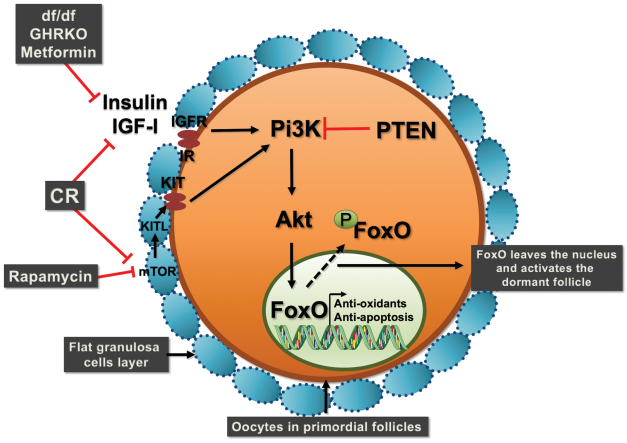

Figure 1. Schematic representation of pathways that regulate primordial follicle activation, which are simultaneously regulated by life-extending therapies. Calorie restriction (CR) and rapamycin inhibit the mTOR pathway in granulosa cells, which in turns regulates oocyte activation of the Pi3K/Akt/FOXO3a pathway. FOXO3a phosphorylation results in its nuclear extrusion and activation of the primordial follicle. Reduced IGF-I and insulin signaling in metformin-treated mice, GH-deficient Ames dwarf, and GH receptor knockout (GHRKO) mice also contribute to reduced Pi3K/Akt activation and reduced FOXO3a phosphorylation, maintaining primordial follicle in the quiescent stage. Full color version is available within the online issue.

(97). There is also evidence that reproductive maturation is influenced by early life events. Fewer primordial follicles are observed in the ovaries of offspring from mothers subjected to CR during gestation (98). Additionally, CR offspring display increased follicular apoptosis at later stages of follicle development (98). In humans, data from the Dutch hunger cohort showed that women exposed to prenatal hunger were more likely to start menopause at an earlier age (99). Despite this, exposure to hunger had no effect on the age of menarche, the proportion of women without children, the age of first birth, or the size of the family (100).

Concluding Remarks

Based on the evidence presented in this review, we can conclude that there is overwhelming data suggesting that in females increased longevity is associated with delayed ovarian aging. Several animal models of extended female longevity also display increased numbers of primordial follicles in the ovaries. Activation of mTOR and FOXO3a pathways also appear as important links between somatic and gonadal aging (Figure 1). Overwhelming evidence supports the observation that the most successful life-extending therapies for females also reduce ovarian aging, suggesting an important active role for the ovary in the life span and healthspan of females.

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Conflict of Interest

None declared.

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