—Review—

The regulation of ovarian follicular growth by anti-Müllerian hormone

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Abstract: Anti-Müllerian hormone (AMH) was originally discovered as the factor responsible for the regression of the Müllerian duct during male sexual differentiation. Through studies of AMH knockout mice, AMH has also been found to regulate primordial follicle recruitment and FSH-dependent cyclic recruitment. However, the details of how AMH influences follicular growth have not been elucidated. Since the early 2000s, when serum AMH concentration was found to be a reliable biochemical marker of ovarian reserve, AMH has been in the spotlight in reproductive medicine. Several studies of AMH have led to new insights on the mechanism of AMH-regulated follicular growth. Here, we review from the earliest studies to the latest findings, AMH regulation of follicle growth with reference to the potential clinical uses of AMH and AMH inhibitors.

Key words: Anti-Müllerian hormone, Ovarian reserve, Polycystic ovarian syndrome, Ovarian failure

Introduction

During the past two decades, anti-Müllerian hormone (AMH) has attracted much attention as an important marker of ovarian reserve. Ovarian reserve is the functional potential of the ovary, reflecting the number and quality of follicles left in the ovary. AMH is produced by granulosa cells of primary, preantral and small antral follicles. Therefore, the AMH level indirectly represents the number of early-growing-stage follicles. AMH has several strengths as a biomarker which account for its widespread clinical use. AMH is highly sensitive to ovarian reserve changes due to advancing age and is stable throughout the menstrual cycle, relatively unaffected by GnRH agonists or short-term use of oral contraceptives. As AMH gained its position as a valuable biomarker, further studies on its function elucidated its role as a major negative paracrine regulator, inhibiting the recruitment of primary follicles from the primordial pool [1, 2]. This inhibitory role of AMH implied its involvement in pathological conditions such as PCOS and triggered new studies investingating how AMH regulates follicular growth. Here we discuss the regulatory mechanism of AMH on follicular growth by reviewing AMH early studies from initial investigations to the most recent results, with reference to its applications in clinical treatments.

Received: December 29, 2017
Accepted: February 17, 2018
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AMH as a Müllerian Duct Inhibitor

AMH plays a vital and classic role in fetal sexual differentiation. In 1947, Alfred Jost demonstrated that a testicular factor other than testosterone was responsible for Müllerian duct regression during male fetal sexual differentiation [3]. This factor, designated as Müllerian inhibiting substance (MIS), or AMH, was later purified and found to be produced by Sertoli cells in the testis [4, 5]. The AMH gene is located on chromosome 19p13.3. Patients with mutations in the AMH gene show persistent Müllerian duct syndrome (PMDS), a disorder in which the uterus, fallopian tubes and the upper part of the vagina are present in an otherwise phenotypically normal male [6].

Early Studies with AMH Knockout Mice

AMH is produced by granulosa cells of small and large preantral and small antral follicles, where 60% of serum AMH is produced by follicles ranging from 2–6 mm in size [7, 8]. Granulosa cells of follicles less than 4 mm in secondary and small antral follicles express the greatest lev-

els of AMH [8]. The early studies of AMH emerged from observations of AMH knockout mice. Initially, the lack of AMH seemed to have no effect on reproductive functions, because female AMH knockout mice appeared to have a normal ovarian phenotype and fertility with a normal litter size [9]. However, additional analysis of the complete follicle population in female AMH knockout mice at 25 days, 4 months and 13 months of age revealed the importance of AMH in follicular growth regulation. Ovaries of 25-day- and 4-month-old AMH knockout females contained more preantral and small antral follicles than wild-type mice. At 13 months of age, primordial follicles were almost depleted in AMH knockout females whereas wild-type displayed significantly more primordial follicles. Further studies indicated that AMH regulates the two critical selection points of follicular growth: when AMH starts and ends its expression i.e., the initiation points of primordial follicle recruitment and acquisition of FSH responsiveness, respectively [2, 10, 11] (Fig. 1). In the absence of AMH, primordial follicle recruitment accelerates leading to primordial follicle pool depletion at a faster rate than in wild-type mice. In AMH knockout mice, the recruitment of primordial follicles is already increasing before estrous cycling has started [2]. AMH knockout mice have more preantral and small antral follicles, as many as 3 times of their wild type controls, with fewer primordial follicles at the age of 4 months. By 13 months of age, AMH knockout mice have a nearly depleted primordial follicle pool with substantially fewer growing follicles [2]. These results show that AMH inhibits primordial follicle recruitment, protecting the quiescent state of primordial follicles from premature depletion [2]. The period of AMH expression during follicular growth suggests that AMH may also regulate FSH-dependent cyclic selection [11]. Studies have shown that AMH downregulates the expression of FSH target genes such as CYP19a1 and LHCGR receptor in rat and porcine granulosa cells [12]. Ovine granulosa cells show decreased FSH-induced estradiol production, whereas theca cells show decreased LH-induced androstenedione production when AMH is present [13]. In human luteinized granulosa cells obtained from women undergoing IVF treatment, AMH inhibits FSH-induced CYP19a1 mRNA and protein expression with a concomitant reduction in estradiol production [14–16]. In an analysis of AMH knockout mice, although FSH treatment resulted in more antral follicles in wild type mice, their number was significantly enhanced in the ovaries of FSH-treated AMH knockout mice [10]. In agreement with this result, FSH-stimulated follicular growth of mouse preantral follicles cultured *in vitro* was reduced in the presence of AMH [10]. These findings suggest

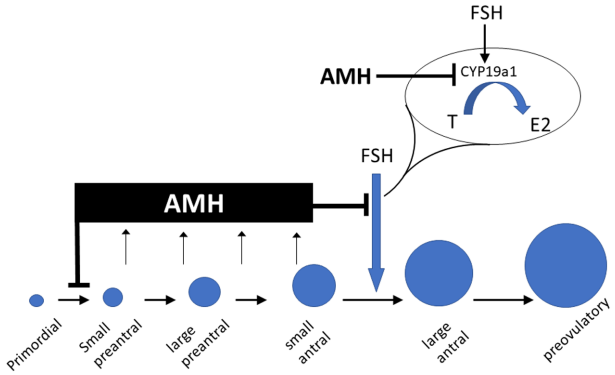

Fig. 1. The regulation of AMH on growing follicles. AMH is produced by granulosa cells of small preantral to small antral follicles. AMH regulates follicular growth at two critical selection points; primordial follicle recruitment and acquisition of FSH responsiveness. AMH inhibits FSH-induced CYP19a1 expression leading to decreased estradiol (E2) levels.

that AMH may regulate the responsiveness of follicles to FSH by suppressing the activity of aromatase, thereby preventing premature maturation of follicles. AMH acts as a double gate-keeper regulating the initial primordial follicle recruitment step and the FSH-dependent cyclic recruitment stage of follicular growth.

Mechanism of AMH-regulated Follicular Growth

AMH has emerged as one of the most informative biochemical markers of the ovary and is widely used in clinical practice. It strongly correlates with the primordial follicle pool [17, 18], has a solid inverse relationship with chronologic age [19, 20], and reliably predicts ovarian response in ART [21, 22]. Clinically, it is monitored in polycystic ovarian syndrome (PCOS) patients and in the diagnosis of ovarian failure [23–25]. As many reports have been made of the clinical efficacy of AMH, several studies have led to new insights into how AMH is involved in follicular growth in these pathological conditions (Fig. 2). PCOS is one of the most common reproductive disorders affecting fertility in women. The typical polycystic appearance of the ovaries is mostly due to AMH-producing small antral follicles, resulting in serum AMH concentration being elevated 2–3 folds compared to women with normal ovaries [23]. The increased number of follicles and resultant increase in granulosa cell mass, together with increased production by individual granulosa cells account for AMH overproduction in PCOS [26–28]. This overproduction of AMH could be due to several factors such as abnormally

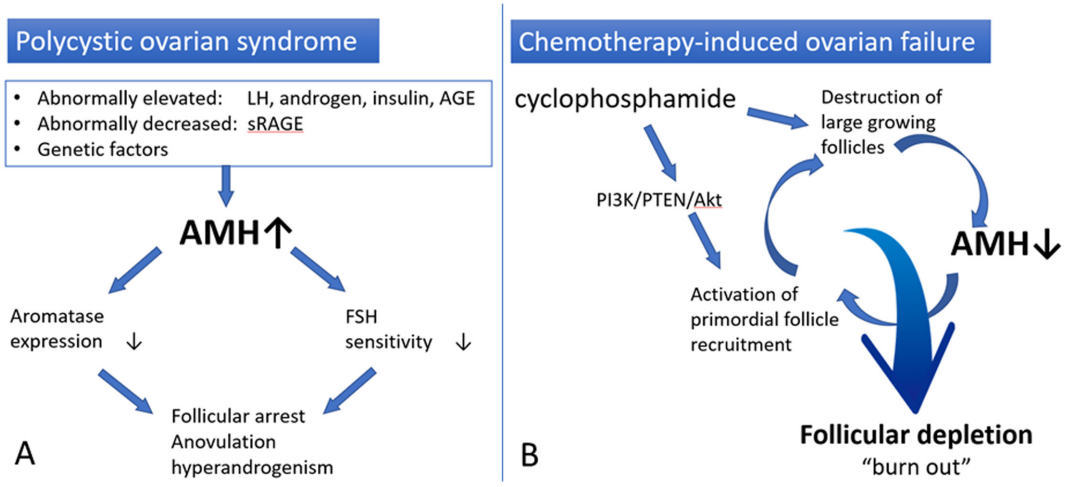

Fig. 2. The involvement of AMH in polycystic ovarian syndrome (PCOS) and chemotherapy-induced ovarian failure. A Several factors contribute to increased AMH. Elevated AMH suppresses aromatase expression and follicular sensitivity to FSH, leading to follicular arrest, anovulation and hyperandrogenism which is the typical phenotype in PCOS. B Chemotherapy agents such as cyclophosphamide (Cy) destroys large follicles. Cy also activates the recruitment of primordial follicles by disrupting the PI3K/PTEN/Akt pathway, which would then grow into the next target of destruction. Reduction in the number of follicles decreases AMH levels leading to further activation of primordial follicle recruitment, forming a vicious cycle resulting in follicular depletion.

elevated LH, androgens, insulin and advanced-glycation end products (AGE), and abnormally decreased factors such as soluble receptor for AGE [27, 29–37]. Although androgen is reported to have the potential to instigate the increase in number of AMH-producing follicles [29, 32], the mechanism of how most of these factors lead to AMH overproduction is still unclear [27, 30, 31, 33–37]. Genetic factors such as variants of the ACVR1 gene also likely contribute to increased AMH [38]. In turn, elevated AMH contributes to the pathophysiology of PCOS. Associations of high AMH concentrations with high androgen levels, such as serum testosterone and androstenedione, and low follicular fluid estradiol concentrations have been shown in PCOS patients [14, 32, 39–41]. This has been suggested to be caused by AMH-induced suppression of aromatase activity and expression [14]. Elevated AMH may inhibit FSH-induced aromatase activity causing the hyperandrogenism, follicular arrest and anovulation typically seen in PCOS.

Premature ovarian failure and infertility are serious side effects of chemotherapy treatments in young female cancer patients. Chemotherapy-induced ovarian failure can be monitored by decreased serum AMH levels [23]. The extent of the damage depends greatly on the type of medication and dose of the chemotherapy agents used [42, 43]. Among the chemotherapy agents, alkylating agents such as cyclophosphamide has the greatest risk of premature ovarian failure [43, 44]. Cyclophosphamide directly and indirectly depletes the ovarian follicular reserve. Cyclophosphamide targets and directly destroys granulosa cells in large follicles only [45]. However, by disrupting the PI3 K/PTEN/Akt pathway, it also activates the recruitment of dormant primordial follicles to the growing pool [45]. Once recruited, these follicles then grow into large follicles, and become the next direct target. The reduced number of growing follicles decreases AMH levels, adding to the accelerated activation of primordial follicle recruitment. This vicious cycle eventually results in follicle depletion of the ovary, creating a "burn out" effect [45, 46].

AMH Supplementation to Protect Ovarian Reserve

Increased AMH in PCOS causes follicular arrest and decreased AMH in chemotherapy-induced ovarian failure causes follicular depletion. These roles suggested that AMH supplementation may have potential as a treatment for protecting ovarian reserve. Kano *et al.* showed that among chemotherapy treated mice, animals treated concomitantly with AMH had significantly more primordial follicles than animals without AMH treatment [47]. Follicle counts suggested the specific inhibition of primordial follicle activation. Other follicular stages were

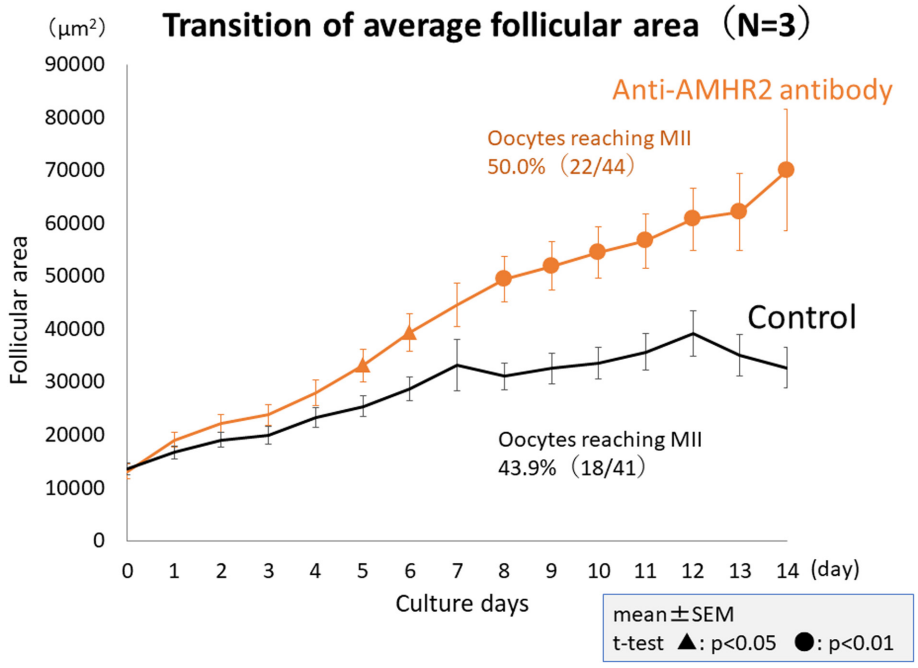

Fig. 3. The transition of average follicular area observed by the sliced ovarian tissue culture system. Ovarian tissue cultured with anti-AMHR2 antibody produced significantly larger follicles compared to control. The retrieved oocytes had a higher rate of reaching MII in ovarian tissue treated with anti-AMHR2 antibody (50%, 22/44) compared to control (43.9%, 18/41).

neither inhibited nor activated, and no increase in the rate of atresia was observed. The inhibition of primordial follicle activation by AMH was also found to be reversible with a rapid reawakening of folliculogenesis [47]. The protective effect of AMH was particularly dramatic in co-administration with DNA-damaging chemotherapy drugs such as platinums and anthracyclins. These medications are toxic to dividing granulosa cells of secondary and antral follicles, leading to the loss of the suppressive effect of AMH on over-recruitment of primordial follicles, indirectly causing follicular depletion [47]. AMH also shows a positive effect in co-administration with alkylating agents, which have direct damaging effects on germ cells as well as indirect over-recruitment effects [47]. AMH may therefore be effective at preventing chemotherapy-induced primary ovarian insufficiency, acting as a potent inhibitor of primordial follicle activation, protecting the ovary from follicular depletion.

AMH Inhibition to Promote Follicular Growth

The role of AMH as an inhibitor of primordial follicle recruitment suggests that blocking AMH may promote follicle recruitment and growth. Recent *in vivo* studies utilizing intraovarian AMH infusion in macaque ovaries showed that only one follicle was evident at midcycle, whereas multiple antral follicles were observed in the ovaries treated with AMH-neutralizing antibody [48]. The sliced ovarian tissue culture system, which we established [49], enables the visualization of follicle development through chronologically tracing individual follicle areas. The goal of our ovarian tissue culture system is to gain a better understanding of folliculogenesis and to establish a complete *in vitro* follicle growth system from primordial follicles. Visualization of follicular development would be useful for evaluating the mechanisms and molecules which regulate folliculogenesis *in vitro* and would be helpful in the quest to find the optimal conditions required for *in vitro* ovarian tissue culture. Our unpublished preliminary data from experiments using this system show that the addition of anti-AMHR2 antibody increased the average follicle areas and increased the rate of oocytes that reached the MII stage (Fig. 3). This is in line with the results of Durlinger *et al.* which demonstrate the suppressive effects of AMH in the recruitment of primordial follicles and FSH-dependent follicle growth [2, 10]. Therefore, it is reasonable to assume that inhibition of AMH action attenuates the suppressive effects of

AMH, leading to increased primordial follicle recruitment and FSH-dependent small to large antral follicle development (Fig. 1).

Conclusion

Over fifty years after its discovery, AMH is recognized as a reliable biomarker of the ovary, and it has been used as one of the most informative biochemical markers for over 15 years. Furthermore, studies of the effects of its regulatory mechanism on follicular growth and its roles in disease conditions have suggested new potential treatments using AMH. Recombinant human AMH analogues are now being administered therapeutically as pharmacologic agents in reproductive medicine [50]. AMH may have therapeutic uses in a broad range of reproductive medicines, such as contraception and fertility preservation, as well as disease conditions such as PCOS and chemotherapy-induced ovarian failure. It is anticipated that AMH inhibitors will also be identified and utilized to induce follicle development. AMH inhibitors may be the key to the establishment of a complete *in vitro* follicle growth system from primordial follicles. They may also play a vital role in developing techniques for the successful autologous transplantation of cryopreserved ovarian tissue. With both AMH and AMH inhibitors, it may be possible to precisely control both acceleration and suppression.

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