Review Article

Current Opinion in Gynecology and Obstetrics

Research Progress of Angiogenin in Reproduction

Xiaotao H¹, Yunxia W²*

¹Department of Integrative Traditional Chinese Medicine and Western Medicine, Affiliated Women and Children's Hospital of Hubei Province, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China
²Department of Pharmacology, Pharmacy School of Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China

*Correspondence: Wu Yunxia, Department of Pharmacology, Pharmacy School of Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China, E-mail: wuyunxia@hust.edu.cn

Received: November 16, 2018; Accepted: January 31, 2019; Published: February 05, 2019

Abstract

Angiogenin (ANG) was previously proved one of the potent proangiogenic factors in the process of formation, remodeling and maturation of new blood vessel, then was found playing a dual role in tumor growth by promoting both tumor angiogenesis and cancerous cell proliferation and promoting neuron neurite growth, recently it has been proved an important regulator in stem cell regeneration and stemness maintenance by affecting nucleic acid hydrolysis and protein synthesis. Here we review the related research about ANG in reproduction. ANG was detected in different levels of follicle except in primordial stage in bovine and human and reveals that it may play role in follicle development and mature. During pregnancy, large amount of ANG dramatically expressed in maternal, amniotic fluid or fetal placenta, it may play a role in embryo implantation, the growth and development of fetus. The occurrence of reproduction related diseases such as infertility, endometriosis, ovarian hyperstimulation syndrome, gestational hypertension, fetal growth retardation and etc seems related with ANG. However, detailed research on the mechanism of ANG in related diseases is lack. Therefore, the further study about the role of ANG is of great significance for the understanding ANG function and may bring promising treatment of fertility, reproduction related diseases.

Keywords: Angiogenin, Reproduction

Introduction

Angiogenin (ANG) is one of the most potent angiogenic proteins, and also belongs to the ribonuclease family and named as RNAse 5, it was firstly found playing a central role in the formation, reshape and mature of new blood vessels [1], then found closely related to the formation, development and metastasis of tumor, neuro growth and development and most recently ANG was found also a stem cell regulator in promoting hematopoietic regeneration by dichotomously regulating quiescence of stem and progenitor cells. ANG participates in a variety of physiological and pathological process [2,3]. It has been reported the expression of ANG in follicle, endometrial matrix, amniotic fluid and fetal placenta in specific time and space, suggesting ANG may involve in follicle development, menstruation, embryo implantation, placental development and fetal growth and development. Women with reproduction related diseases were found abnormal expression of ANG in serum or plasma comparing with normal healthy women, but all the mechanisms are not clear yet. Here we review the progress of ANG in reproduction.

Molecular biology characteristics of ANG

ANG, one of the most potent protein with strongly promoting angiogenesis activity was firstly isolated from colonic carcinoma medium in Harvard medical school by Vallee BL in 1985 [1]. ANG, composed of 123 amino acid residues, a single alkaline secreted protein, also
ANG belongs to ribonuclease (RNase) family, named RNase5, its genes located on chromosome 14 and shared same promoter with RNase4, its stability is very good. Although has lower RNase activity, but its nucleic acid hydrolase activity is necessary for its promoting angiogenesis activity. Structure analysis found that ANG protein crystal has three main structure domains: cell surface receptor binding sites, RNase activity centre, nuclear sequence of regulating the ribosomal RNA synthesis [4-10]. ANG plays dual role in the development of the cancer, it can both promote tumor angiogenesis and promote cancer cells proliferation [11-13]. ANG also exists in normal human tissues and body fluids, such as serum, amniotic fluid, follicle fluid and etc. Accumulated 30 years of research, people gradually realize ANG plays very important role in many physiological and pathology conditions such as wound healing, menstrual period, pregnancy, follicle and embryonic development, nerve cells survive and growth, immunology, stress, defensive even stem cell regulating aspects and etc. [14-18].

ANG in physiology of reproduction

**ANG in follicle:** Follicle dysplasia or ovulation dysfunction will affect menstruation and pregnancy, and then lead to infertility. Follicle development is related to angiogenesis and many vascular growth factors. ANG strongly promotes the angiogenesis, therefore, it might involve in the development of follicles. Heungshik [19] found ANG mRNA expression existed in bovine ovaries, not in the primordial follicle but in primary follicles, secondary, tertiary and Musharrafs follicles; Mature follicles and granular layer cells expressed ANG very strongly; but atresic follicles had only weak ANG expression in follicle epithelial cells, not inside or outside of the follicle membranes; also ANG expression changed in different levels of the follicle development. Kaori Kago [15] firstly found ANG expressed in ovaries in women undergoing in vitro fertilization (IVF), Protein Imprinting and RT-PCR technology were used in detection of ANG, ANG was found in follicle fluid, granulosa cells and granular cell culture media, and ANG concentration was affected by human chorionic gonadotropin (HCG), cycline adenosine phosphate and low oxygen environment regulation. Women undergoing IVF, ANG concentration in follicle fluid in mature follicles was significantly higher than that in immature follicles, but vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) did not show significant difference. In addition, they found that ANG was unique angiogenesis factor with positively related to the maturity of follicles, ANG concentration was not found significant change before and after mature oocytes fertilization. Therefore ANG may has no direct relation with the oocyte fertilization but related with follicle development and mature [20].

**ANG in menstrual cycle:** In the female menstrual physiological cycles, the growth of blood vessels is necessary for endometrium thickening [21]. It was found that the concentration of serum ANG increased significantly 2-3 days after the peak luteinizing hormone secretion in women with normal menstrual cycle [22], therefore ANG may play a role in the later stage of menstrual cycle after ovulation. Keiji [23] found that the levels of serum ANG was not significantly different in the normal menstrual cycle of unfertilized female with normal blood pressure. Therefore, whether or not ANG changes in various stages during the menstrual cycle needs further examination in more samples.

**ANG in embryo implantation, placenta formation and embryonic development:** ANG was expressed in endometrial cavity or glandular epithelium and mesenchymal cells, and time-space expressed in different trophoblast cells in decidual tissue during implantation. ANG expression increased significantly in decidua in the endometrium at middle-late secretion, and ANG can stimulate the proliferation of endothelial cells and vascular smooth muscle from decidua, so ANG may involve in embryo implantation, placenta formation and embryonic development [24-27]. In addition, Hayashi [28] found that during 7 to 15 weeks of pregnancy, the levels of serum ANG kept decreasing, but after 15 weeks, the levels of serum ANG kept rising, so ANG may relate to the whole process of pregnancy including embryo implantation, placenta formation and embryonic development.

ANG in pathology of reproduction

**ANG and infertility:** The incidence of infertility is increasing in recent years, the etiology is complex, including follicle developing and ovulation, fallopian tubal and endometrial factors, etc. ANG was found expressed in the endometrium and might play important role in promoting the growth and development of endometrium, and ANG was also found expressed in ovary and might regulate follicle developing and maturing, ANG secretion abnormal will affect all these progress and cause infertility [20]. Studies confirmed that the serum angiogenin mRNA level in endometrial proliferation phase of infertility patients with endometriosis increased significantly compared with healthy women [29]. ANG not only existed in woman genital duct but also distributed in...
mens’ testicles, it had been confirmed ANG distributed in peritubular myoid cells by using immunohistochemical and in situ hybridization technology, ANG may play an important role in male reproductive cells by regulating the formation and transportation of sperm cells [30].

**ANG and OHSS:** Original aim of ovarian stimulation is to use hormone to promote ovulation, but due to the high ovarian response, it usually will produce a large number of vascular active substances and steroid hormone, increase the permeability of blood vessel walls, triggering a series symptoms such as edema and pleuroperitoneal fluids of harmful, serious and sometimes can be life-threatening, that is ovarian hyperstimulation syndrome (OHSS). The exact pathogenesis is not clear at present. But it was found that the ANG levels in serum and ascites of patients with OHSS significantly higher than that in normal healthy women, and high concentration of ANG strongly related with increased vascular permeability [31]. Miro also speculated ANG might be the key factor of OHSS, it likely promoted the development of OHSS combining with other angiogenic factors [32,33], but the mechanism of ANG in the pathogenesis of OHSS is still not very clear, needs further research.

**ANG and endometriosis:** Incidence of endometriosis in women of childbearing age to be as high as 10% ~ 15%, the main symptoms is pain and infertility. Endometriosis has seriously impact on women's health because it is difficult to heal and easy to relapse. It was found that ANG levels in serum and ascites of patients with endometriosis were significantly higher than that of healthy people in the follicle phase, but in the luteal phase had no obvious differences [34]. Nobuhiro also found ANG concentration in peritoneal fluid in patients with endometriosis on proliferation and secretion increased compared with that of healthy people, but no obvious difference between the secretion and proliferation, however, as the illness grew worse, ANG level in the peritoneal fluid increased more [35].

**ANG and gestational hypertension:** Gestational hypertension is related with pregnancy, including gestational hypertension, preeclampsia and eclampsia. They affect maternal and child health seriously. The occurrence may be related to over erosion, placental trophoblastic cells ischemia hypoxia, cell apoptosis, metabolic or angiogenesis disorder and so on. Of them, angiogenesis regulation disorder is one of the important mechanisms of the disease, many factors involved in regulating angiogenesis, but ANG may be one of the most important regulatory factors. It was found that ANG levels in serum of pregnant women with preeclampsia changed significantly, ANG levels of mild and severe preeclampsia patients are significantly higher than normal pregnant women, at last, increased ANG expression in placenta may also lead to low birth weight. Although still unclear increased maternal serum ANG is a cause or a result of maternal blood pressure increasing, but inhibition maternal serum ANG may be a way for the treatment of pregnancy-induced hypertension [36-39].

**ANG and fetal growth restriction (FGR):** FGR is also called the intrauterine growth restriction (IUGR), refers to the abnormal fetal size in the uterine not reaching their genetic growth potential. The clinical diagnosis is difficult due to the complexity of etiology, it is not only a threat to the health of the fetus during pregnancy, also increases the incidence of various diseases after childbirth. In most cases, the main reason is abnormal placentation development, lacking of nutrients and oxygen supply, leading to fetal growth slowdown. It was showed ANG levels in placenta of patients with IUGR increased significantly, almost 2 folds higher than in normal placenta [40,41]. Therefore, ANG might relate with FGR.

**Conclusion**

To sum up, in physiological condition, ANG may play role in follicle development and menstrual cycle, and may also play important role in embryo implantation, the growth and development of fetus during pregnancy because large of ANG dramatically expresses in maternal, amniotic fluid or fetal placenta. In pathological condition, the occurrence of reproduction related diseases such as infertility, endometriosis, OHSS, gestational hypertension,
FGR and etc seems closely related with ANG. However, the research about ANG in reproduction is lack and preliminary. Therefore, the further study about the role of ANG in reproduction is of great significance for the understanding the role of ANG and treatment of fertility, reproduction related diseases.

Acknowledgement

This work was financially supported by the National Major Special Program of China (No. 2012ZX09103101-047) and National Natural Science Foundation of China (NSFC, No. 81373873). No potential conflicts of interest in all authors.

References


41. Obstetrics: Overexpression and secretion of angiogenin may play a role in IUGR. *Obgyn and Reproduction Week.* 2003;3.


Copyright: © Xiaotao et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.