Rewarding Conversation Between Oocyte and Cumulus Cells Directs the Process of Folliculogenesis

Oosit ve Kumulus Hücreleri Arasındaki Değerli İletişim Folikülogenez Sürecini Yönlendirir

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ABSTRACT

The process of folliculogenesis needs a balanced environment to create a mature oocyte that is expected to have characteristics in order to form the ability of a healthy fertilisation. Previous studies have been focused on endocrine effects of hypothalamic–pituitary system on ovarian functions. Influences of this system have been studied for many years. Besides of extra-ovarian factors, recent studies have focused on intraovarian factors which forms the relationship between oocyte and cumulus cells. It has been shown that even the maturity of antral follicule and oocyte has been effected from this communication. These factors which takes part at process of folliculogenesis, were shown to be efficient even at the success of assisted reproductive technologies. We studied general lines of this conversation based on main research articles that continue to be relevant at this topic.

Key Words: Cumulus cell, oocyte, folliculogenesis, assisted reproductive technologies

Received: 07.30.2019 **Accepted:**08.09.2019

ÖZET

Folikülojenez süreci, sağlıklı bir fertilizasyonun gerçekleşmesinde gerekli özelliklere sahip olması beklenen olgun oositin oluşumu için dengeli bir ortama ihtiyaç duyar. Önceki çalışmalar hipotalamik-hipofiz sisteminin ovaryan fonksiyonlar üzerindeki endokrin etkilerine odaklanmıştır. Bu sistemin etkileri yıllardır çalışılmaktadır. Son çalışmalar ekstra ovaryan faktörlerinin yanı sıra, oosit ve kumulus hücreleri arasındaki ilişkiyi oluşturan intraovaryan faktörlere odaklanmıştır. Antral folikül ve oosit olgunluğunun da bu iletişimden etkilendiği gösterilmiştir. Folikülogenez sürecinde yer alan bu faktörlerin, yardımcı üreme tekniklerinin başarısında dahi etkili olduğu gösterilmiştir. Bu konuyla ilgilenmekte olan araştırma makalelerine dayanarak bu iletişimin genel hatlarını inceledik.

Anahtar Sözcükler: Kumulus hücresi, oosit, folikülogenez, yardımcı üreme teknikleri

Geliş Tarihi:30.07.2019 **Kabul Tarihi:** 09.08.2019

INTRODUCTION

The process of folliculogenesis needs a balanced environment to create a mature oocyte that is expected to have characteristics in order to form the ability of a healthy fertilisation. Previous studies have been focused on endocrine effects of hypothalamic–pituitary system on ovarian functions (1). The data obtained in this field have been shared with the effect of pituitary gonadotropin hormones (FSH, LH, GnRH) and gonadal hormones during folliculogenesis process. However, the maintenance of healthy ovarian function and follicle development are also influenced by the paracrine / autocrine-acting local growth factors and cytokine releases (2, 3).

Intracytoplasmic sperm injection (ICSI) had been of great importance in assisted reproductive techniques (ART), and can be summarized as injection of a single sperm into an egg under a microscope. This technique, was firstly described in 1978, and had a great impact in those years. Surgeon Patrick Steptoe was awarded the Nobel Prize in 2010 for his work at the time (4). Despite all the advanced techniques provided in the scope of assisted reproductive techniques, pregnancy cannot be achieved in approximately 40% -50% of the patients undergoing the procedure (5). Selection of the best quality sample from the oocyte pool has a great importance in the success achieved by assisted reproduction techniques (ART). The importance of oocyte and follicle development on fertility is known (6).

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doi:http://dx.doi.org/10.12996/gmj.2019.110

On the other hand high quality oocyte selection is expected to increase implantation and pregnancy rates (5, 7). It has been shown in many studies that the perfect two-way interaction between oocyte and surrounding somatic cells (granulosa, cumulus cells) is highly determinant in egg quality (6, 8-11).

DISCUSSION

Ovarian follicles can be considered as functional units of the female reproductive system as well as ovaries. In a heathy female reproductive cycle, those follicles are under the influence of many neural, neuroendocrine, endocrine, paracrine / autocrine control mechanisms for obtaining a healthy completed ovulation process. (3, 12). In addition to these effects, the bi-directional interaction between the oocyte and the surrounding somatic cells determines the fate of the developing oocyte as well as the follicle function. In fact, besides the effect of cytoplasm and molecular system functioning of the oocyte on complete progression of embryogenesis steps, bi-directional communication between the oocyte and surrounding cells have been expounded as ascendant determinants at these durations (13). Studies examining these complicated interactions share that oocyte secretion factors play a key role in determining the fate of oocytes as a result of their effects on the cumulus cells (8, 9).

The primary effect of oocyte on follicle development and differentiation is based on its specific factors. Among these factors, Growth Differentiation Factor - 9 (GDF-9) and Bone Morphogenetic Factor - 15 (also known as BMP-15, GDF-9B), which are members of the family of Transforming Growth Factor - Beta (TGF-β), are of great importance. (14). TGF-β is the largest family of extracellular protein groups found in mammals. Proteins of this group bind to the transmembrane type-1 and type-2 serine threonine kinase receptors after synthesis, leading to activation of intracellular signal cascades (such as SMADs). This pathway can be effective in many physiological and pathophysiological processes (15). Especially in the last decade, many important studies on BMP system, mainly on rats, have been shared in the literature. However, the synthesis of BMP molecules between species varies. For example; While BMP4 and BMP7 are frequently encountered in theca and stoma cells in rats (16), synthesis of both molecules (BMP4, BMP7) occurs only in human oocyte structure. (17). GDF-9 and BMP-15, which are one of the the largest subgroups of TGF-β family and synthesized by oocytes, are also referred to as osteoinductive factors due to their stimulating effects on bone and cartilage production (3, 18). In modern terminology, a subgroup of BMP-15 and GDF-9 molecules is found under the heading BMP (3). This connection between the somatic cells and the signal molecules provided by the oocyte plays a role in many critical functions of the early stages of follicle development, such as the migration of germ cells and the complete completion of the early stages of ovarian development. (1, 19, 20).

For the first time in 1959, the effect of oocyte on follicle development was investigated on the rabbit model by Falck et al. In this study, the inhibition of luteinization of the oocyte cells placed in the ectopic area was demonstrated. The datas obtained from this research are considered as the first example showing the controlling role of oocyte on follicle development. (21). Numerous studies conducted over the years have shown that the key mechanisms of action of molecules synthesized by oocytes play a role in controlling the follicle development of the oocyte. Research results have shown that molecules synthesized by oocytes have a major impacts on healthy egg development through the interaction of somatic cells surrounding the oocyte (22-26). The complex relationship between oocyte and surrounding cumulus cells continues to attract great attention for many women with infertility and ovarian dysfunction complaints who resort to assisted reproductive techniques with the hope of finding solutions.

This close relationship, which is known to work in two ways, is also important in female fertility. Efficient interaction between oocyte and surrounding cells is effective in many stages from oocyte adequacy to a healthy embryo. GDF-9 and BMP-15 molecules, which play a major role in this interaction, play an important role in the interaction between oocyte and cumulus cells and have an effect on oocyte cytoplasmic - nuclear maturation processes, successful fertilization and healthy embryo production (13, 27). In many studies on GDF-9 and BMP-15 factors, the relationship between both factors and fertility was shared in different experimental models and in humans (13-15).

TGF-β superfamily signaling molecules are known to act with type-1 and type-2 serine / threonine kinase receptors located in the transmembranal region. This interaction results in phosphorylation of Sma- and Mad-related protein transcription factors (28). There are 5 type-2 receptors (BMPR2, ACVR2A, ACVR2B, TβR2 and AMHR2) in total, while 7 type-1 receptors (ALK1-7), also known as activin receptor-like kinases, are known. All receptors have a common structure: extracellular domain (N-terminal), transmembranal domain and intracellular domain (C-terminal) showing serine threonine kinase activity. Each ligand of the TGF-β superfamily can bind to the N-terminal extracellular domain of different combinations of type-1 and type-2 receptors to activate intracellular signaling complexes (29). n the light of the shared data, phosphorylation of SMAD 1-8 transcription factors occurs as a result of binding of TGF-β superfamily signal molecules to type-1 and type-2 receptors in standard pathways. In general opinion; The presence of a pathway leading to the connection of two different ligand - receptor complexes is accepted. For the first point of view: BMP group members progress with SMAD1,5,8 activated by ALK2, ALK3 and ALK6 receptors bound by AMH and some growth and development factors (GDF). In the second pathway, SMAD2,3 transcription factors are activated by stimulation of ALK4, ALK5 and / or ALK7 receptors by TGF-β and activins. (30). It is accepted that BMP group members influence SMAD 1,5,8 transcription factors. In addition, there are publications on the pathways independent of SMAD transcription factors. Mitogen-interacting protein kinases (MAPK) are thought to be the major factor in the SMAD independent pathways of the BMP family. (31). In data presented in the literature, the GDF-9 factor is mainly mediated through ALK-5 (32, 33) and BMP-R2 (34, 35) receptors; It is known that BMP-15 molecule acts with ALK-6 and BMP-R2 receptors (3, 15).

In the first steps of the folliculogenesis process, oocytes are surrounded by granulosa cells. These cells are the first cells that provide physiological support to the developing oocyte (36). In the first stages of development, granulosa cells undergo a series of cyto-differentiation processes to provide the support needed by the oocyte. From the formation of primordial follicles to the pre-antral stage, granulosa cells are formed. Many hormones and growth factors are involved in this process (37). Formation of granulosa cells is critical for processes such as antral follicle formation, oocyte development halting during meiosis. At this stage, granulosa cells are differentiated into two different cell groups in humans and other mammals. The first group is the cumulus cells surrounding the oocyte, while the second group is composed of mural granulosa cells that encircle the follicle from outside and play a primarily steroididegenic role (25). Although cumulus cells contain many common genes together with granulosa cells, there are many unique transcriptomas specific to cumulus cells. This particular arrangement of cumulus cells plays an important role in the realization of many functions specific to these cells. For example, Slc38a3 (which encodes SLC38A3 protein, is involved in sodium-mediated neutral amino acid transport) and the Amh gene (effective in the synthesis of Anti-Müllerian hormone (AMH)) are more abundant in cumulus cells than granulosa cells. Secondary oocytes, polar bodies and cumulus cells, which are paused during the metaphase 2 stages of development, are found in the completed cumulus oocyte complex. Slc38a3 expression in the antral follicle structure is limited in the cumulus cells; In granulosa cells, however, it is present in lesser amounts or not at all. This difference in the cumulus cells located near the oocyte plays a role in the amino acid transition to the oocyte and in the cooperation between the two cells (cumulus cells - oocytes). Cytoplasmic protrusions of cumulus cells reach the oocyte through the sheath called zona pelusida. These protrusions are involved in the formation of gap junctions, which are of great importance in the interaction between cumulus cells and oocytes. With this connection, cumulus cells play an essential role in oocyte development (38). The special connection that plays a major role in the relationship between cumulus cells and surrounding somatic cells that allows the passage of small molecules (such as ions, metabolites, small signal molecules) (39). In humans, the most known effect in the connection between two cumulus cells in developing follicles is considered as connexin 43 (Cx43). However, connexin 37 (Cx37) is the primary structure in the connection between the cumulus cell and oocyte (38). It is known that the development of follicles containing oocytes is of great importance in female fertility. In addition, the role of somatic cells was shown to be influential in the arrest of oocyte in meiosis 1 until ovulation. Wigglesworth et al. showed that somatic cells played a major role in that arrest at the first meiotic stage until follicle and oocyte reached the desired maturity. They reported that cyclic guanosine monophosphate (cGMP) produced in somatic cells reached the oocyte through gap junctions and was effective in pausing the oocyte in meiosis (6). In a healthy oogenesis process, elevated levels of adenosine monophosphate (cAMP) in the oocyte play an essential role for expected arrest in meiosis (40). As the amount of Luteinizing Hormone (LH) secreted by the pituitary gland increases in later stages of development, cAMP phosphodiesterase (PDE3A) in the oocyte activates and reduces the amount of cAMP (41). This process initiates the first stages of meiosis in the oocyte. Prior to the LH peak, PDEA3 activity was inhibited by cGMP transmitted from cumulus cells through connections called gap junctions. cGMP is known to be secreted from both cumulus cells and mural granulosa cells in the follicle (42, 43).

In the light of this information, the effect of cumulus cells and granulosa cells was accepted in the meiotic arrest of the oocyte. In the study conducted by Wigglesworth et al., it was shared that the oocyte has played the main role. Oocyte-derived paracrine factors (Oocyte-derived paracrine factors (ODPFs)) were found to increase the expression of natriuretic peptide receptor 2 (Npr2) mRNA in cumulus cells, thereby controlling cGMP release by a series of reactions. This result suggests that the oocyte acts as a manager in the two-way interaction between oocytes and somatic cells (6).

GDF-9 and BMP-15 molecules can achieve the same effect on the same hormone by following different pathways. For example, the research results presented by Chang et al. shared the inhibitory activity of both GDF-9 and BMP-15 on progestreon with different pathways. According to the results of the research; The BMP-15 molecule inhibits progesterone production via steroidogenic acute regulatory protein (StAR) to prevent follicular luteinization. In contrast, the GDF-9 molecule acts on hypophysial gonadotropins to reduce progestreon levels. The rapid decrease observed in the level of both factors as a result of ovulation in the corpus luteum leads to an increase in StAR level and subsequent progesterone production (3).

Some of the effects of GDF-9 and BMP-15 molecules on oocyte development also proceed through the synthesis of essential compounds for oocyte metabolism. For example, in a study of Su et al. showed that the common effect of GDF-9 and BMP-15 molecules was affected by the biosynthesis of cholesterol in the cumulus cells and consequently provided the necessary metabolic support for oocyte maturation (20). Similar results were also shared with the research results of Sugiura et al. In the light of the research data, it is accepted that GDF-9 and BMP-15 molecules synthesized by oocytes ultimately affect the level of glycolysis in cumulus cells and thus play a major role in oocyte development (44).

One of the another effect of cumulus cells on folliculogenesis is formed by matrix components of cumulus oocyte complex (COC). Hyaluronic acid, an important component for COC, is concentrated in the matrix of the complex. Apart from endocrine system regulation in the control of hyaluronic acid level; GDF-9 and BMP-15 factors also play a role in autocrine and paracrine interaction (19). Hyaluronic acid synthase 2 (Has 2) is involved in the synthesis of hyaluronic acid, which is called the backbone of the matrix because of its great importance in the realization of matrix functions, and this enzyme level is controlled by LH. In the further stabilization of this structure, a complex protein network including versican, tumor necrosis factor stimulating gene - 6 protein (TSG-6), inter-α trypsin inhibitor, pentraxin 3 (PTX3) proteins is involved (3, 8, 19). GDF-9 and BMP-15 molecules are responsible for increasing the regulation of the associated genes, Has 2 and PTX 3, which are responsible for the expansion of cumulus cells with similar effect (3, 15).

In the light of the data presented, the effect of oocyte-secreted signaling molecules (mainly BMP-15 and GDF-9 molecules) on the architecture of ovarian physiology, as well as their effects on differentiation of granulosa cells, at all stages of oocyte maturation process, ovulation-luteinization stages and embryo quality also known to be involved in key processes of the female reproductive system (3, 8). Based on these results, it can be thought that abnormal synthesis of these factors may be associated with infertility and embryo implantation processes, PCOS, primary ovarian insufficiency (POI), endometriosis, which can be observed in female patients (25, 45-47).

Genetic approaches are of great importance in researches on the effects of GDF-9 and BMP-15 molecules on the female reproductive system. The BMP-15 gene is known to be located on the X chromosome and plays a major role in all subsequent stages of folliculogenesis starting from the primordial follicle stage (48). The gene responsible for coding the GDF-9 protein is located in the long (q) arm of chromosome 5. GDF-9 protein shows activity starting from primary follicle stage (49). Although GDF-9 and BMP-15 molecules contain very similar protein structures, they show similarities with their effects on the mechanism of action and ovarian functions.

CONCLUSION

Recent studies indicate that the communication between GDF-9 and BMP-15 is in a synergistic pattern and acts as the GDF-9 / BMP-15 heterodimer called cumulin (cumulin). Thus, this stimulation affects the functions of cumulus cells and ultimately plays a role in improving oocyte quality (15, 50). The signal molecules secreted by the oocyte affect the cumulus cells, especially the folliculogenesis process; they have been shown to be determinant in many key processes such as ovulation, fertilization and healthy embryo acquisition. However, there is still a need for planned scientific studies in larger groups for the use of signaling molecules of this process to increase the success rate of assisted reproductive techniques.

Conflict of interest

No conflict of interest was declared by the authors.

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