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REVIEW

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The insulin-like growth factor and its players: their functions, significance, and consequences in all aspects of ovarian physiology

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Abstract

Background: Insulin-like growth factor (IGF) has unique and well-known functions in female fertility, according to documents reporting improved yield of oocytes, reinforced quality of the embryo, and enhanced live births with simultaneous reduction of miscarriage. However, there is no detailed information on the bio-mechanisms linking such clinical differences.

Main body: IGF and its receptors are expressed in a variety of tissues in the reproductive system such as granulosa cells, oocytes, and theca cells. Hence, the development of female gametes may be directly regulated by IGF, thereby affecting gamete quality and so its competence for implantation. IGF is a central player in changing the fate of cells during survival and proliferation through the modulation of leading signaling pathways, including Jak/STAT, MAP kinase/ERK, and PI3K/Akt, and subsequent impacts on steroidogenesis and cell division.

Conclusion: The current review aims to scrutinize the performance of IGF to regulate the normal ovarian, and its impacts on cell signaling pathways and resulting alterations in steroidogenesis and cell proliferation. The function of IGF and its receptor has been reviewed in female fertility at both molecular and biochemical levels.

Keywords: Insulin growth factor (IGF), Ovary, Folliculogenesis

Background

Fertility and pregnancy refer to the process of releasing an oocyte, fertilizing it with sperm, implanting an embryo in the uterus, and, eventually, the growth of the embryo until birth. Each month, a number of oocytes begin to grow in fluid-filled sacs called follicles inside the ovaries. Ovulation is the process by which one of the oocytes is expelled from the follicle. Ovulation occurs about 2 weeks before menstruation begins. Following releasing of the oocyte from the ovary, the remaining compartments of the follicle become a cyst called the corpus luteum which begins to secrete a hormone that increases the thickness of the endometrium, thus preparing the uterus for the presence of a fertilized egg [1].

The effective and close bidirectional interactions of the oocyte with its neighboring cells, granulosa, during folliculogenesis are required for the later development of the embryo and pregnancy outcome. One of the pivotal functions of granulosa cells, relevant to oocyte competence, accompanied by cooperation with follicle-stimulating hormone (FSH) and its receptor (FSHR), is the estrogen biosynthesis from androgen precursors via the enzyme aromatase. The outcome of this cooperation has a fundamental role in ovarian functions, follicular development, and folliculogenesis, and female infertility can occur due to gene rearrangements, mutations, or aberrant protein production. Since the ovaries do not function, eggs do not mature and are not liberated from the ovaries [2, 3].

The performance of gonadotropins to regulate the granulosa cell ontogeny is well clarified, and the diverse

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fate of ovarian transplants under the stimulation of measurable gonadotropins indicates the existence of additional mechanisms of intraovarian modulation. According to the results of studies, intraovarian control is probably performed using topical steroid modulation. However, intraovarian peptides may also have the potential to locally modulate follicular growth. In this regard, there is much evidence of the activity of multiple growth factors. Among the potential ontogeny modulators of granulosa cells, insulin-like growth factors (IGF) seem to be a pivotal actor with unique functions. There is evidence that IGF function, in combination with gonadotropins such as FSH and luteinizing hormone (LH), has a synergistic effect on the promotion and proliferation of granulosa and theca cells [4].

Despite studies in this field, different results are found among the researches. This review summarizes the state of the science regarding new mechanism of dynamic control within the ovary in which IGFs can be a pivotal message and granulosa cell as their place to produce, receive, and act.

Main body

Follicle development from preantral to preovulatory stage

The follicular phase is the first step for menstrual cycle. Mechanisms regulating follicle development and growth are controlled by altering the ligand levels (growth factors and hormones). From an endocrine point of view, the mechanisms of central nervous system (CNS), anterior pituitary, and ovary cascade, regulate the folliculogenesis. In fact, gonadotropin-releasing hormone (GnRH) stimulates gonadotroph cells to produce pulsatile LH and FSH. Finally, these hormones regulate follicle development and growth [5–7].

Usually, the ovaries in the human beings express a prevailing follicle during each menstrual cycle, which leads to ovulation. The prevailing follicle in any cycle must completely and timely fulfill all processes of folliculogenesis. During these stages, the selected follicle resists all negative episodes that act to eradicate other follicles [5–7].

Oocyte support is the basic function of the follicle. At the time of the oocytes production, the ovarian follicles that surround the oocytes develop and transform from the primordial follicle into preovulatory follicles (folliculogenesis). The follicle contains primary oocytes by preovulatory stage, which is blocked in prophase meiosis 1. At the end of the preovulatory phase, the oocyte insists on meiosis and becomes a secondary oocyte, which is blocked in metaphase 2. This mechanism is influenced by the increase of LH hormone [7].

Within development of primary follicle, the granulosa cell communicates with the oocyte through channels made up of connexin proteins, causing dispersion of metabolites, ions, and other compounds, and has a direct effect on the process of folliculation, ovulation, and fertility [5–7]. One or more flattened granulosa cells exist in the primary follicle, which surround the oocyte in one layer, and then deformed to a cubic structure and express FSH receptors, which indicates the beginning of primary follicle development. FSH receptor expression stimuli include FSH, activin, cyclic adenosine monophosphate (cAMP), and TGF. The oocyte genome is also activated, and transcription of genes begins, and the primary paracrine messenger pathways are formed, which are essential for communication between the follicle cells and the oocyte [5–7].

The formation of a secondary follicle requires more granulosa cell accumulation, which forms several layers around the oocyte, accompanied by the transition of the stroma-like theca cells to construct two layers of external and internal theca cells. The receptors for hormone LH are expressed by the theca cells. The LH can trigger the synthesis of androgens from theca cells that are converted to estrogen via the granulosa cells and a series of biochemical changes and aromatization. As a result, estrogen levels increase [5–7]. Following the elevated FSH level, the antral follicles produce inhibin and estrogen, with negative feedback on FSH. The follicles with smaller number of FSH receptors are unable to grow more and will gradually degenerate. Eventually, only one follicle will survive, and it will be called the dominant follicle. This follicle grows rapidly, reaching 18 to 23 mm in diameter, to become a preovulatory follicle. Finally, after the final follicle is selected, a sudden increase of FSH and LH stimulates the cells of the various follicle components to induce messages that collectively lead to ovulation [7, 8].

An overview on the insulin-like growth factors (IGFs) functions in granulosa cells

There is evidence that IGF function, in combination with gonadotropins such as FSH and LH, has a synergistic effect on the proliferation and promotion of theca and granulosa cells. Based on animal studies, treatment with IGF and FSH increases the differentiation of granulosa cells in rat ovaries, while no alteration is seen in proliferation [9]. In contrast, the augmentation of IGF to rat follicles leads to an increase in both granulosa and theca cells [10]. Nevertheless, it is unclear whether IGF promotes cell proliferation directly via the IGF receptors expressed in them or whether it occurs indirectly by triggering granulosa cell-secreted secondary growth factors, thereby influencing the theca cells directly [10, 11]. IGF-mediated proliferation process of theca cell has been verified in ex vivo model of sheep, to the extent that

high IGF levels led to theca cell overgrowth [12]. This impact is validated in vitro, where IGF levels were utilized to assess the damaging effect on rat perinatal follicles, potentially due to stromal cell and theca growth and nutrient depletion [13]. IGF supplementation of the alginate-based growth medium containing bovine secondary follicles resulted in increased E2 synthesis. Furthermore, increased E2 production can maintain follicular structure and performance, leading in greater follicle growth [14] (Fig. 1).

Interestingly, metabolic disorders and elevated oxidative stress disturb the insulin-associated signaling within the ovary and can dysregulate the dynamics of the ovarian function through the impair the ovarian reserve, survival, and quality of the eggs [15]. In women with PCOS, insulin resistance with compensatory hyperinsulinemia induces androgen overproduction in the ovaries, which can lead to hyperandrogenism. Insulin acts on ovarian androgen production via IGF type 1 receptors [16].

Expression of IGF in primates and rodents

Based on previous findings, the FSH as an essential agent has a role to generate the follicles (before ovulation) and differentiate the granulosa cells, but the presence of FSH alone is not enough, and other factors are necessary for growth and differentiation. Some studies have shown that in rodents that lack FSH or FSH receptors, follicular progression is blocked beyond the preantral stage [3, 4]. A block exists on the production of preovulatory follicle in mice with IGF-1 deficiency [5], highlighting a need for active IGF system in the maturation of follicle until the phase of pre-ovulation. The stimulation of CYP19A1 secretion via FSH requires the activity of IGF-1 receptor (IGF-1R) in humans and rodents [6, 7]. Hence, the follicular transition from preantral stage to preovulatory phase needs the IGF and FSH signaling pathways. However, detailed information is not available on how these processes are regulated by FSH and IGFs, especially in humans.

Humans and rodents have significant differences in the IGF system of their ovaries. Granulosa cells in the rodents are more responsible for the synthesis of IGF-1 [8]. Conversely, the granulosa cells in human have higher levels of IGF-2 mRNA, but not detectable IGF-1 mRNA [7, 9, 10]. As a result, the follicular fluid of prevailing follicles in humans contains IGF-2 up to 10 times higher than IGF-1 [11, 12]. Greater intrafollicular IGF-2 levels can explain why a 1.6-fold elevation in intrafollicular IGF-1 lacks any impact on follicular maturation in primates [13]. However in the 3-D culture medium, adding IGF-1 can enhance the production of mature oocytes, and injection of IGF-1 before ovulation induction will increase the count of retrieved oocytes [17].

The positive correlation of intrafollicular IGF-2 levels with oocyte maturation and follicular maturation confirms the essential function of IGF-2 in the regulation of follicular growth in humans [12, 14, 15]. Based on this evidence, the IGF-2 has a pivotal function in the IGF system in the granulosa cells in humans. Previous observations also highlighted the stimulatory role of IGF-2 in the proliferation [18] and expression of progesterone and estradiol in luteinized granulosa cells in humans [19, 20]. The IGF-2 in primates can enhance the steroidogenesis and accelerate the synthesis of vascular endothelial growth factor in the preovulatory follicles [19, 21, 22]. The aggregation of progesterone and estradiol is triggered by the IGF-2 in granulosa cells of small (2–7 mm) and preovulatory follicles, while the IGF-2 does not impact on the proliferation [22]. The axial function of IGF-2 in follicular maturation through autocrine actions is confirmed via preferential gene expression and

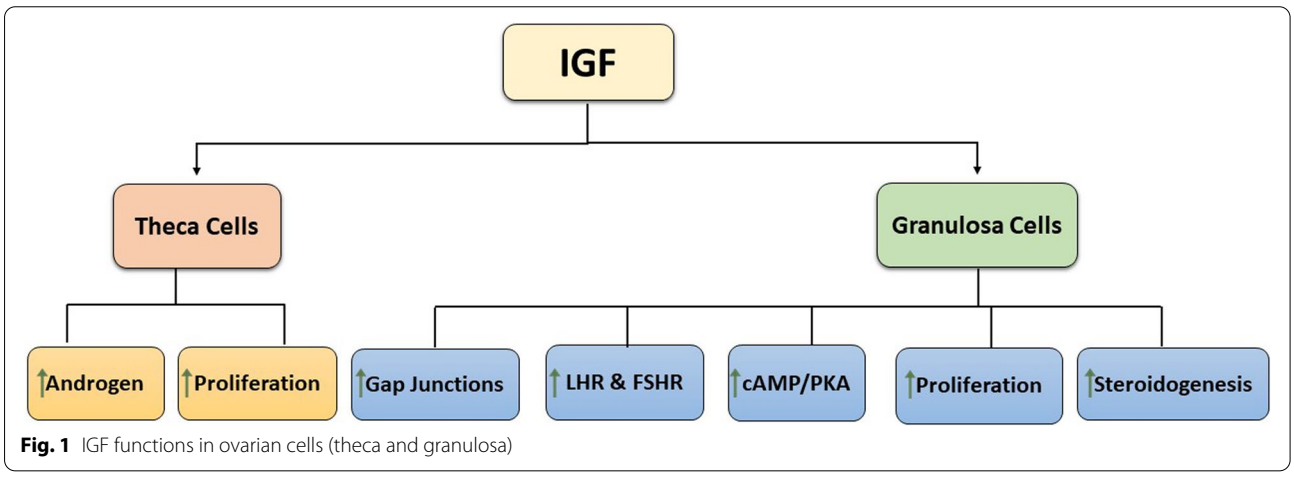

Fig. 1 IGF functions in ovarian cells (theca and granulosa)

IGF-2 production by prevailing follicle granulosa cells in humans [9].

Interaction of IGF with FSH and LH

Simultaneous effect of LH and FSH on their gonadotropin supplementation receptors reduces signaling, which is essential for differentiation, proliferation, and steroidogenesis, and the two signals increase E2 and P4 production through cAMP and PKA. The two LHR and FSHR are receptors associated with G protein, which transmit intracellular cascade through cAMP adenylate cyclase activity, and PKA activation, after which the CREB transcription factor is phosphorylated. cAMP response element-binding protein (CREB) transcribes various genes by binding to cAMP in DNA (including aromatase and sex steroids precursor). In the granulosa cells, the interaction of GH with GHR modulates the function of FSH, as well as induces LHR [9, 23]. Such LHR generation is the major indicator for the differentiation of granulosa cells and theca cells, can be affected by the ovarian induction of IGF, while proliferating granulosa cells, and acts as a paracrine. IGF can alter and enhance the sensitivity of theca or granulosa cells to stimulation of gonadotropin, and thus regulate the secretion of sex steroid, and liberation into follicles, finally leading to cell growth enhancement s paracrine/autocrine steroidization factors. According to two-cell theory, steroidogenesis is regulated in the ovary based on dependent and independent procedures, so that the theca cells are triggered by LH to generate androgens that are converted to diverse estrogens due to the expressed aromatase in the granulosa cells [14]. Interestingly, investigations on females with diminished ovarian reserve have shown that the supplementation with IGF increases LHR, FSHR, and GHR expression in isolated human granulosa cells. IGF supports the maturation process of luteinization because of increasing LHR density and decreasing preovulatory FSHR expression. Cytosolic aggregation of Camp and PKA signaling activation can be initiated by the simultaneous effect of GHR and IGFR, which possibly affects the gonadotropin response [18, 19].

IGF-1, like GH, triggers the theca and granulosa cell differentiation and proliferation via the enhancement of the FSH function in granulosa cells. It has been shown that IGFR is absolutely necessary to induce PI3K/Akt pathway and differentiate granulosa cells by FSH [20, 21, 24, 25]. In a study by Zhao et al., the primary follicles were triggered by IGF-1 through the measurement of DNA increase in follicular cells. In their study, IGF-1-cultured cells have preferred morphology because of elevated count of junctions between the granulosa cells and theca cells as well as the granulosa cells and oocytes. Moreover, in this study, the availability of IGF-1 and FSH enhanced the growth of preantral follicles following the FSHR activation [26]. Animal studies using gene knockouts have implied a more direct and greater impact of IGF than GH on reproduction [22]. In this context, female rats with completely sterile IGF-1R knockout had no antral follicles and exhibited a decrease up to 90% in the serum E2 level [27]. Inactivating IGF-R or IGF-1 by knockout is not mostly compatible with life. The knockout rat by IGF-1 significantly reduced FSH receptor expression, thereby reducing aromatase expression and E2 secretion, which leads to infertility in both genders in some cases. Under in vitro condition, Magalhaes-Padiha et al. showed greater growth of triggered preantral follicles by IGF-1, probably because of cell proliferation, since IGF-1 can enhance the granulosa cell nuclear maturation in preantral follicle [22].

The expression of gonadotropin receptor might be regulated by IGF signaling. IGFR and FSH in combination can result in different intracellular signaling pathways like cAMP formation, thereby triggering CREB and PKA alongside induction of PI3K/Akt and MAPK/ERK1/2 pathways. Such signaling mechanisms elevate the activity of aromatase and production of LHR. IGF-1 or 2 and FSH act together and interact with corresponding receptors to create aromatase activity. IGF-1 exerts unique and stimulatory influences on the granulosa cells and according to reports increases the production of steroidogenic CYP19A1, 3-beta-hydroxysteroid dehydrogenase, CYP11A1, and the expression of IGF-1R and FSHR. Considering to results, IGF-1 activates steroidogenic regulatory genes and apoptosis by activating the PI3K/Akt signaling in the bovine granulosa cell. IGF-1/2 can both trigger secretion of sex steroids implicated in the growth of follicles [14, 28–31].

The combination of IGF-1 and LH enhances P granulosa cells and has a regulatory impact on the production of E2 in luteal cells. Significantly, IGF-1R plays an important role to increase FSH-stimulated StAR expression, as an essential factor for cholesterol transport to mitochondria, which is the first stair to produce sex steroids and pregnenolone. In addition, according to reports, great IGF level impedes the performance of anti-Mullerian hormone (AMHAMH) that is exclusively secreted in the gonadal tissues. AMH is transforming growth factor beta (TGF-B) belonging to the family growth hormone, which decreases growth and performance of antral and preantral follicles in mammals. This issue may clear the performance of IGF to regulate follicle selection and growth. Based on these results, the IGF is a prominent actor to regulate the growth of follicle via the proliferation and differentiation of granulosa cells, production of steroid, and gonadotropin-stimulating activity. Table 1 summarizes these associated effects [14, 31–33].

Table 1 The involvement of IGF in ovarian physiology and infertility

Author and ref.	Year	Model	Effects mediated by IGF
Dri et al. [15]	2021	Metabolic disorder	Impaired the ovarian reserve, survival, and quality of the eggs
Firmansyah et al. [16]	2022	Polycystic ovarian syndrome	Insulin resistance with compensatory hyperinsulinemia-induced androgen overproduction
Dai et al. [17]	2022	Three-dimensional culture of ovarian preantral follicles	Three-dimensional culture of ovarian preantral follicles
Walters et al. [34]	2006	Bovine antral follicles	Increased size of follicle
			Increased production of estradiol
			Increased health of oocytes
Mani et al. [29]	2010	Bovine granulosa cells	Increased rate of proliferation
			Increases production of estradiol
			Increased production of HSD3B1, CYP11A1, BAX, CYP19A1, FSHR, and IGF1R
Zhou et al. [35]	2005	Caprine preantral follicles	Increased rate of proliferation
			Increased survival rate of preantral follicle
Magalhaes-Padilha et al. [22]	2012	Caprine preantral follicles	Increased rate of normal follicles
			Increase rate of antrum formation
			Increased meiotic resumption in rates
Baumgarten et al. [21]	2014	Cumulus granulosa cell in human	Increased rate of proliferation
			Increased rate of differentiation
			PI3K/AKT mediated
Zhou et al. [36]	1997	Ovaries in mice	Increased production of granulosa cell FSHR
Hastie et al. [37]	2006	Ovine ovary	Increased IGF-2 expression in large follicles
			Decreased IGF-2 expression in atretic follicles
			Increased IGFBP-5 expression in atretic follicles
Campbell et al. [25]	1995	Ovine and bovine granulosa cells	Increased rate of cell proliferation
			Increased production of estradiol
Guthrie et al. [38]	1998	Granulosa cell culture of pig	Decreased induction of spontaneous apoptosis
Zhao et al. [26]	2001	Preantral follicle in rats	Increased diameter of follicle
			Promoted morphology of follicle
			Increased cortical granules

Expression, regulation, and secretion of IGF

The GHR-GH interaction activates conventional and unconventional signaling pathways. In conventional one, the pituitary gland triggers hepatic GH cells to liberate GHR into circulation via transcription factors induced by IGF, GH, and GHR. The interactions of ligand receptor lead to adsorption and autophosphorylation in the GHR cytoplasmic domain, and the JAK2/GHR complex subsequently phosphorylates STAT molecules, modifies gene transcription, and significantly results in influences on the cell proliferation. STAT5b can more significantly and directly regulate the production of IGF-1 and also mediate the production of GH-induced IGF-1 in the granulosa cells of rats. Unconventional signaling usually has no dependence on JAK2 and includes using non-receptor tyrosine kinases, CY phospholipase stimulation, and organelle cytosolic calcium flow.

It is unclear which system or hormone has significance since the ovarian performance is affected by systemic IGF and GH, GH-independent IGF, or GH-induced peripheral IGF. Nevertheless, the GH-IGF axis as a pivotal growth factor is implicated in folliculogenesis. The IGF-1 mRNA expression is increased by the GH in the precursor follicles of rats, leading to the IGF-1 synthesis from sheep granulosa cell. In addition, IGFBP-3 counteracts anti-apoptotic influence of GH, underlining the elevation of locally IGF-1 synthesis by the exogenous GH and subsequently resulting in increased survival of follicle. As a result, the ovarian GH-IGF interaction is complex because it is used by granulosa cells in autocrine and paracrine procedures and needs no stimulation of GH [14, 39–43].

Systemic IGF contains IGF-1 and -2, corresponding receptors, and six IGFBPs, which regulate the bioavailability of IGF. The paracrine synthesis of such members is of great significance, while sheep folliculogenesis, and peripheral IGF, elevates due to the decrease of binding proteins expression. While IGF-2R and IGFBP-5

increase, IGF-2 expression decreases in atretic follicles. Based on these findings, reduced peripheral bioavailability of IGF leads to follicle elimination, and the synthesis of IGF is pivotal for the survival of follicles. Ovarian IGF levels are also related to the folliculogenesis stage. Hence, there is low level of IGF in theca cells resulting from follicles medium in size, also in neonatal ova, while IGF-2 expression is high in the isolated granulosa cells from antral follicles. Thus, apparently, a dynamic performance can be seen for the activity of IGF and GH because of follicle maturation and growth [37, 44–51].

IGF signaling pathway in granulosa cells during human ovarian follicle development

Despite numerous differences in the reproductive systems of men and women, the behavior versus gonadotropins, such as the synthesis and secretion of sex steroids and cell proliferation, is highly similar in both systems. According to studies, it is possible that any effect of IGF applies its effect by affecting the synthesis pathways, secretion of sex steroids and cell proliferation, and enhancing steroidogenesis, followed by the synthesis of products that exert their specific influences on the cell survival and proliferation [14].

The cAMP/PKA pathway is triggered by the FSH, because of stimulating FSHR, and subsequently, CREB mediates the transcription of diverse genes. Such a trend increases the production of proteins related to steroidogenesis like StAR, aromatase, and LHR [52, 53]. CREB directly regulates the aromatase gene [54], which produces estrogens by converting androgens, whereas the StAR causes the mitochondrial transport of cholesterol for the synthesis of testosterone, P4 and E2, in steroid cells. Besides these events, activation of FSHR and LHR GPCR can lead to other main cell signaling events, which affect steroidogenesis. One of these pathways is pivotal route of PI3K/Akt cascade, as is an obvious regulatory mechanism for cell survival, proliferation, and metabolism [55], which is directly stimulated via FSHR, after directly interacting with adapter proteins of 14-3-3τ [56]. LH can also stimulate the PI3K/Akt pathway, and its activity is increased due to FSH [57, 58].

The multifunctional signaling center of Akt regulates cell proliferation, metabolism, and mortality [14, 59]. Akt is activated by FSH, which is needed to produce α-inhibin, CYP19, 3β-HSD, and LHR [60]. Evidence suggests the production of FSHR-induced aromatase needed for activation of PI3K/Akt and cAMP/PKA mechanisms [14, 61]. Recent studies on granulosa cells in rodent and human confirmed the intact IGF-1R signaling needed for FSHR-induced Akt phosphorylation [27, 60]. It also appears that the FSHR function necessarily requires PI3K/Akt signaling and is supported by the stimulation of IGF-IGFR Akt. Based on multiple investigations, the FSH is unable to increase the expression of LHR, CYP19, and STAR in exposure to the IGF inhibitors [60]. Intracellular IGF signaling connects to FSHR and LHR signaling by setting PI3K/Akt cascade. Proinsulin and IGF have almost the same structure, with both IGFR and insulin (IR) receptors binding. The IGF-IR interaction results in phosphorylation and adsorption of insulin receptor 1 (IRS1) or insulin receptor 2 (IRS2) by activating PI3K and then Akt [14].

One of the advantages of triggered IGF in PLC/PKC pathway is the enhancement of CREB-induced transcription. IGFR can directly activate Cγ (PLCγ), followed by phospholipid hydrolysis to produce diacylglycerol, or DAG, and inositol-4,4,4-triphosphate, or IP3 [43]. IP3 increases the cytosolic calcium flux of the organelles, and DAG also activates PKC. PKC can directly stimulate CREB-mediated gene transcription such as StAR and/or aromatase [62]. According to studies, PKC stimulation increases the expression of StAR and leads to production of progesterone in granulosa cells [62, 63]. It is noteworthy that FSHR can activate the PKC pathway, which occurs through the formation of IP3 and DAG by FSHR, followed by the cumulus cell proliferation and the oocyte meiotic maturation [64], which indicates the convergence between IGF signaling and gonadotropin GPCRs. The connection between these signaling systems in part justifies ex vivo or in vitro physiological influences.

When MAPK/ERK1/2 and p38 MAPK signaling pathways begin, the result is the common denominator of signaling pathways, which alter gene expression, metabolism, and cell proliferation [43]. The function of ERK1/2 leads to an increase in cellular mitogenic messages, which is indirectly triggered by PKA through the increased intracellular calcium induced by PLC/PKC events, both of which, according to the description, have been stimulated by IGF activity [53, 65]. The p38 MAPK in the granulosa cells is implicated in production of pro-apoptotic signals [65]. Nevertheless, there is limited information about the behavior of MAPK/ERK1/2 pathway in steroidogenesis [53, 66]. However, in some studies, stimulation of IGF-mediated progesterone production in the ovarian cells in human depends on p38 MAPK and MAPK/ERK1/2 pathways [67]. The PI3K/Akt and pro-MAPK/ERK1/2 signaling is triggered by IGF, and the activation of IGF-1R occurs in mass granulosa cells [21] (Fig. 2).

Conclusion

Ovarian follicles, along with the oocyte and supporting cells, determine the female reproductive cycle and thus fertility. Endogenous variables, auto-, para-, and endocrine mechanisms, all impact ovarian function. The main function of granulosa cells, relevant to oocyte

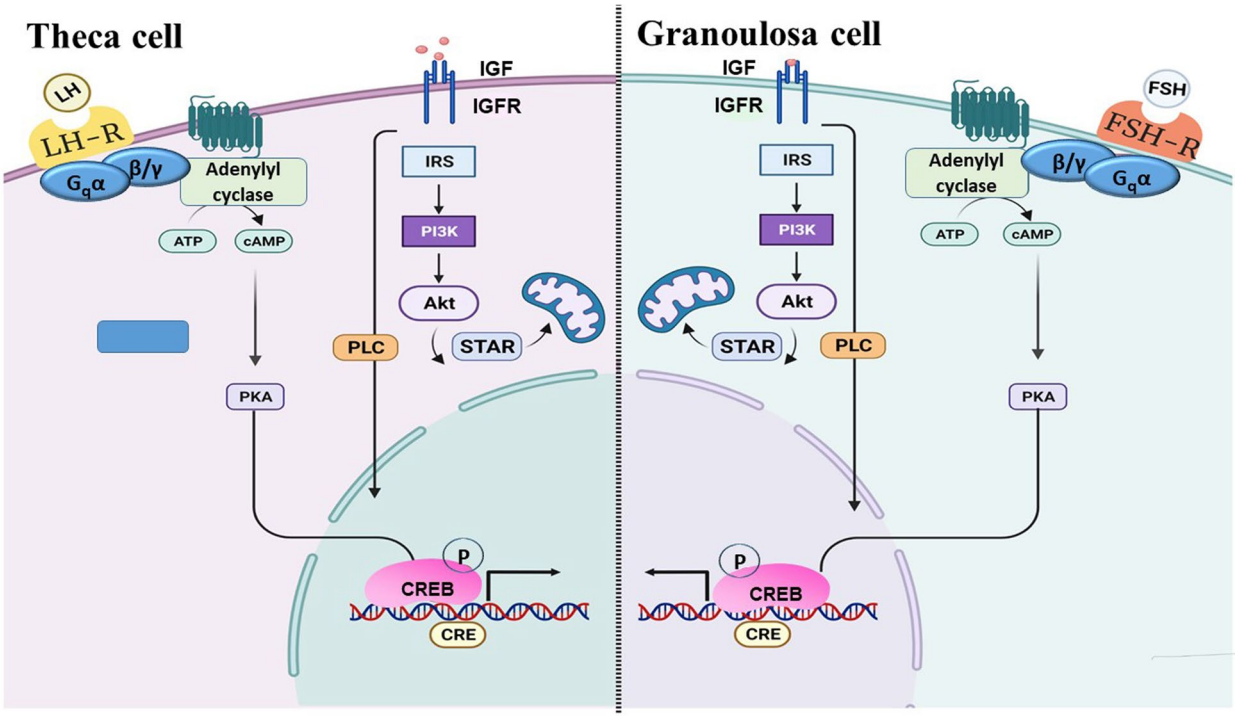

Fig. 2 IGF signaling in theca and granulosa cells. Created with BioRender.com

development and ovarian functions, is steroidogenesis, for which different signaling pathways, including Jak/STAT, PI3K/Akt, and pro-MAPK/ERK1/2, regulate this fundamental process, all of which have a shared modulator named IGF. IGF and its receptor are found in reproductive tissues and cells and may directly govern gamete development and influence its quality.

Abbreviations

FSH: Follicle-stimulating hormone; CNS: Central nervous system; GnRH: Gonadotropin-releasing hormone; cAMP: Cyclic adenosine monophosphate; IGF: Insulin-like growth factors; CREB: cAMP response element-binding protein; hCG: Human chorionic gonadotropin; PI3K/Akt: Phosphatidylinositol 3-kinase/protein kinase B; MAPK/ERK1: Mitogen-activated protein kinase/extracellular signal-regulated kinases; CYP19A1: Cytochrome P450 family 19 subfamily A member 1.

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Authors' contributions

PA and AA contributed to the design of the study, interpretation of data, and drafted the manuscript. EH was involved in editing the manuscript and approved the final submission. MB was involved in revising the manuscript and approved the final submission. All authors reviewed the final manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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