Circular RNAs in Mammalian Ovaries

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Circular RNAs (circRNAs) are an abundant class of endogenous non-coding RNAs (ncRNAs) generated from exonic, intronic, or untranslated regions of protein-coding genes or intergenic regions. The diverse, stable, and specific expression patterns of circRNAs and their possible functions through cis/trans regulation and protein-coding mechanisms make circRNA a research hotspot in various biological and pathological processes. It also shows practical value as biomarkers, diagnostic indicators, and therapeutic targets.

circRNAs ovary follicle development

1. Background

The genome-wide profiles of ovarian circular RNAs (circRNAs) were mainly reported in humans, mice, pigs, and goats. In humans, circRNA studies have been focused on pathological examination of ovarian cancer, polycystic ovarian syndrome (PCOS), and ageing. Luckily, studies in animals provided more knowledge regarding ovary growth, changes in estrus, as well as follicle development, and atresia. Comparisons between different reproductive performances and breeds were also reported (**Figure 1**). Here, the researchers reviewed the global studies of each field first and summarized the proven function of individual circRNAs in **Table 1**.

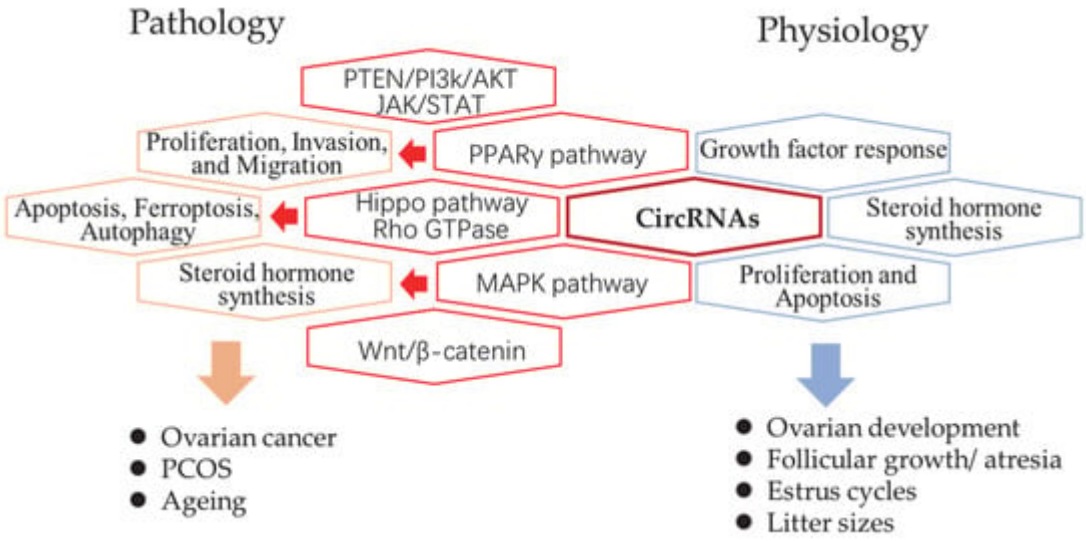

Figure 1. The summary of circRNAs related pathways in pathology and physiology processes of the mammalian ovary. The revealed circRNA-related signaling pathways (red hexagon) and their related biological processes in pathology (orange hexagon) and physiology (blue hexagon).

2. CircRNAs in Ovarian Cancer

CircRNAs in ovarian dysfunction attracted close attention due to their tight interaction with miRNAs. In 2015, a comprehensive assessment compared circRNA levels across several normal and cancerous tissues, including ovarian cancer, and discovered a global reduction in circular RNA abundance in cancer compared to normal tissues, therefore suggesting a negative correlation between circular RNA abundance and cell proliferation [1]. Ning et al. also performed circRNA-sequencing in epithelial ovarian cancer (EOC) and normal ovarian tissues and identified 4388 differently expressed circRNAs [2]. Almost simultaneously, Teng et al. analyzed circRNA expression profiles in EOC and normal ovarian tissues, in which the expressions of 5551 circRNAs were differentially expressed [3]. Gao et al. sequenced and compared circRNA in high-grade serous ovarian cancer (HGSOC) specimens and normal ovarian tissues. Among 710 differentially expressed circRNAs, circRNA1656 was confirmed down-regulated in HGSOC tissues and ovarian cancer cell lines [4]. Furthermore, Zhao et al. investigated the expression of circRNAs in paired cisplatin-sensitive and cisplatin-resistant tissues of ovarian cancer by microarray analysis and reported 339 aberrantly expressed circRNAs [5]. Cdr1as was proven to sensitize ovarian cancer to cisplatin by regulating the miR-1270/SCAI axis. Based on these high-throughput studies, a detailed functional analysis in single-circRNA level was reported in continuance, which showed great potential as biomarkers for ovarian cancer.

3. CircRNAs in PCOS

PCOS is the most common endocrine disorder in women of reproductive age. To reveal the functions of circRNAs in the development of PCOS, circRNA profiles from cumulus cells and follicle fluid were assessed, respectively. Che et al. determined 311 increased and 721 decreased circRNAs in cumulus cells from PCOS compared to control participants who underwent IVF using microarray [6]. With these data, Li et al. further combined data of microRNA and mRNA in PCOS to predict circRNAs which may serve as RBP regulators or miRNA sponges [7]. This research conducted a weighted correlation network analysis (WGCNA) to mine PCOS-associated circRNA-miRNA-gene networks and circRNA-RNA binding protein (RBP) networks. Moreover, Wang et al. performed a delicate study by sequencing ribosomal RNA-depleted total RNA from exosomes of follicle fluids. They identified 167 up-regulated and 245 down-regulated circRNAs in PCOS patients [8].

4. CircRNAs during Maternal Ageing

The decline of female reproductive capacity with age, termed ovarian senescence, results in a gradual reduction in the quantity and quality of oocytes. Cheng et al. first compared circRNAs in GCs from in vitro fertilization (IVF) patients with young (≤30) and advanced (≥38) ages using human circRNA microarrays. This research revealed 46 up-regulated and 11 down-regulated circRNAs in aged samples. Later, Cai et al. compared circRNA expression profiles between healthy ovarian cortex from young (25–28) and ageing (44–46) groups and identified 194 up-regulated and 207 down-regulated circRNAs enriched in oxidation-reduction, steroid hormone biosynthesis, and insulin secretion pathways, during ageing [9].

5. CircRNAs and Ovary Development

CircRNA profiles during ovarian development, estrus cycles, and follicular growth were explored mainly using large animals such as pigs and goats. CircRNA landscape in adult and neonatal ovaries was first examined and compared in mouse ovarian tissue using high-throughput sequencing. Estrogen signaling was found to be the most significant pathway that up-regulates in adult ovaries [10]. In pigs, more specifically, ovarian circRNA profiles at three developmental stages (0, 30, and 240 days after birth) were identified and compared with other eight tissues (heart, liver, spleen, lung, kidney, testis, skeletal muscle, and fat). This research revealed ovary-specific/enhanced circRNAs and provided valuable resources for ovarian circRNA study [11]. In addition, the profiles of ovarian circRNAs across pre-, in-, and post-pubertal stages were reported. The research identified 631 stage-specific circRNAs generated from genes involved in steroid biosynthesis, progesterone-mediated oocyte maturation, and autophagy [12].

Regarding the estrus cycle, Liu et al. analyzed the circRNA profiles of Yunshang black goat ovarian tissues among high and low fecundity groups in the follicular phase and luteal phase, and conclude that circRNAs play a key role in both the prolificacy trait and transformation of the follicular phase to the luteal phase in the estrus cycle [13]. At the follicle level, Xu et al. reported 290 differentially expressed circRNAs between large (diameter > 4 mm) and small (diameter < 4 mm) follicles in Dazu black goats. This research also simultaneously generated profiles of mRNAs, long non-coding RNAs (lncRNAs), and microRNAs (miRNAs), creating a good start and helpful reference for integrated ncRNA study during follicle development [14]. To explore the roles of circRNA in growth factors response, Fu et al. [15] profiled circRNAs of bovine cumulus cells treated with or without growth factors (bone morphogenetic protein 15 (BMP15), growth differentiation factor 9 (GDF9), and BMP15+GDF9). This research suggested that GDF9 induced a more significant circRNA shift than BMP15, and BMP15 may play a role in assisting GDF9. Changed circRNAs were involved in pathways, including thyroid hormone signaling ubiquinone and terpenoid-quinones, which affected the proliferation and apoptosis of CCs.

6. CircRNAs and Follicular Atresia

circRNA profiles in healthy and atretic antral follicles were first deep sequenced by Guo et al., and 192 circRNAs were reported to be differentially expressed during the atresia process [16]. Based on this research, detailed functions of circRNAs serving as miRNA sponges in the connective tissue growth factor (CTGF) regulatory pathway [16], inhibin–activin balance [17], and cell viability [18] have been reported. It is widely accepted that GCs play a significant role in the follicular development and atresia processes, thus determining the fate of follicles [19]. Therefore, Meng et al. performed a more specific study to profile circRNAs generated from porcine granulosa cells isolated from healthy atretic antral follicles [20], which is a perfect supplement and advancement to the earlier research. This research further confirmed circRNA functions in oxidative stress inhibition and cell apoptosis pathways.

7. CircRNA and High Reproductive Traits

To explore the circRNA functions in reproductive performance, the circRNA function in litter size was investigated in pigs, goats, and sheep. In pigs, circRNA profiles of ovaries from large and small litter sizes groups were performed by Xu et al. [21], and 56 down-regulated and 54 up-regulated circRNAs were observed in the large litter sizes group. Parallelly, a similar study of ovaries from MeiShan (local breed with large litter) and Large White pigs was performed and revealed 37 up-regulated and 48 down-regulated circRNAs [22]. The pre-ovulatory follicles of the Boer goat and Macheng black goat, which is highly fertile with a twin and multiparous lamb rate of 70%, were compared [23]. This research not only examined goat ovarian circRNA profile for the first time but also identified 37 differentially expressed circRNAs in high litter size breeds. A more delicate analysis was performed in ovarian tissues from both follicular and luteal phases of Harper sheep that were either consecutive monotocous or polytomous. Totals of 183 and 34 differentially expressed circRNAs were identified in h follicular and luteal phases, respectively, and TGF-β and thyroid hormone signaling were highlighted to affect the litter size through circRNAs [24]. However, all these studies suggested that in the ovary, the number of circRNAs that varies between breeds or reproductive performance is relatively low. During the follicle cycle, destined ovarian follicles grow rapidly, which is based on the rapid division of granulosa cells. Therefore, such observations agree with the speculation of a negative correlation between circRNA levels and cell division rate in cancer studies. Moreover, an interesting study in rats revealed potential functions of circRNAs in continuous light-induced ovarian dysfunction, which provided novel clues of circRNA shift in response to temporary environmental changes [25].

Table 1. Circular RNAs and their role in the different ovaries.

Species	Tissue	CircRNA	Target miRNA/Gene/Protein	Function	Ref.
human	OC	Cdr1as	miR-1270/SCAI	sensitizes ovarian cancer to cisplatin	[5]
		circ-ITCH	miR-145/RASA1	inhibit tumour progression	[26]
		has_circ_0051240	miR-637/KLK4	suppresses cell proliferation, migration, and invasion	[27]
		circEPSTI1	miR-942	inhibit cell growth and invasion, induces apoptosis	[28]
		circRNA CDR1	miR-135b-5p/HIF1AN	decreasing the occurrence and progression of ovarian cancer	[29]
		circLARP4		down-regulated in cancerous ovarian cells	[30]
		hsa_circ_0007444	miR-23a-3p/DICER1		[31]
		circPLEKHM3	miR-320a/SMG1	exacerbated the effect of curcumin on ovarian cancer cell proliferation and apoptosis, as well as the anti-tumour effect	[32]

Species	Tissue	CircRNA	Target miRNA/Gene/Protein	Function	Ref.
		circABCB10	miR-1271	promotes cell proliferation and invasion but inhibits apoptosis	[33]
		circRNA1656	miR-1301-3p/miR-4660-SIRT3	down-regulated in HGSOC	[4]
		circ-CSPP1	miR-1236-3p	promotes proliferation, invasion, and migration	[34]
		has-circ-001567		promotes cell proliferation and invasion	[35]
		circ-SMAD7	KLF6	promotes cell proliferation and invasion	[36]
		circ_0025033	miR-184/LSM4	promotes the progression of ovarian cancer	[37]
		circHIPK3		related to cell growth, migration, and apoptosis	[3]
		circ_0023942	CDK-4	inhibit granulosa cell proliferation	[38]
		circ_0043533	miR-1179	related to Bcl-2, CDK2, and Cyclin D1	[39]
		circ_RANBP9	miRNA-136-5p/XIAP	exacerbates POS	[40]
	PCOS	circASPH	miR-375/MAP2K6	promotes cells proliferation	[41]
		circRHBG	miR-515/SLC7A11	knockdown of circRHBG promotes ferroptosis in PCOS	[42]
		circ_0005925	miR-324-3p/MAP2K6	Promotes Granulosa Cell Growth	[43]
		circ_0043532	miR-182/SGK3	promote cell proliferation	[44]
	ovary	circDDX10		ovarian aging	[9]
	KGN	circUSP36	PTBP1/NEDD4L	enhance autophagic granulosa cell death	[45]
	GCs	circDDX10		affecting the proliferation and apoptosis and steroid hormone synthesis	[46]
Pig	ovary	circ-TCP11	miR-183	associated with swine litter size	[21]

Species	Tissue	CircRNA	Target miRNA/Gene/Protein	Function	Ref.
	ovary	circSCIN	miR-133, miR-148a/b	affecting estrogen secretion	[22]
	GCs	ssc-circINHA-001	miR-214-5p, miR-7144-3p, miR-9830-5p/INHBA	mediated Inhibin–Activin balance	[17]
	GCs	circSLC41A1	miR-9820-5p/SRSF1	resists porcine granulosa cell apoptosis and follicular atresia	[18]
	GCs	circ-ANKHD1	miR-27a-3p/SFRP1	decreased the cell apoptosis rates	[47]
Bovine	GCs	circ_n/a_75	miR-339a	growth factor response	[15]
		circ_n/a_303	miR-2400 and miR-30c		[15]
Goat	follicles	chi_circ_0008219	miR-34c-5p, miR-483, miR-1468-3p	higher fecundity rate	[23]
Mouse	GCs	circEGFR	miR-125a-3p/CYP19A1	promoted granulosa cell apoptosis	[10]

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