Role of Cytokines in Early and Late Folliculogenesis

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Proper folliculogenesis is critical cellular differentiation to get a competence in oocytes and to develop with a normal type organism. Successful follicle formation and initiation of follicle growth must involve genetic networks both in germ and in somatic cells, and involves cell-autonomous and non-cell-autonomous factors. Interactions between oocytes and pre-granulosa cells are crucial for the initial formation of primordial follicles. With periodicity, cohorts of primordialfollicles are recruited into a growth phase that culminates in meiotic maturation and ovulation of a mature egg(s) into the oviduct in preparation for fertilization. It is well established that folliculogenesis proceed under the cross control of hormones and the signal modulation by paracrine factors, autocrine factors or juxtacrine factors. Preantral follicle development is regulated primarily by paracrine and autocrine mechanisms. Large follicles require both intraovarian and extraovairan regulation. Along with secreted signaling factors, transcription factors also play an important role in the interactions between somatic and germ cells during folliculogenesis. In here, we will discuss focused on role of cytokines in early and late folliculogenesis, and how do the mammalian ovary to get the ability to produce and to respond to a complex milieu of intraovarian and extraovarian regulatory factors that are essential for efficient reproductive function in female. Cytokine (a group of signaling compounds between cell-to-cell, cell-to-tissue or cell-to-organism) networks are involved in folliculogenesis, ovulation and luteinization, and modulate these processes. The initial stages of folliculogenesis are independent of pituitary gonadotropins and involve cell-autonomous and non-cell-autonomous factors. Germ cell lineage derived from the proximal epiblast migrates into the extraembryonic mesoderm, and a subset differentiates to form a precursor pool of germ cells, first detected in the allantois. Octamer-binding transcription factor-4 (OCT-4, cell-autonomous), and bone morphogenetic protein-4 (BMP4) and BMP8B (non-cell-autonomous factors) have been implicated in the progression of these cells towards a germ cell fate. Wnt4 signaling is required to maintain the female germ line. Primordial follicle formation requires the active role of pre-granulosa cells in syncytial breakdown and of oocytes in recruiting pre-granulosa cells. Once formed, primordial follicles represent the entire pool of germ cells available during the reproductive life of the female. At this time, Wnt4, a signaling molecule that is found in somatic rather than in gem cells, appear to be important in post-meiotic maintenance of oocytes and in primordial follicle formation. At this time tumor necrosis factor alpha (TNF alpha) interacts with progesterone (P4) and it can override the inhibitory actions of P4 on follicle assembly. Some of the cytokines are known to involve in primordial-to-primary follicle transition. Genes expressed in the germ cells such as factor in the germline alpha (Figla), newborn

ovary homeobox protein (Nobox), proto-oncogene tyrosine-protein kinase Kit (Kit) and neurotrophic tyrosine kinase receptor type 2 (Ntrk2), as well as genes expressed in the surrounding somatic cells such as forkhead box protein L2 (Foxl2), Kit ligand (Kitl) and nerve growth factor (Ngf), play critical functions in the process. Initiation of follicular growth and progression beyond the primary follicle stage appear to involve interactions between Kit (c-kit) and Kitl (Kit ligand, also know as stem cell factor (SCF)), either secreted from or on the surface of granulose cells. Kitl interact with basic fibroblast growth factor (bFGF) in the induction of ovarian primordial to primary follicle transition. The known other factors involved in primordial-to-primary follicle transition are including platelet-derived growth factor (PDGF), leukemia inhibitory factor (LIF), keratinocyte growth factor (KGF), FGF-2, BMP-4, and BMP-7. Recruitment of primordial follicles to join the growing pool is positively related to the size of the ovarian reserve. Anti-Mullerian hormone (AMH) is present in granulose cells surrounding oocytes, and has been implicated in the recruitment of primordial follicles into the growth phase of folliculogenesis. The timing of progression of primary follicles to the early-antral stage is depending on species. Primary-to-secondary follicle transition and subsequent follicle growth to the late preantral/early antral stage are regulated mainly by local factors. Oocyte originated cytokines, GDF9, BMP15 and FGF2, implicated as positive regulators of preantral follicle growth. Thecal origins, BMP4, BMP7 and TGF-, implicated as positive regulators of preantral follicle growth. Granulosa cell originated cytokines, TGF-, activins and AMH, implicated as positive regulators of preantral follicle growth and regulate its own microenvironment. Follicle stimulating hormone (FSH) is required for antral follicle development. There is ability of multiple BMPs to interact in a complex manner with both IGF- and FSH-dependent signaling pathways. A changing intrafollicular balance between mutually opposing granulosa cell-derived inhibins and activins contributes to granulose cell proliferation/ differentiation, theca cell androgen synthesis and oocyte support and development. Activin play a positive role in oocyte maturation and acquisition of developmental competence. Granulosa cell-derived activin, BMP-2, -5 and -6, theca cell-derived BMP-2, -3b, -4 and -7 and oocyte-derived BMP-6 and 15 promote granulosa cell proliferation, follicle survival and prevention of premature luteinization and/or atresia. GDF-9 expressed by oocytes may exert its effect via regulation of gonadotrophin action. AMH reduces the FSH responsiveness of preantral and small antral follicles. The keratinocyte growth factor (KGF) and Kitl are known to interact to coordinate the growth of later-stage antral follicles. BMP-binding proteins (e.g. follistatin, noggin, chordin, gremlin, BAMBI) can modulate the BMP action. Intraovarian HGF supports folliculogenesis by mediating steroidogenesis and suppressing apoptosis. Dominant follicle selection in monovular species may depend on differential FSH sensitivity amongst a growing cohort of small antral follicles. Microvascular networks and angiogenic factors affect the oocyte and follicular growth, particularly the selective growth of oocytes and follicles. Epidermal growth factor (EGF) involves in angiogenesis in ovary. Changes in intrafollicular activins, GDF-9, AMH and several BMPs may contribute to this selection process by modulating both FSH- and IGF-dependent signalling pathways in granulosa cells. The product of NAIP gene in granulosa cells protects ovarian follicular cells from apoptosis. TNFis found in the cytoplasm of cumulus cells surrounding the maturing oocytes, and suppressed the spontaneous fragmentation of oocytes. Also, macrophages secrete TNF, which binds to oocytes to stimulate the process of degeneration.

Nodal is involved in promoting follicular atresia. The growths of all oocytes in normal antral follicle are strictly regulated. The cascade from the granulosa cell-produced Kitl to the oocyte surface Kit, and to the oocyte PI3 kinase pathway, may play an important role in the regulation of growth rate of mammalian oocytes. Ovulation is induced with LH surge in large follicles. Within a few hours of the LH surge, follicular hyperemia and edema occurrence are mediated by vasoactive agents such as histamine, kinins, and prostaglandins. IL-1 induced abundantly and specifically keratinocyte chemoattractant (KC) chemokine via NF-κB signaling in mouse granulose cells. FSH did not affect NF-κB signaling or IL-1-induced KC chemokine promoter activity. TNF-induces the expression of serum amyloid A3, a main acute-phase protein in granulosa cells. It is also known that prostaglandin E2 plays a crucial role in the ovulation process. Oocyte derived BMP-6, BMP-15 and GDF-9, have the ability to act as inhibitors of luteinizing activity in cultured granulose cells. On the other hand the selective expression of certain components of the BMP-system within the corpus luteum (CL) may act to regulate both luteinization and luteolysis. A role for inhibin A and/or its free -subunit in primate CL formation and progesterone production has been proposed. Activin A may delay granulosa cell luteinization and/or atresia and decrease basal and hCG-induced progesterone production in both cultured human and monkey granulose-lutein cells, further reinforcing a positive role for inhibin in promoting luteal formation. The effect of activin A could be reversed by its binding protein follistatin, the expression of which was upregulated by hCG in granulose-lutein cells. TGF-1, 2 also contribute to CL formation. Ovarian dysfunction and pathological phenotypes have been increased continuously in man caused by environmental disruption. Ovarian cancer, autoimmune ovarian disease, polycystic ovary syndrome, and ovarian hyperstimulation syndrome are closely associated with inflammatory mediators such as cytokines. Recently considerable progress has been made towards elucidating the complex intraovarian control mechanisms that, in concert with systemic signals, coordinate the recruitment and progression of primordial follicles through to ovulation and CL formation. Using microarray methodology, we could find many cytokines which are expressed during folliculogenesis or ovarian development. Recently we reported that endothelin 2 (ET-2), produced by progesterone receptor (PR) in mural granulosa cells, acts in a paracrine or autocrine manner on multiple cell types within the preovulatory follicle to control the final events leading to its rupture. Based on them, unique signaling pathway in the preovulatory follicle, involving LH, PR, ET-2, and its downstream target molecules, plays a critical role during ovulation. Other groups also try to explain how cytokines cowork during folliculogenesis. Based on them, it is suspected that the mammalian ovary get the ability to produce and respond to a complex milieu of intraovarian and extraovarian regulatory factor through the getting competence a premordial cell by communication between gonadotropins, cytokines, signaling molecules and transcription factors. However, so far, it is too limited to explain the precise mechanisms of folliculogenesis or other pathological phenotypes. Therefore it is needed the further studies to expend our understanding of the roles of cytokines. This knowledge will lead to the development of new approaches for manipulating ovarian function and improving fertility in domesticated livestock and man.