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A review article on angiopoietins: A crucial ovarian local growth factor

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Abstract
Follicular blood vessel network status is an essential criterion in determining the selection of dominant follicle/s. Angiogenesis is a process of vascular growth which is vital for follicular development and ovulation. The development, proliferation, and growth of these capillaries are controlled by angiogenic factors produced by granulosa and theca cells. Gonadotropins (FSH and LH) function as the primary survival factors for ovarian follicles and the anti-apoptotic effects are probably mediated by the ovarian growth factors. Of these growth factors Angiopoietin (ANPT)-Tie signaling pathways have pivotal roles in regulating angiogenesis. A balanced action of Angiopoietins-Tie pathway along with vascular endothelial growth factor plays a vital role in vascular stabilization thus ensuring the preferential delivery of nutrients and gonadotropins to dominant follicles, compared with the subordinated follicles. Thus Angiopoietin-Tie pathway is vital for the remodeling and maturation of the developing vasculature, which helps in the formation of dominant follicle/s.

Keywords: Angiogenesis, angiopoietin, ovarian growth factor, dominant follicle

1. Introduction
In mammalian species, the first milestone towards successful reproduction is considered as the development of a preovulatory follicle and as such, it is imperative that the mechanisms of follicle development are fully understood to improve and control reproductive function in humans and animals alike (Campbell *et al.*, 2003) [1]. The ovarian follicular development process is highly related to the formation of the new capillary network (Jiang *et al.*, 2003) [2]. Doyle, (2008) [3] reported that the healthy follicles are highly vascularized whereas those undergoing atresia are having poor vascularity, suggesting, there exist a strong relationship between follicular vascularization and follicular function.
Angiogenic factors regulate vascularization, and among them, angiopoietin-Tie (ANPT-Tie) systems are of fundamental importance (Choudhary *et al.*, 2010) [4] and are responsible for the maturation and stabilization of blood vessels (Maisonpierre *et al.*, 1997) [5]. It has progressively become evident that angiopoietins as well as their endothelial cell-specific tyrosine kinase receptors, controls angiogenesis as a modulator of vascular stabilization (Yancopoulos *et al.*, 2000) [6]. Angiopoietins, one of the elemental endothelial growth factors, change the development and reproduction of blood vessels during angiogenesis. Mainly there are two major types of angiopoietins, angiopoietin-1 (ANPT-1) and angiopoietin-2 (ANPT-2), and both are connected with the same endothelial receptor, Tie-2. ANPT-1 binds to a Tie2 receptor and then activates downstream signaling, thereby confirming the endothelial and vascular structure. However, ANPT-2 possesses different physiological properties and expressions than that of ANPT-1. Through the effect of vascular endothelial growth factor (VEGF), ANPT-2 interrupts ANPT-1-Tie-2 signaling and then contributes to structural and functional changes of newly forming blood vessels.
Recent findings have suggested that angiogenic factors also play an essential role in the modulation of follicular survival (or death) (Abramovich *et al.*, 2009) [7]. Detailed understanding of the exact mechanism of ovarian follicular dynamics might open up new insight into the treatment of infertility, which could further improve the reproductive performance in animals.

2. Folliculogenesis
The ovarian follicle, which is the basic functional unit of the ovary and provides the essential microenvironment for oocyte growth and maturation consists of an oocyte surrounded by follicular cells (granulosa and theca cells) (Telfer, 1996) [8].

Depending on the developmental stages and gonadotropin dependence, follicular growth can be divided into three phases (Craig *et al*., 2007) [9]. These phases encompasses follicular growth through primordial, primary, and secondary stages (gonadotropin-independent phase), transition from preantral to early antral stage (gonadotropin-responsive phase), and continual growth after the early antral stage (gonadotropin-dependent phase), which in turn involves follicle recruitment, selection, and ovulation (Kumar *et al*., 1997) [10]. In the second (gonadotropin- responsive) phase, the follicular growth is primarily regulated by intra-ovarian regulators (e.g., growth factors, cytokines, and gonadal steroids) and does not need gonadotropins for growth, although the presence of FSH also stimulates its growth (Fortune, 2003) [11]. The changeover of the follicle from the pre-antral to an early antral stage is the "penultimate" stage of development concerning gonadotropin dependence and follicle destiny (growth versus atresia) (Orisaka *et al*., 2006) [12]. Inadequate growth support is the major reason for follicular atresia whereas the selected follicles for further development are supposed to receive specific and precise gonadotropic and intra-ovarian regulatory signals for survival (Hu *et al*., 2004) [13].

According to Hodgen (1982) [14], the following terms were given for describing folliculogenesis:

1. Recruitment is a process in which, a group of follicles begins to mature in a milieu of adequate pituitary gonadotropins to permit progress towards ovulation.
2. Dominance is the process by which a single follicle acquires and supports its eminence over the other recruited follicles, which undergoes atresia.

3. Angiogenesis in ovarian follicle

Angiogenesis, a process leading to the formation of new blood vessels by sprouting from the existing ones, this includes basement membrane breakage, endothelial cell migration, the proliferation of the endothelial cell, and capillary lumina development (Folkman and Klagsbrun, 1987) [15]. During the estrus cycle, active angiogenesis always occurs in the wall of ovarian follicle simultaneous with growth, recruitment, selection and acquiring of dominance by the follicle. This ovarian follicular angiogenesis which commences early during follicular development will continue throughout follicle growth. Increase in number and size of the blood vessels in the theca cell layer occurs as the follicle develops, but the blood vessels do not penetrate the granulosa cell layer by virtue of the intact intervening basal membrane located between the granulosa and theca interna layers (Suzuki *et al*., 1998.; Redmer and Reynolds, 1996) [16,17]. Unlike the preantral follicles which lack an independent vascular supply, antral follicles gradually acquire a vascular sheath in the theca cell or layer (Redmer and Reynolds, 1996) [17].

In tandem with the growth of antrum within the follicles, the thecal layer develops a vascular sheath consisting of two capillary networks, located in theca externa and interna. These capillary networks are bridged to each other, and all capillary blood exits from the theca interna into small vessels which will be connected with the ovarian stromal veins (Hazzard and Stouffer, 2000) [18]. Since all capillaries are formed outside the basement membrane of the follicle, until about the time of ovulation, the granulosa layer remains avascular. Preferential delivery of gonadotropins to individual follicles is ensured at the last stage of folliculogenesis, by increased vascularization, resulting in increased blood flow to individual follicles which plays a crucial role in the selective maturation of pre-ovulatory follicles (Zeleznik *et al*., 1981) [19]. Hence, the rate of vascular development appears to be critical in the selection of a follicle which is destined to ovulate. Experiments have shown that angiogenesis is escorted by vasodilation, a functional modification for the event of ovulation, and by the development of theca endocrine function (Jiang *et al*., 2003) [2], which emphasizes the role of thecal angiogenesis in follicular development (Tamanini and De Ambrogi, 2004) [20]. Thecal blood vessels development and growth are supposed to be under the control of various angiogenic factors produced by thecal and granulosa cells and among these factors, angiopoietins plays a pivotal role.

4. Angiopoietins

Angiopoietins are soluble secreted glycoproteins, which exist in various multimeric forms with a molecular weight of approximately 70 kDa and involved in the development and stability of blood vessels (Drenkhahn *et al*., 2004) [21]. The angiopoietin (ANPT) family comprises angiopoietin 1 (ANPT-1) and angiopoietin 2 (ANPT-2) and their receptors tyrosine kinase with immunoglobulin-like and EGF-like domains 1 and 2 (Tie1 and Tie2) (Shimizu *et al.,* 2007, Hayashi *et al*., 2004) [22, 23]. The first ligand member of the angiopoietin family to be discovered, ANPT1, was identified by its ability to bind Tie2 extracellular domain. Angiopoietin-1 (ANPT-1) and Angiopoietin-2 (ANPT-2) shares approximately 60% amino acid identity (Shimizu *et al.,* 2007) [22]. It is known that angiopoietins form multimers to exert their functions. For some instance, multimeric forms of ANGPT-1 is critical to phosphorylate Tie-2 receptor (Kim *et al.,* 2005) [24].

Since the ligand for Tie1 has not been discovered, it is regarded as an orphan receptor, whereas, angiopoietins are the ligands for Tie2 (Suri *et al*., 1996) [25]. The intracellular domains of Tie receptors (Tie1 and Tie2) have the sequence homology of about 76% (Schnurch and Risau, 1993) [26]. It has been shown that with the help of Tie2, angiopoietins activates the orphan receptor Tie1 (Saharinen *et al*., 2005; Yuan *et al*., 2007) [27, 28].

5. Functions of angiopoietins

Even though ANPT-1 and ANPT-2 have similar binding affinities towards Tie2, ANPT-1 acts as an agonist which phosphorylates the receptors and promotes vascular stabilization by congregating perivascular cells to maintain vascular integrity (Maisonpierre *et al.,* 1997) [5]. While ANPT-2, acts as an endogenous antagonist of ANPT-1, also binds to Tie2 receptors but does not mediate receptor phosphorylation (Hanaha, 1997) [29]. ANPT-2 alone destabilizes blood vessels and disrupts angiogenesis (Thurston *et al.,* 2000) [30] and eventually causes regression of blood vessels in the absence of survival signals such as VEGF. Thus ANPT-2 competitively antagonizes ANPT -1 mediated stabilization of blood vessels (Maisonpierre *et al.,* 1997) [5].

A prerequisite for new blood vessel formation is an increase in the ANPT-2: ANPT-1 ratio which is interwoven with the destabilization of blood vessels. The ratio of ANPT-1 and ANPT2 in coordination with VEGF determines vascular stabilization and regression (Schams *et al.,* 2004) [31]. Thus, the ratio of ANPT -2 to ANPT-1 is critically important for both angiogenesis and regression of blood vessels (Wulff *et al*., 2000) [32].

In the mature follicles, the expression of ANPT-2 mRNA is found to be decreasing and this resulted in a decline in the ANPT-2: ANPT-1 ratio (which is considered as an index of instability of blood vessels), that further indicated the attainment of stability of blood vessels. The follicles which undergo early atresia show a higher ANPT-2: ANPT-1 ratio and higher Tie2 mRNA expression than other follicles at healthy or later atretic stages. This finding implies that the blood vessels become unstable at the initial stage of follicular atresia (Hyashi *et al*., 2003) [33].

The destabilized blood vessels is expected to face any of the two fates, that is when VEGF is high, active angiogenesis results in the formation of a new blood vessel network (high ANPT-2: ANPT-1 ratio, high VEGF), whereas a lack of VEGF support results in a regression of blood vessels (high ANPT-2: ANPT-1 ratio, low VEGF). A low ANPT-2: ANPT1 ratio with low VEGF results in a stabilization of blood vessels (Hyashi *et al*., 2003) [33]

6. Mechanism of action of angiopoietins

The Angiopoietins mostly acts via phosphoinositide-3–kinase protein kinase B (PI3K-AKT) pathway (Testa and Tsichlis, 2005) [34] which activates downstream regulatory proteins by a cascade of reactions and mediates their functional activities like cellular proliferation, growth, and cytoprotective role on many cellular system including granulosa cells (GCs) (Papapetropoulos *et al.,* 1999) [35]. The binding of ANPT-1 to Tie2 stimulates PI3K activity, which is a family of enzymes involved in many of the cellular functions such as cell growth, proliferation, differentiation, motility, and survival.

7. Angiopoietin-tie signaling pathway

The angiopoietin-Tie signaling pathway comprises angiopoietin ligands and Tie1 and Tie2 (also called as TEK) receptor tyrosine kinases (RTK) (Partanen *et al*., 1992; Schnurch and Risau, 1993; Dumont *et al*., 1994, Lee *et al*., 2004, Peters *et al*., 2004) [36, 26, 37, 38, 39]. The Tie receptors have a very similar domain structure with three epidermal growth factor (EGF) like domains implanted between three immunoglobulin (Ig) like domains, and accompanied by three fibronectin type III-like domains in their extracellular domains and a split tyrosine kinase domain in the intracellular domain (Partanen *et al*., 1992; Sato *et al*., 1993) [36, 40]. The intracellular domains show 76% sequence homology in Tie1 and Tie2, while the extracellular domains are less conserved and there is only about 33% sequence homology (Schnurch and Risau, 1993) [26]. Since the ligand for Tie1 has not been discovered, it is considered as an orphan receptor, while Tie2 has angiopoietins as the ligands (Suri *et al*., 1996) [25]. However, it has been shown that angiopoietins can activate Tie1 receptors most likely via Tie2 (Saharinen *et al*., 2005 [27]; Yuan *et al*., 2007 [28]). The activated Tie2 triggers certain downstream signaling pathways, that includes the Dok/-related docking protein (Dok-R; also known as DOK2) and growth factor receptor-bound protein2 (GRB2), which further on activate some other effector molecules that results in cell migration (Jones and Dumont, 1999; Master *et al*., 2001) [41, 30]. The SH2 domain containing phosphatase (SHP2) and the phosphoinositide 3-kinase (PI3K) pathways are responsible for mediating the cell survival signals (Augustin *et al*., 2009; Fukuhara *et al*., 2008; Saharinen *et al*., 2008) [42, 43, 44].

The angiopoietins make use of a special mechanism for Tie receptor activation by promoting translocation of the Tie receptors to the cell-cell and cell-matrix contacts. ANPT-1 induces translocation of Tie2 to a cell-cell junction in contacting cells and also causes the gathering of homotypic Tie2-Tie2 *trans*-associated complexes. As a result, vascular integrity is established through the activation of the Akt-eNOS signaling pathway. When cell-cell contact is absent, matrix-bound Ang1 induces translocation of Tie2 to cell-matrix contacts and Tie2 activation which induces cell migration through activation of Dok-R and Erk pathways (Fukuhara *et al*., 2008 [43]; Saharinen *et al*., 2008 [44]).

8. The significance of angiopoietin in ovarian follicular growth

The ANPT-Tie system is supposed to have a central role in the regulation of ovarian follicular dynamics including development, maturation, and ovulation of follicles in rat (Maisonpierre *et al.,* 1997) [5], human, (Yancopoulos *et al.,* 2000) [6], monkey (Hazzard *et al.,* 1999) [45], pig (Shimizu *et al.,* 2003) [46], ewe (Chowdhury *et al.,* 2010) [47], and cow (Goede *et al.,* 1998) [48]. Change of mRNA expression of ANPT-1, ANPT-2, and Tie-2 in theca interna is associated with follicular development and atresia. During the pre-LH surge stage, in large follicles where a higher thecal ANPT-2: ANPT-1 ratio in the presence of low thecal VEGF favors the disruption of existing blood vessels. During the LH surge stage, both the thecal ANPT-2: ANPT-1 ratio and thecal VEGF were much higher, thus favoring active angiogenesis. During the post-LH surge stage, the thecal ANPT-2: ANPT-1 ratio was still high but lower than during the LH-surge stage, suggesting the beginning of stabilization of newly formed blood vessels.

9. Non-angiogenic functions of angiopoietin

Steroidogenesis:- Ovarian granulosa cells (GCs) of buffaloes were treated with different concentrations of ANPT-1/ANPT-2, estradiol secretion was found to be highest when GCs were treated with a high concentration of protein for 72 hours, suggesting angiopoietins also exerts an effect on steroidogenesis (Mishra *et al*., 2016) [49]

Anti-apoptotic effect: - The expression of BAD (bcl2-associated death promoter) with caspase 3 (Sequential activation of caspases plays a central role in the execution-phase of cell apoptosis) was found to be decreasing in buffalo ovarian granulosa cells (GCs) as the time of incubation of cultured GCs with each protein (ANPT-1/ANPT-2) or in combination was increased. (Mishra *et al*., 2016) [49].

10. Conclusion

The earlier concept of regulation of ovarian cycle was strictly confined to gonadotropins, but recent research is focusing on the role of local ovarian factors which are equally important in supporting the development of follicles and their survival. Among them angiopoietin, which is concerned with blood vessel formation and stabilization, plays a significant role in ovarian follicular development.

Angiogenesis is an inevitable process in ovarian follicular dynamics. Evidence suggests that maintenance of the theca vascular bed and follicular health are strictly related. In developing follicles, the pre-existing endothelial cells that create the vascular network in the theca layer, distinctly develop in response to the stimulus of several growth factors such as vascular endothelial growth factor (VEGF), angiopoietin-1 (ANPT-1) and angiopoietin-2 (ANPT-2). The changing profile of angiopoietin and their receptor TIE-2 is

theca cells during follicular development are closely linked to the development and regression of vascular network in a cyclic ovary. The new blood vessel development in the ovary is critical to guarantee the necessary supply of nutrients and hormones to promote follicular growth.

Over and above the angiogenic function, angiopoietin also executes a significant role in bringing about steroidogenesis and anti-apoptotic effect in ovarian follicle. Hence angiopoietin can be considered as a crucial ovarian follicular growth factor for the development of healthy follicle.

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