Reviews of Reproduction (1997) **2**, 139–146

Ovarian follicular dominance: the role of intraovarian growth factors and novel proteins

David G. Armstrong[1] and Robert Webb[2]

[1]*Division of Development and Reproduction, Roslin Institute (Edinburgh), Roslin, Midlothian EH25 9PS, UK; and* [2]*Department of Agriculture and Horticulture, University of Nottingham, Sutton Bonington Campus, Loughborough, Leicestershire LE12 5RD, UK*

Folliculogenesis is associated with the development of a group of follicles at various stages of maturation from which a species-specific number of follicles are selected for continued growth. These selected follicles, after being exposed to the requisite hormonal environment, ovulate in response to the preovulatory gonadotrophin surge. Follicular dominance is the mechanism by which the selected follicle(s) undergoes rapid development in an environment where growth and development of other follicles, recruited at a similar time, are suppressed. These processes are controlled by the interaction of endocrine signals and locally produced ovarian growth factors. The response of the two major follicular cell types, granulosa and theca cells, to gonadotrophins is regulated by the local production of growth factors. Mechanisms controlling growth factor action occupy a central role in the regulation of folliculogenesis. In this review, we highlight the influence of the extracellular matrix in this process by describing its involvement in regulating the activity of components of the insulin-like growth factor system, transforming growth factor β superfamily, fibroblast growth factors and the epidermal growth factor/transforming growth factor α family. In addition, some recent studies on the role of protein factors produced by the dominant follicle in maintaining dominance and inhibiting the growth of subordinate follicles are described.

Ovarian folliculogenesis is a dynamic process characterized by a marked proliferation and differentiation of the somatic cell components of the follicle. The developing follicle provides the optimal environment for the maturation of the oocyte in readiness for its subsequent fertilization after ovulation. The primary regulators of folliculogenesis are the gonadotrophins, which regulate ovarian follicular development via classic endocrine mechanisms. In addition to this systemic mechanism, it has become increasingly apparent that additional intraovarian mechanisms are involved in the control of folliculogenesis. The concept of intraovarian control of ovarian function arose in the 1970s and is now recognized as a complex regulatory system involved in modulating the response of follicles to circulating gonadotrophins (Adashi and Roban, 1992).

Ovarian follicles are known to produce a range of locally acting peptide/protein growth factors. These can either interact directly with the same cell type from which they are produced (autocrine action) or with other cell types within the developing follicle (paracrine action) to stimulate or attenuate the cellular response to gonadotrophins. Additional mechanisms, such as juxtacrine (activation of receptors on adjacent cells by membrane bound growth factors) and intracrine (stimulation of the cell in which the factor is produced without prior secretion of the factor from the cell) are also recognized as mechanisms through which granulosa and theca cells can control their behaviour.

Folliculogenesis is associated with the development of a group of follicles at various stages of development from which a species-specific number of follicles is selected for continued growth (Webb *et al.*, 1992; Fortune 1994; Campbell *et al.*, 1995; Gong and Webb, 1996). According to Goodman and Hodgen (1983) folliculogenesis can be divided into three separate stages: (1) recruitment, the stage during which a pool of growing follicles begin to grow rapidly; (2) selection, a process whereby follicles are selected for further growth; and (3) dominance, the process whereby the dominant follicle(s) undergoes rapid development while the growth of subordinate follicles is suppressed. This pattern of follicle development is associated with changes in expression of mRNA encoding gonadotrophin receptors (Xu *et al.*, 1995a) and steroidogenic enzymes (Xu *et al.*, 1995b) and allows selected follicles, when exposed to the requisite hormonal environment, to ovulate in response to the preovulatory gonadotrophin surge. Endocrine signals (for example, gonadotrophins, inhibins and steroids), as well as locally produced growth factors, are responsible for the control and coordination of these processes. Functional models for follicle selection and the control of ovulation rate in ewes have been described (Scaramuzzi *et al* 1993) that take some of these concepts into account.

In this review, we will describe some of the more recent ideas on the intraovarian control of folliculogenesis. The mechanisms whereby locally produced growth factors control the development of dominance will be described. The disruption of this local control system in subordinate follicles, by putative factors produced by dominant follicles, coupled with alterations in the endocrine signals, will also be discussed. Where possible we will illustrate the mechanisms described using data from experiments in cattle. However, it must be stressed that, although the growth factors described in this review are expressed in the

© 1997 Journals of Reproduction and Fertility
1359-6004/97 $10.00

Downloaded from Bioscientifica.com at 08/23/2022 12:49:05PM
via free access

ovary and influence the behaviour of granulosa and theca cells *in vitro*, their actions *in vivo* remain to be clarified. In this respect the development of transgenic mice in which genes can either be 'knocked out' or overexpressed, provide invaluable approaches for analysing the role of ovarian growth factors in the control of folliculogenesis (Nishimori and Matzuk, 1996).

Local regulation of the ovary and the development of dominance

The characteristic waves of follicle growth observed during the mammalian oestrous cycle are associated not only with morphological and functional changes in granulosa and theca cells, but also with changes in the vasculature and nervous system of the developing follicle. Distinct groups of locally produced factors can be defined that are associated with the controlled development of each of these processes. The disruption of any of these mechanisms will affect folliculogenesis and it is assumed that the development of follicular dominance and ovulation require the correct integration of all of these processes at each stage of follicular development.

Much is known about the temporal and spatial expression of many classes of growth factor, and their receptors, during follicle development. Cell culture studies have also begun to reveal the factors involved in the control of their expression. However, unlike the classic endocrine hormones, which are stored in the cells within which they are synthesized, many growth factors are constitutively secreted and stored in a functionally inert form in extracellular depots either alone or in association with specific binding molecules (Logan and Hill, 1992). It has become increasingly apparent that additional mechanisms, distinct from growth factor expression and receptor binding, are involved in controlling growth factor activity *in vivo* (Flaumenhaft and Rifkin, 1992). The mechanisms involved in the controlled release of an active growth factor, both at the correct site within the developing follicle and at the correct stage of development, have received little attention. The various mechanisms described here are dependent upon sequence motifs within the growth factor, or its specific binding protein, that are recognized by components of the extracellular matrix (ECM) or cell membranes. The involvement of specific proteases in the controlled release of active growth factors from their extracellular storage depots and how this relates to the development of follicular dominance are discussed. Four well-defined local regulatory systems are used to highlight the different mechanisms available for the temporal and spatial control of ovarian growth factor action, namely, the insulin-like growth factor (IGF) system, components of the transforming growth factor β (TGF-β) superfamily, the fibroblast growth factors (FGFs) and the epidermal growth factor (EGF)/transforming growth factor α (TGF-α) family.

Insulin-like growth factor system

The ovary is a major site of hormone-regulated IGF production in mammalian (Adashi and Roban, 1992; Giudice, 1992) and non-mammalian (Armstrong and Hogg, 1996) species. IGFs function as modulators of gonadotrophin action at the cellular level and stimulate granulosa and theca cell proliferation and differentiation. They show distinct species-specific patterns of expression in follicular tissue. In rodents (Oliver *et al*., 1989) and pigs (Zhou *et al*., 1996), the expression of mRNA encoding IGF-I is confined to granulosa tissue. In contrast, in humans, mRNA encoding IGF-II , but not mRNA encoding IGF-I, is localized to granulosa tissue (Zhou and Bondy, 1993). We have detected the expression of mRNA encoding IGF-II in thecal tissue of bovine ovarian follicles (Fig. 1) and a similar spatial distribution has been described in sheep (Perks *et al*., 1995). The expression of mRNA encoding IGF-I in ruminants is controversial; Leeuwenberg *et al.* (1995) detected mRNA encoding IGF-I in ovine granulosa and theca tissue, whereas Perks *et al.* (1995) failed to detect its expression in ovarian follicles from ewes. We have recently demonstrated that non-luteinized bovine granulosa cells do not produce IGF-I in serum-free cultures (Gutierrez *et al.*, 1997). The functional significance of these differences in the expression of mRNA encoding IGFs between species is unknown. It may, however, reflect changes in the relative roles of IGF-I and -II (acting either as endocrine or intraovarian regulators of follicular growth) that have evolved to fit the particular pattern of follicular development required to maximize reproductive potential in particular species.

The bioactivity of the IGFs is controlled by their association with a family of specific IGF binding proteins (IGFBPs). To date, six distinct IGFBPs have been characterized, following either their purification or cDNA isolation and sequencing (Clemmons *et al*., 1995). As with the IGFs, the spatial expression of these binding proteins within ovarian follicles is species-specific. For example, in cows (Armstrong *et al*., 1996a) and sheep (Besnard *et al*., 1996a) expression of mRNA encoding IGFBP-4 and -2 is restricted to theca and granulosa tissue, respectively (Fig. 1). In contrast, expression of mRNA encoding IGFBP-4 is localized to granulosa cells in pigs (Grimes *et al*., 1994).

How do these binding proteins control the activity of IGFs *in vivo*? IGFBPs are often found in association with the ECM and cell membranes. Immunohistochemical localization of IGFs has shown that they co-distribute with the IGFBPs and, thus, provide an extracellular store of IGFs that can be targeted to specific cell populations by IGFBP–cell membrane interactions and the action of specific IGFBP proteases (Hill *et al*., 1989). In the bovine ovary, our immunohistochemical and cytochemical observations have demonstrated the presence of IGFBP-2 and -4 on the theca and granulosa cell plasma membranes, in the basement membrane and within the ECM surrounding theca cells (Glazyrin *et al*., 1996).

Binding of IGFBPs to the ECM and cell surface molecules depends on specific amino acid motifs within the primary structure of IGFBPs. For example, IGFBP-2 contains the integrin recognition sequence (RGD) and it is expected that the association of IGFBP-2 with granulosa and theca cells is via the integrins on their plasma membranes. The association of IGFBP-4 with the ECM is probably via heparin-binding sites on the surface of the protein since IGFBP-4 binds to heparin-labelled Sepharose *in vitro* (Clemmons *et al.*, 1995). IGFBP-2, as well as binding to integrin molecules on the cell surface, can also bind to the basement membranes of epithelial cells and so would also be expected to bind to heparin-like molecules in the proteoglycans of the ECM. In this case, however, although IGFBP-2 itself has no affinity for heparin *in vitro*, binding of IGF causes a conformational change in the structure of the binding protein, resulting in its adherence to heparin (Arai *et al*., 1996).

Downloaded from Bioscientifica.com at 08/23/2022 12:49:05PM
via free access

The release of IGFs from the IGFBPs is controlled by the action of specific IGFBP proteases and many cell types have now been shown to produce these enzymes *in vitro* (Parker *et al.*, 1995). Specific IGFBP proteases have been detected in follicular fluid from ewes (Besnard *et al.*, 1996b) and the amounts and activity of these enzymes change during folliculogenesis. In addition, the production of IGFBP proteases by rat granulosa cell cultures has been shown to be stimulated by FSH (Fielder *et al.*, 1993). These various observations suggest that there are complex regulatory mechanisms controlling IGF bioactivity within the developing follicle, involving both the association of IGFBPs with the ECM and the release of IGFs from the extracellular storage depots by the action of specific IGFBP proteases.

In the ovarian cell culture systems examined so far, IGFBPs attenuate the actions of IGFs (Monget *et al.*, 1993). Therefore, a decrease in follicular IGFBP production would be expected to enhance the biological activity of locally produced IGF and increase the response of the follicle to gonadotrophins. The observed decrease in the concentrations of IGFBP-2, -4 and -5 in follicular fluid during the development of dominance supports this hypothesis (Armstrong *et al.*, 1996b). In cows (Armstrong *et al.*, 1996a) and sheep (Besnard *et al.*, 1996a), the decrease in IGFBP-2 concentration in follicular fluid during follicle growth was shown to be due to a loss of expression of mRNA encoding IGFBP-2 in granulosa cells in dominant follicles.

Using serum-free bovine granulosa cell cultures, we have shown that FSH, at physiological concentrations, inhibits expression of mRNA encoding IGFBP-2 (Armstrong *et al.*, 1996c). These results indicate that a key feature in the development of follicular dominance in cows is the FSH-dependent inhibition of the expression of mRNA encoding IGFBP-2 in granulosa cells. The resultant increase in IGF bioactivity in these follicles should increase the FSH responsiveness of their granulosa cells (Fig. 2a). In contrast to the expression of mRNA encoding IGFBP-2 in granulosa cells, the expression of mRNA encoding IGFBP-4 in thecal tissue does not change during follicular growth (Armstrong *et al.*, 1996a; Besnard *et al.*, 1996a). In this case, the decrease in IGFBP-4 concentration in follicular fluid during the development of dominance is due to a corresponding increase in the activity of a specific IGFBP-4 protease (Besnard *et al.*, 1996b).

In conclusion, the results summarized indicate that the bioactivity of ovarian IGFs is controlled by three separate mechanisms: (1) changes in the temporal and spatial expression of mRNA encoding IGFBP during folliculogenesis; (2) regulation of IGFBP binding to the ECM and plasma membranes; and (3) the action of specific IGFBP proteases. However, the precise role of individual binding proteins within the developing follicle, remains obscure. By combining *in situ* hybridization and immunocytochemical studies, in which the temporal and spatial pattern of expression of the components of the IGF-system is related to the location of the IGFBPs within the extracellular matrix *in vivo*, with studies in which the control of these genes are examined in granulosa and theca primary cell cultures, further insights into the mechanisms whereby IGFBPs control the bioactivity of intraovarian IGF will be forthcoming.

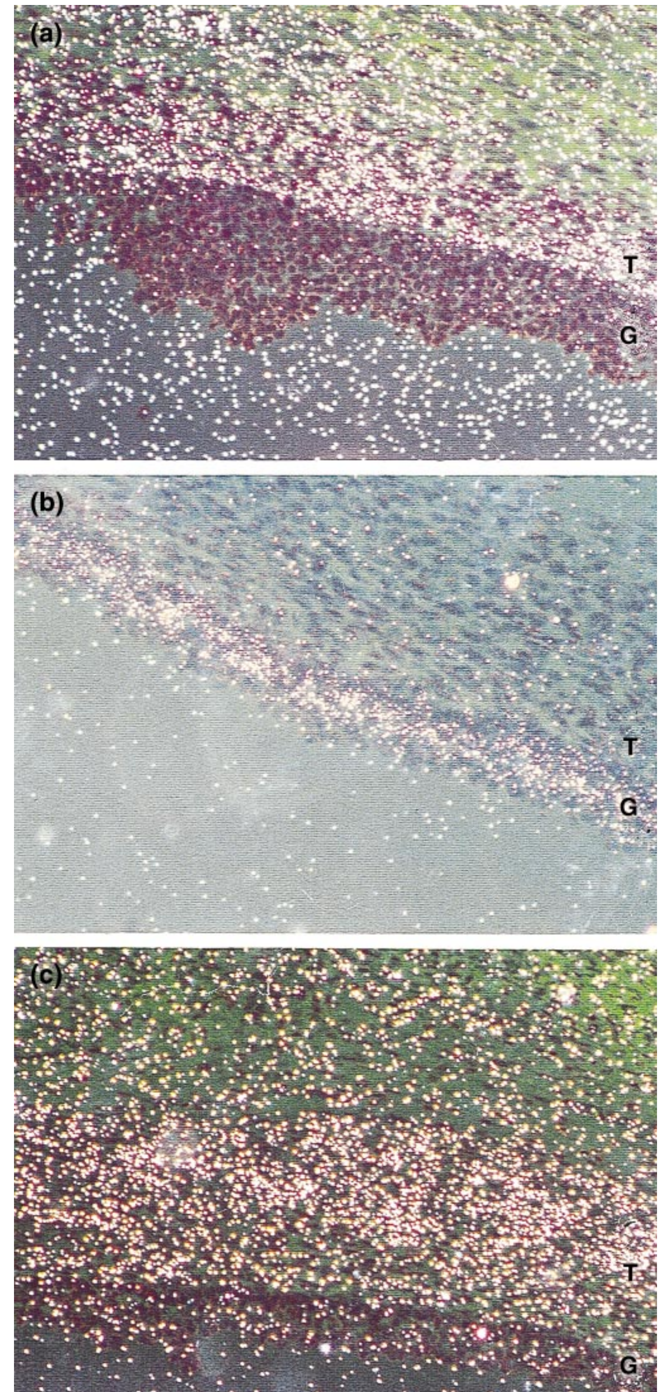

Fig. 1. Dark field illumination of bovine ovarian sections hybridized to ^{35}S-labelled antisense insulin-like growth factor II (IGF-II) (a) insulin-like growth factor-binding protein 2 (IGFBP-2) (b) and IGFBP-4 (c) RNA probes. Expression of mRNA encoding IGF-II and IGFBP-4 is confined to thecal tissue (T), whereas expression of mRNA encoding IGFBP-2 is localized in granulosa cells (G).

Transforming growth factor β superfamily

The TGF-β superfamily is made up of a number of proteins with the potential to act as intraovarian regulators of ovarian function: for example, the TGF-βs and the activin/inhibin system. mRNAs encoding TGF-β are expressed in thecal cells from mammalian (Mulheron *et al.*, 1991) and non-mammalian (Law *et al.*, 1995) species. In cows, TGF-βs inhibit granulosa and theca

Downloaded from Bioscientifica.com at 08/23/2022 12:49:05PM
via free access

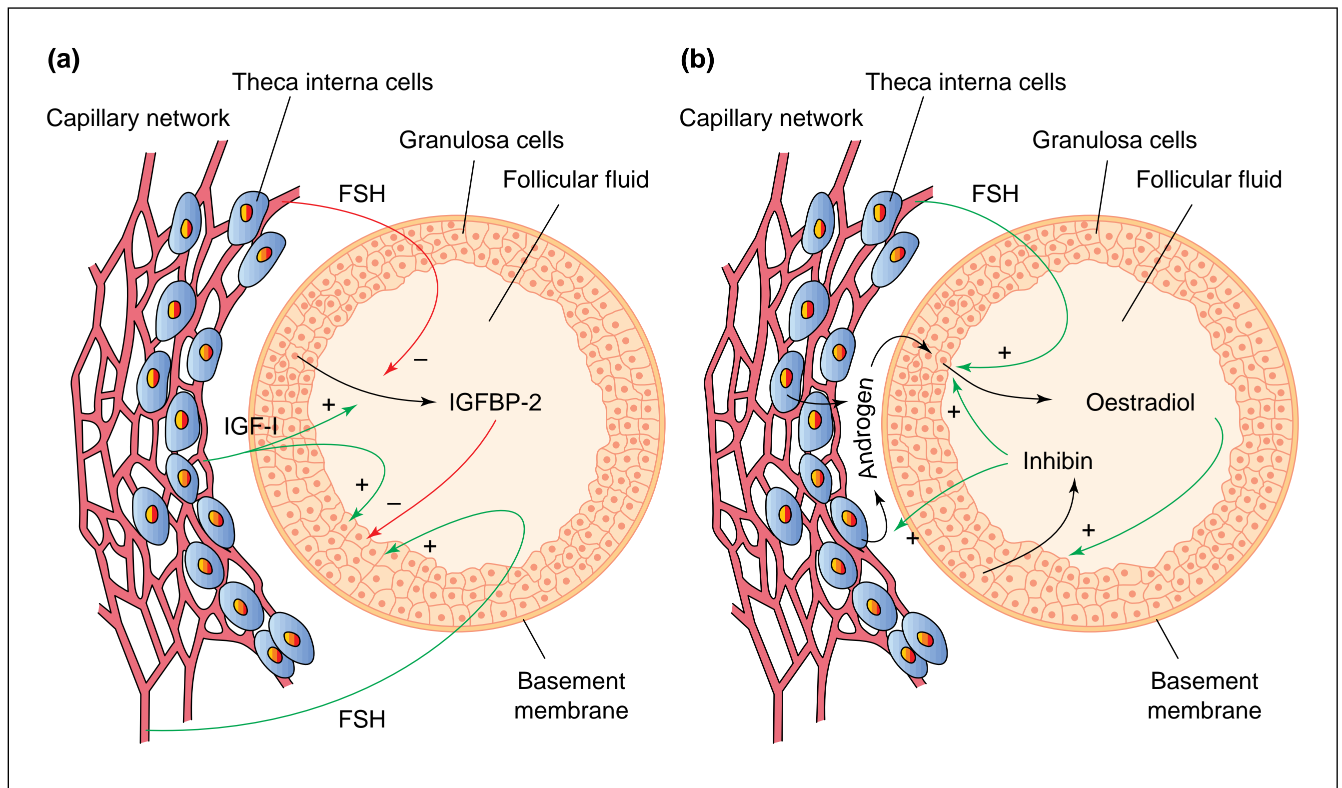

Fig. 2. Intrafollicular positive and negative feedback systems in the ruminant ovary. (a) The production of insulin-like growth factor-binding protein 2 (IGFBP-2) by granulosa cells is regulated by insulin-like growth factor I (IGF-I) and FSH. The IGF-I-enhanced FSH stimulation of granulosa cell proliferation and differentiation is, in turn, inhibited by IGFBP-2. (b) Inhibin production is stimulated by aromatizable androgens and oestrogens. Inhibin, in turn, enhances the FSH stimulation of oestradiol production by granulosa cells.

cell proliferation while enhancing gonadotrophin-stimulated steroidogenesis (Roberts and Skinner, 1991). Overall, these data indicate that TGF-βs are local regulators of ovarian function.

In contrast to IGFs, TGF-βs are released from cells in a latent form that does not bind to the high affinity TGF-β receptor (Harpel *et al.*, 1992) and the critical step in the regulation of TGF-β activity appears to be its conversion into the active form. There is limited information on the regulation of this process in ovarian follicles. The latent TGF-β complex is a single gene product, the N-terminal portion of which constitutes the propeptide or latency-associated peptide (LAP) and the C-terminal portion of which constitutes the mature growth factor. Each of these components exist as separate disulfide-linked homodimers which associate with each other to form the latent TGF-β complex, which subsequently becomes bound to components of the ECM (Harpel *et al.*, 1992). The involvement of LAP in the regulation of TGF-β activity was highlighted by experiments showing that purified LAP can reassociate with TGF-β *in vitro* and inhibit its activity in Chinese hamster ovarian cell cultures (Gentry *et al.*, 1987). Proteolysis provides a physiological mechanism for the activation of latent TGF-β, and both plasmin and cathepsin D have been shown to activate latent TGF-β in culture (Lyons *et al.*, 1990). Therefore, the regulation of TGF-β activity is controlled by the activity of proteases that release mature TGF-β from the ECM-associated latent complex. The conversion of plasminogen to plasmin within the follicle and the presence of plasminogen activator inhibitors would, therefore, be expected to be critical in the control of TGF-β activity during folliculogenesis. This mechanism would be expected to influence the development of dominance since, as described earlier, TGF-βs act synergistically with gonadotrophins to control the differentiation of follicular cells. Hence, as with the IGF system, specific extracellular proteases may play a central role in the regulation of TGF-β bioactivity during follicle growth and the development of dominance.

Other members of the TGF-β superfamily include the activins and inhibins. In addition to the well known endocrine role of inhibin in controlling FSH secretion, there is increasing evidence of a role for these proteins as local regulators of ovarian function (Hillier *et al.*, 1991; Wrathall and Knight., 1995). For example, in sheep, inhibin enhances FSH-stimulated production of oestradiol by granulosa cells in culture, and both oestradiol and aromatizable androgens stimulate granulosa production of inhibin (Campbell and Webb, 1995), creating an intrafollicular self-inductive cascade that enhances gonadotrophin-stimulated hormone production (Fig. 2b). This intrafollicular positive feedback loop is an obvious mechanism through which development of follicular dominance can be controlled.

The high structural homology of the activins and inhibins with the TGF-βs implies that their activity may be regulated by interactions with the N-terminus of their propeptide, as is the case with TGF-βs. In this respect, antibodies to the N-terminal

Downloaded from Bioscientifica.com at 08/23/2022 12:49:05PM
via free access

fragment of the pro-αN–αC subunit of inhibin (αN inhibin) have been shown to affect reproductive performance; however, details of its mode of action are limited (Russell and Findlay, 1995). The pro-region of the activin primary translation product is necessary for the correct folding and disulfide bond formation of the active dimeric growth factor (Gray and Mason, 1990). The physiological relevance of these observations in the control of follicular development is currently unknown.

Fibroblast growth factors

The FGFs are a family of heparin-binding growth factors, the effects of which are mediated via tyrosine kinase receptors (Fernig and Gallagher, 1994). Within the ovary, the most studied member of this family is FGF-2 (basic FGF). Production of this growth factor has been demonstrated in bovine granulosa cells (Neufield *et al.*, 1987) and it has been shown to stimulate bovine thecal cell proliferation (Spicer and Stewart, 1996). FGF-2 immunoactivity has been detected in rodent follicles (Wordinger *et al.*, 1993) and the growth factor inhibits FSH-stimulated induction of LH receptor expression in granulosa cells and reduces specific binding of IGF in thecal tissue. FGFs are potent angiogenic factors by virtue of their stimulatory effect on endothelial cell proliferation. However, their precise role in the regulation of ovarian angiogenesis remains uncertain (Redmer and Reynolds, 1996). Indeed, the role of the various FGF isoforms in the regulation of ovarian function has so far received little attention.

The FGFs have a high affinity for heparin sulfate (HS)-like molecules in the ECM and plasma membranes. As with the other growth factors described in this review, their association with the ECM is a key component in regulating their activity. However, it appears that the binding of FGFs with HS-like molecules is a prerequisite for normal biological activity. For example, the potency of FGF-1 is up to 100 times greater in the presence of heparin (Thorton *et al.*, 1983) and the interaction of FGF-2 with HS-like molecules in the ECM is necessary for binding to FGF receptors (Yayon *et al.*, 1991).

The interaction of the various FGF isoforms with the ECM can regulate both the stability and the diffusible properties of the growth factors. Heparin-like molecules are released continuously from cell membranes and the ECM by the action of specific proteases. The association of these soluble heparin molecules with FGFs inhibits subsequent binding of FGFs to the ECM, thus facilitating their diffusion through the tissue from their site of synthesis (Flaumenhaft *et al.*, 1990). The sulfation pattern of heparin also appears to be critical in the control of FGF binding to the ECM and cell membranes (Fernig and Gallagher, 1994). Hence, enzymes that affect ECM structure would be expected to regulate both the affinity of FGFs for components of the ECM and their diffusion rates through the matrix.

Follicle growth and atresia and the development of dominance are associated with considerable changes in the structure of the ECM as a result of tissue remodelling. From the above discussion, such changes would be expected to alter the bioactivity of ovarian FGFs with resultant changes in granulosa and theca cell function and follicular angiogenesis. There is much work to be done to define the roles of the ECM in controlling FGF activity during folliculogenesis.

Epidermal growth factor family

EGF and its structural homologue TGF-α are mitogenic factors that act through a common receptor that has been detected in granulosa cells from bovine and ovine species. As with the FGFs, TGF-α stimulates bovine theca and granulosa cell proliferation while inhibiting gonadotrophin-stimulated differentiation of cells (Roberts and Skinner, 1991). mRNA encoding TGF-α is expressed in thecal tissue from cows and, using an ovarian autotransplant model, TGF-α has been shown to inhibit ovarian function in ewes (Campbell *et al.*, 1994). These results indicate that TGF-α from thecal cells influences granulosa cell proliferation via paracrine mechanisms.

An interesting feature of these growth factors is that they are synthesized as large molecular weight glycosylated precursors containing a hydrophobic membrane-spanning domain. Membrane-anchored forms of EGF and TGF-α can stimulate EGF receptors on adjacent cells (Prigent and Lemoine, 1992). Within the ovary, such juxtacrine mechanisms are probably involved in restricting expression of genes to groups of cells within a particular tissue.

Extracellular proteases and the structure of the extracellular membrane

It is clear that growth factor activity is controlled by a number of different mechanisms and that the ECM occupies a central role in many of these regulatory processes. The ovary produces a range of different extracellular proteases that modulate the structure of the ECM (Luck, 1994). For example, the plasminogen–plasmin system and matrix metalloproteinases (including collagenase, gelatinase and stromelysin) are expressed in ovarian follicles (Salamonsen, 1996), as are specific protease inhibitors, such as plasminogen activator inhibitor (Liu *et al.*, 1991) and tissue inhibitor of metalloproteinases-1 and -2 (Smith *et al.*, 1995). The spatially and temporally controlled expression of these proteases and their inhibitors is involved in maintaining and remodelling the ECM within the developing follicle. These mechanisms regulate both the binding and the release of growth factors from their extracellular storage sites within the ECM and are probably key components of the intraovarian regulatory mechanisms controlling folliculogenesis and the development of dominance.

Factors produced by large preovulatory follicles and maintenance of follicular dominance

Follicular dominance appears to be controlled by a number of mechanisms acting in concert. These include alterations in peripheral FSH concentrations by oestradiol and inhibin secreted by the dominant (ovulatory) follicle, as well as the possible production of local ovarian factors, which can inhibit the development of subordinate follicles directly (Campbell *et al.*, 1995). Evidence that follicular dominance and inhibition of the growth of subordinate follicles are due to the production of follicle growth inhibitory factors (FGIFs) by dominant follicles has been increasing. It has been demonstrated that steroid- and inhibin-depleted follicular fluid can inhibit follicular development in sheep and cattle (Campbell *et al.*, 1991; Law *et al.*, 1992; Wood *et al.*, 1993). Partially purified follicular fluid fractions

Downloaded from Bioscientifica.com at 08/23/2022 12:49:05PM
via free access

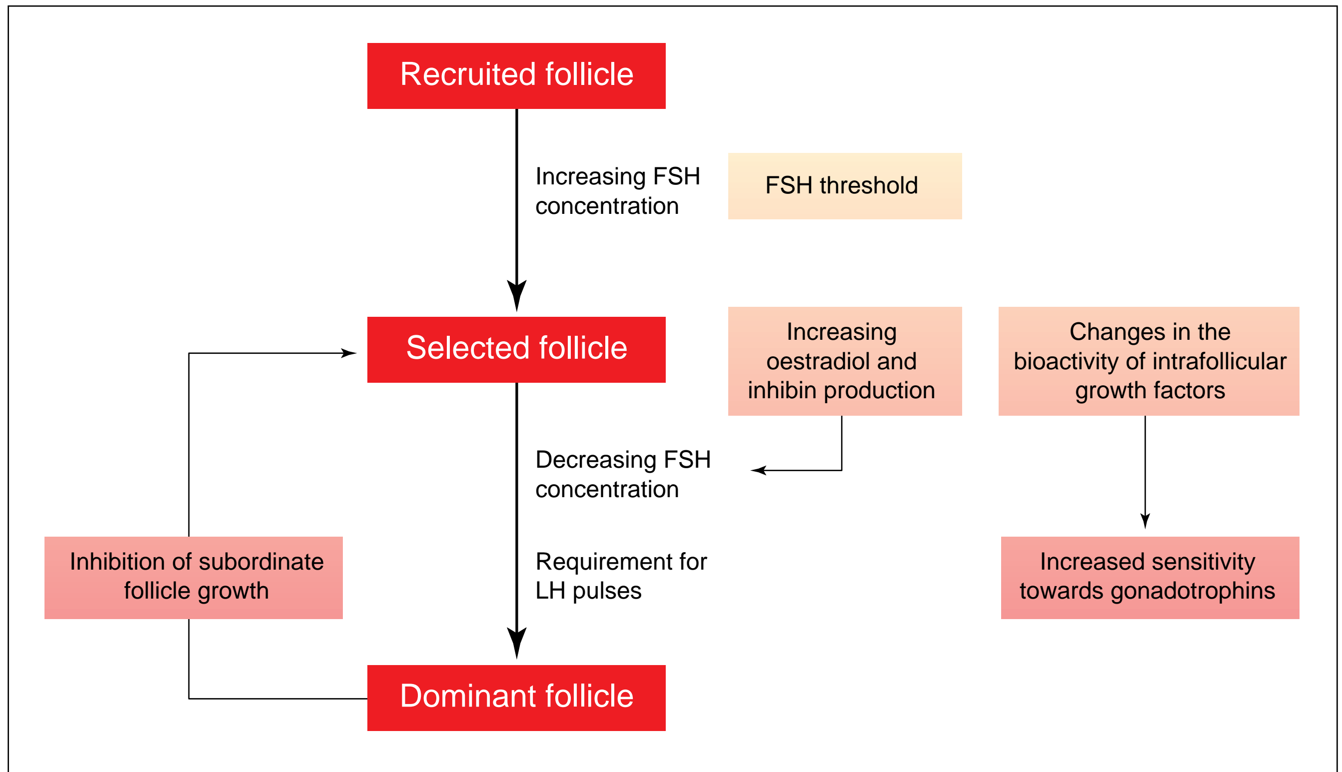

Fig. 3. A model for the development of follicular dominance in cattle. Follicle selection occurs when FSH concentrations are increasing and surpass the FSH threshold which regulates the number of follicles selected for further growth (Baird, 1987). The differentiation of granulosa cells during the selection process results in increased circulating concentrations of oestradiol and, possibly, of bioactive inhibin which inhibit the release of FSH from the pituitary gland. The selected follicles then change their dependence from FSH to LH (Campbell *et al.*, 1995). Thus, mechanisms controlling the initiation of dominance occur in an environment of decreasing FSH support and rely on intraovarian mechanisms that regulate both the bioactivity/bioavailability of ovarian growth factors and the vascularization of the dominant follicle. These changes result in an increase in both the sensitivity and exposure of the selected follicle towards gonadotrophins. The inhibition of subordinate follicle growth relies on the production of specific follicle growth inhibiting factors that selectively inhibit the growth of subordinate follicles through mechanisms that have still to be fully characterized.

have also been shown to inhibit both cell proliferation and aromatase activity in cultured ovine, bovine and porcine granulosa cells (Baxter *et al.*, 1995; Picton and Hunter, 1995).

The cow is an excellent model system for investigating these putative FGIFs. Unlike sheep and pigs, cows are mono-ovulators and the action of FGIFs probably ensures that > 95% of animals produce a single ovulation per oestrous cycle. FGIFs are expected to act via systemic mechanisms since dominant follicles can inhibit the growth of follicles in the contralateral ovary. However, the mechanism by which FGIFs inhibit the growth of subordinate follicles is unknown. Since they inhibit FSH-stimulated granulosa cell proliferation and aromatase activity, it is possible that FGIFs interfere with the activity of locally produced growth factors that control the response of granulosa cells to FSH. Another possibility is that FGIFs inhibit vascularization of subordinate follicles. It has been known for some time that dominant follicles have a more extensively vascularized theca layer compared with other antral follicles and that this is associated with an increased uptake of gonadotrophins from the circulation (Zeleznick *et al.*, 1981; Redmer and Reynolds, 1996). Therefore, any factor that affects the blood supply of a developing follicle should have a pronounced effect on its development. Whatever the mechanism(s) through which these putative FGIFs acts, the dominant follicle must be resistant to their actions (perhaps through the loss of specific receptors) to allow its continued preovulatory development.

Conclusion

Follicle selection and the development of dominance involve the integration of systemic and local mechanisms. A conceptual model for the regulation of this process is presented (Fig. 3) which highlights the central role occupied by intraovarian growth factors and the mechanisms regulating their bioactivity. In this review, we have stressed the role of the ECM and extracellular proteases in this process and have discussed the involvement of putative FGIFs, produced by dominant follicles, which inhibit subordinate follicle growth. The optimum integration of these mechanisms determines the response of individual follicles to gonadotrophins.

The purification and characterization of FGIFs should lead to the development of alternative strategies for manipulating follicle growth and should provide new insights into the regulation of folliculogenesis. Future studies, directed at analysing

Downloaded from Bioscientifica.com at 08/23/2022 12:49:05PM
via free access

structural changes in the ECM during tissue remodelling and the involvement of the extracellular proteases that regulate these changes, should also lead to a better understanding of how growth factors control the response of granulosa and theca cells towards gonadotrophins.

References

Key references are indicated by asterisks.

***Adashi EY and Roban RM** (1992) Intraovarian regulation. Peptidergic signalling systems *Trends in Endocrinology and Metabolism* **3** 243–248

Arai T, Busby W and Clemmons DR (1996) Binding of insulin-like growth factor (IGF) I or II to IGF-binding protein -2 enables it to bind to heparin and extracellular matrix *Endocrinology* **137** 4571–4575

Armstrong DG and Hogg CO (1996) Insulin-like growth factor-I (IGF-I), IGF-II and type 1 IGF receptor gene expression in the ovary of the laying hen *Journal of Reproduction and Fertility* **106** 101–106

Armstrong DG, Baxter G, Hogg CO and Webb R (1996a) Insulin-like growth factor binding protein-2 and -4 mRNA expression in bovine ovarian follicles *in vivo*: the effect of follicle size and atresia *Journal of Reproduction and Fertility Abstract Series* **18** Abstract 72

***Armstrong DG, Hogg CO, Campbell BK and Webb R** (1996b) Insulin-like growth factor (IGF) binding protein production by primary cultures of ovine granulosa and theca cells. The effect of IGF-I, gonadotropin and follicle size *Biology of Reproduction* **55** 1163–1171

Armstrong DG, Gutierrez CG, Hogg CO, Campbell BK and Webb R (1996c) The expression of insulin-like growth factor binding proteins in primary cultures of bovine granulosa and theca cells *Journal of Reproduction and Fertility Abstract Series* **17** Abstract 30

Baird DT (1987) A model for follicular selection and ovulation: lessons from superovulation *Journal of Steroid Biochemistry* **27** 15–23

Baxter G, O'Shea T, Campbell BK and Webb R (1995) Effects of bovine follicular fluid (bFF) fractions, which delay oestrus in sheep and cattle, on proliferation and steroid production by cultured granulosa cells *Journal of Reproduction and Fertility Abstract Series* **15** Abstract 189

Besnard N, Pisselet C, Monniaux D, Locatelli A, Benne F, Gasser F, Hatey F and Monget P (1996a) Expression of messenger ribonucleic acids of insulin-like growth factor binding proteins-2, -4 and -5 in the ovine ovary: localization and changes during growth and atresia of antral follicles *Biology of Reproduction* **55** 1356–1367

Besnard N, Pisselet C, Zapf J, Hornebeck W, Monniaux D and Monget P (1996b) Proteolytic activity is involved in changes in intrafollicular insulin-like growth factor binding protein levels during growth and atresia of ovine follicles *Endocrinology* **137** 1599–1607

Campbell BK and Webb R (1995) Evidence that inhibin has autocrine and paracrine actions in controlling ovarian function in sheep *Journal of Reproduction and Fertility Abstract Series* **15** Abstract 140

Campbell BK, Picton HM, Mann GE, McNeilly AS and Baird DT (1991) The effect of steroid- and inhibin- free ovine follicular fluid on ovarian follicles and ovarian hormone secretion *Journal of Reproduction and Fertility* **93** 81–96

Campbell BK, Gordon BM and Scaramuzzi RJ (1994) The effect of ovarian aterial infusion of transforming growth factor-α on ovarian follicle populations and ovarian hormone secretion in ewes with an autotransplant ovary *Journal of Endocrinology* **143** 13–24

***Campbell BK, Scaramuzzi RJ and Webb R** (1995) Control of antral follicle development and selection in sheep and cattle *Journal of Reproduction and Fertility Supplement* **49** 335–350

***Clemmons DR, Busby WH, Arai T, Nam TJ, Clarke JB, Jones JI and Ankrapp DK** (1995) Role of insulin-like growth factor binding proteins in the control of IGF actions *Progress in Growth Factor Research* **6** 357–366

***Fernig DG and Gallagher JT** (1994) Fibroblast growth factors and their receptors: an information network controlling tissue growth morphogenesis and repair *Progress in Growth Factor Research* **5** 353–377

Fielder PJ, Pham H, Adashi EY and Rosenfeld RG (1993) Insulin-like growth factors (IGFs) block FSH-induced proteolysis of IGF-binding protein-5 (BP-5) in cultured rat granulosa cells *Endocrinology* **133** 415–418

***Flaumenhaft R and Rifkin DB** (1992) The extracellular regulation of growth factor action *Molecula Biology of the Cell* **3** 1057–1065

Flaumenhaft R, Moscatelli D and Fifkin DB (1990) Heparin and heparin sulfate increase the radius of diffusion and action of basic fibroblast growth factor *Journal of Cell Biology* **111** 1651–1659

***Fortune JE** (1994) Ovarian follicular growth and development in mammals *Biology of Reproduction* **50** 225–232

Gentry LE, Webb NR, Lim GJ, Brunner AM, Ranchalis JE, Twardzik DR, Lioubin MN, Marquardt H and Purchio H (1987) Type 1 transforming growth factor beta amplified expression and secretion of mature and precursor polypeptides in Chinese hamster ovary cells *Molecular and Cellular Biology* **7** 3418–3427

***Giudice LC** (1992) Insulin-like growth factors and ovarian development *Endocrine Reviews* **13** 641–669

Glazyrin AL, Armstrong DG, Gutierrez CG, Bramely TA and Webb R (1996) Expression of IGF-binding protein-4 messenger ribonucleic acid and ultrastructural localization of the gene product in the bovine ovary *Journal of Reproduction and Fertility Abstract Series* **17** Abstract 31

Gong JG and Webb R (1996) Control of ovarian follicle development in domestic ruminants: its manipulation to increase ovulation rate and improve reproductive performance *Animal Breeding Abstracts* **64** 195–204

Goodman AL and Hodgen GD (1983) The ovarian triad of the primate menstrual cycle *Recent Progress in Hormone Research* **39** 1–73

Gray AM and Mason AJ (1990) Requirements for activin A and transforming growth factor-1 proregions in homodimer assembly *Science* **247** 1328–1330

Grimes RW, Barber JA, Shimasaki S, Ling N and Hammond JM (1994) Porcine ovarian granulosa cells secrete insulin-like growth factor-binding proteins-4 and -5 and express their messenger ribonucleic acids: regulation by follicle-stimulating hormone and insulin-like growth factor-I *Biology of Reproduction* **50** 695–701

Gutierrez CG, Campbell BK, Armstrong DG and Webb R (1997) Insulin-like growth factor-I (IGF-I) production by bovine granulosa cells *in vitro* and peripheral IGF-I measurement in cattle serum: an evaluation of IGFBP extraction protocols *Journal of Endocrinology* **153** 231–240

***Harpel JG, Metz CN, Kojimi S and Rifkin D** (1992) Control of transforming growth factor-β activity. Latency versus activation *Progress in Growth Factor Research* **4** 321–335

Hill DJ, Clemmons DR, Wilson S, Han VKM, Strain AJ and Milner RDG (1989) Immunological distribution of one form of insulin-like growth factor (IGF)-binding protein and IGF peptides in fetal tissue *Journal of Molecular Endocrinology* **2** 31–38

Hillier SG (1991) Regulatory functions for inhibin and activin in human ovaries *Journal of Endocrinology* **131** 171–175

Law AS, Baxter G, Logue DN, O´Shea T and Webb R (1992) Evidence for the action of a bovine follicular fluid factor(s) other than inhibin in suppressing follicular development and delaying oestrus in heifers *Journal of Reproduction and Fertility* **96** 603–616

Law AS, Burt DW and Armstrong DG (1995) Expression of transforming growth factor-β mRNA in chicken ovarian follicular tissue *General and Comparative Endocrinology* **98** 227–233

Leeuwenberg BR, Hurst PR and McNatty KP (1995) Expression of IGF-I mRNA in the ovine ovary *Journal of Molecular Endocrinology* **15** 251–258

Liu YX, Peng XR and Ny T (1991) Tissue specific and time coordinated hormone regulation of plasminogen-activator-inhibitor type I and tissue-type plasminogen activator in the rat ovary during gonadotropin-induced ovulation *European Journal of Biochemistry* **195** 549–555

***Logan AL and Hill DJ** (1992) Bioavailability. Is this a key event in regulating the actions of peptide growth factors? *Journal of Endocrinology* **134** 157–161

***Luck MR** (1994) The gonadal extracellular matrix *Oxford Reviews of Reproductive Biology* **16** 34–85

Lyons RN, Gentry LE, Purchio AF and Moses HL (1990) Mechanisms of activation of latent recombinant transforming growth factor beta 1 by plasmin *Journal of Cell Biology* **110** 1361–1367

Monget P, Monniaux D, Pisselet C and Durand P (1993) Changes in insulin-like growth factor-I (IGF-I), IGF-II and their binding proteins during growth and atresia of ovine ovarian follicles *Endocrinology* **132** 1438–1446

Mulheron GW, Danielfour D and Schomberg DW (1991) Rat thecal interstitial cells express transforming growth factor-β type 1 and 2, but only type 2 is regulated by gonadotropins *in vitro. Endocrinology* **129** 368–374

Neufield G, Ferrara N, Schweigerer L, Mitchell R and Gospodarowicz D (1987) Bovine granulosa cells produce basic fibroblast growth factor *Endocrinology* **121** 597–603

Nishimori K and Matzuk MM (1996) Transgenic mice in the analysis of reproductive development and function *Reviews of Reproduction* **1** 203–212

Oliver JE, Aitman JR, Powell JF, Wilson CA and Clayton RN (1989) IGF-I gene expression in the rat ovary is confined to granulosa cells of developing follicles *Endocrinology* **124** 2671–2679

Downloaded from Bioscientifica.com at 08/23/2022 12:49:05PM
via free access

Parker A, Gockerman A, Busby WH and Clemmons DR (1995) Properties of an insulin-like growth factor binding protein-4 protease that is secreted by smooth muscle cells *Endocrinology* **136** 2470–2476

Perks CM, Dennining-Kendall PA, Gilmour RS and Wathes DC (1995) Localization of messenger ribonucleic acids for insulin-like growth factor I (IGF-I), IGF-II and the type 1 IGF receptor in the ovine ovary throughout the estrous cycle *Endocrinology* **136** 5266–5273

Picton HM and Hunter MG (1995) Purification and characterization of a porcine follicular fluid protein which inhibits aromatase activity in granulosa cells *in vitro. Journal of Endocrinology Supplement* **147** Abstract P96

***Prigent SA and Lemoine NR** (1992) The type 1 EGFR-related family of growth factor receptors and their ligands *Progress in Growth Factor Research* **4** 1–24

***Redmer DA and Reynolds LP** (1996) Angiogenesis in the ovary *Reviews of Reproduction* **1** 182–192

Roberts AJ and Skinner MK (1991) Transforming growth factor-α and -β differentially regulate growth and steroidogenesis of bovine thecal cells during antral follicle development *Endocrinology* **129** 2041–2048

***Russell DL and Findlay JK** (1995) The N-terminal peptide of the inhibin α subunit. What are its endocrine roles? *Trends in Molecular Endocrinology* **6** 305–311

***Salamonsen LA** (1996) Matrix metalloproteinases and their tissue inhibitors in endocrinology *Trends in Endocrinology* **7** 28–34

***Scaramuzzi RJ, Adams NR, Baird DT, Campbell BK, Downing JA, Findlay KM, Henderson KM, Martin GB, McNatty KP, McNeilly AS and Tsonis CG** (1993) A model for follicle selection and determination of ovulation rate in the ewe *Reproduction, Fertility and Development* **5** 459–478

Smith GW, McCrone S, Peterson SL, and Smith MF (1995) Expression of messenger ribonucleic acid encoding tissue inhibitor of metalloproteinases-2 within ovine follicles and corpora lutea *Endocrinology* **136** 570–576

Spicer LJ and Stewart RE (1996) Interaction among basic fibroblast growth factor, epidermal growth factor, insulin and insulin-like growth factor-I (IGF-I) on cell numbers and steroidogenesis of bovine thecal cells: role of IGF-I receptors *Biology of Reproduction* **54** 255–263

Thorton SC, Mueller SN and Levine EM (1983) Human endothelial cells. Use of purified heparin in cloning and long-term serial cultivation *Science* **222** 623–625

***Webb R, Gong JG, Law AS and Rusbridge SM** (1992) Control of ovarian function in cattle *Journal of Reproduction and Fertility Supplement* **45** 141–156

Wood SC, Glencross RG, Bleach EC, Lovell R, Beard AJ and Knight PG (1993) The ability of steroid-free bovine follicular fluid to suppress FSH secretion and delay ovulation persists in heifers actively immunized against inhibin *Journal of Endocrinology* **136** 137–148

Wordinger RJ, Brun-Zinkernagel AM and Chang IFC (1993) Immunohistochemical localization of basic fibroblast growth factor (bFGF) within growing and atretic mouse follicles *Growth Factors* **9** 279–289

Wrathall JHM and Knight PG (1995) Effects of inhibin-related peptides and oestradiol on androstenedione and progesterone secretion by bovine theca cells *in vitro. Journal of Endocrinology* **145** 491–500

Xu ZZ, Garverick HA, Smith GW, Smith, MF, Hamilton SA and Younquist RS (1995a) Expression of follicle-stimulating hormone and luteinizing hormone receptor messenger ribonucleic acids in bovine follicles during the first follicular wave *Biology of Reproduction* **53** 951–957

Xu ZZ, Garverick HA, Smith GW, Smith, MF, Hamilton SA and Younquist RS (1995b) Expression of messenger ribonucleic acid encoding cytochrome P450 side-chain cleavage, cytochrome P450 17α-hydroxylase, and cytochrome P450 aromatase in bovine follicles during the first follicular wave *Endocrinology* **136** 981–989

Yayon A, Klagsbrun M, Esko JD, Leder P and Ornitz D (1991) Cell surface, heparin-like molecules are required for binding basic fibroblast growth factor to its high affinity receptor *Cell* **64** 841–848

Zeleznik AJ, Schiler HM and Reichert LE (1981) Gonadotropin-binding sites in the Rhesus monkey ovary: role of the vasculature in the selective distribution of human chorionic gonadotropin to the preovulatory follicle *Endocrinology* **109** 356–361

Zhou J and Bondy CA (1993) Anatomy of the human ovarian IGF system *Biology of Reproduction* **48** 467–482

Zhou J, Adesanya OO, Vatzias G, Hammond JM and Bondy CA (1996) Selective expression of insulin-like growth factor system components during porcine ovary follicular selection *Endocrinology* **137** 4893–4901

Downloaded from Bioscientifica.com at 08/23/2022 12:49:05PM
via free access