MINIREVIEW

The Role of GATA in Mammalian Reproduction

HOLLY A. LAVOIE[1]

Department of Cell and Developmental Biology and Anatomy, University of South Carolina School of Medicine, Columbia, South Carolina 29208

GATA transcription factors are emerging as critical players in mammalian reproductive development and function. GATA-4 contributes to fetal male gonadal development by regulating genes mediating Müllerian duct regression and the onset of testosterone production. GATA-2 expression appears to be sexually dimorphic being transiently expressed in the germ cell lineage of the fetal ovary but not the fetal testis. In the reproductive system, GATA-1 is exclusively expressed in Sertoli cells at specific seminiferous tubule stages. In addition, GATA-4 and GATA-6 are localized primary to ovarian and testicular somatic cells. The majority of cell transfection studies demonstrate that GATA-1 and GATA-4 can stimulate inhibin subunit gene promoter constructs. Other studies provide strong evidence that GATA-4 and GATA-6 can activate genes mediating gonadal cell steroidogenesis. GATA-2 and GATA-3 are found in pituitary and placental cells and can regulate α-glycoprotein subunit gene expression. Gonadal expression and activation of GATAs appear to be regulated in part by gonadotropin signaling via the cyclic AMP-protein kinase A pathway. This review will cover the current knowledge regarding GATA expression and function at all levels of the reproductive axis. Exp Biol Med 228:1282–1290, 2003

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Normal reproductive function depends on the proper development and function of the hypothalamic-gonadotrope-gonadal axis. Members of the GATA family of transcription factors are emerging as essential players in reproductive cell lineage determination during development and as mediators of reproductive function in the adult. In mammals, the GATA family is composed of six members, typically divided into two families based on location, structure, and function (1). GATA-1/2/3 members are most often but not exclusively associated with the hematopoietic cell lineages and nervous system development (2–5). GATA-4/5/6 factors are commonly associated with organ development, including the heart, gut, vasculature, and parts of the genitourinary system (5–8). With the exception of GATA-5 (7), the ablation of GATA family members results in embryonic lethality showing the obligatory developmental role of these factors. Just recently, GATA-4 has become the focus of several studies showing that it plays a role in male sex determination, steroidogenesis, and possibly cell survival (9–11). The purpose of this review is to summarize to date the data available on GATA factors at all levels of the reproductive axis, with emphasis on GATA-4.

Structure of GATA

All vertebrate GATA factors have two highly conserved zinc finger domains, C-X_2-C-X_{17}-C-X_2-C with greater sequence divergence outside these domains (1). These factors recognize and bind with high affinity to the DNA consensus motif, WGATAR, and closely related sequences (1, 6). The two adjacent zinc fingers are designated as N-terminal and C-terminal fingers denoting their proximity to the amino or carboxyl terminus (1, 6). DNA binding activity has been localized to the C-terminal zinc finger and adjacent basic region (12). In addition, this same region acts as the nuclear localization domain. Structural (NMR) analysis of GATA-1 has shown that the C-terminal zinc finger interacts with the major groove of DNA and the basic

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[1] To whom requests for reprints should be addressed at Department of Cell and Developmental Biology and Anatomy, University of South Carolina School of Medicine, Building 1, Columbia, SC 29208. E-mail: hlavoie@med.sc.edu

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region interacts with the minor groove, and it is assumed that other GATA factors act similarly (13). GATA-4 interaction with other transcription factors has been demonstrated to occur primarily through the C-terminal zinc finger (6, 14, 15). GATA family members have one or two major transcriptional activation domains in their N-terminal region (6, 12, 16, 17). A minor transactivation domain has been reported in the C-terminal region of GATA-4 (18).

Cofactors can act via either the N-terminal or C-terminal GATA zinc fingers. Cofactors, FOG (Friend of GATA)-1 and FOG-2, interact with the N-terminal finger of GATA family members (19–22). FOG-1 and -2 are multitype zinc finger proteins that interact with GATA factors as transcriptional co-activators or co-repressors depending on the cellular context and specific target genes (22–24). FOG-1 and FOG-2 vary in their tissue distribution. Overexpression studies with FOG-2 have demonstrated repression of GATA-4 dependent transcription of several cardiac- and gonadal-specific gene promoters (20, 25). The co-activators p300/CBP interact with the C-terminal zinc finger of GATAs and promote the ability of multiple GATA factors to promote target gene transactivation (26–32).

Localization of GATA Factors in the Fetal and Adult Ovary

In mammals, GATA-4 and GATA-2 messages and/or proteins have been localized to the developing ovaries of mice, humans, and/or pigs. Immunohistochemical studies showed that GATA-4 was present in the primitive gonad of XX mouse embryos at 11.5 day postcoitum (dpc) (33). In one mouse study, GATA-4 was observed in the follicular somatic cells of differentiating ovaries (13.5–14.5 dpc), and appeared downregulated thereafter (33). In addition, GATA-4 immunoreactivity was not observed in neonatal ovaries (day 7). In contrast, another more recent immunohistochemical study in mice, using antigen retrieval methodology, found GATA-4 expressed in all stages of embryonic ovaries (34). These investigators also confirmed that GATA-4 mRNA, detected by either *in situ* hybridization or Northern blot, was strongly expressed in developing, neonatal, juvenile, and adult mouse ovaries (34, 35). GATA-6 has not been investigated in fetal ovaries, but its message was negligible in neonatal mouse ovaries (35). In human fetal ovaries, GATA-4 immunoreactivity was observed in follicular granulosa cells and stromal cells between 13 to 33 weeks of gestation (earlier and later fetal stages not analyzed) (11, 36). In embryonic pig, immunohistochemical studies localized GATA-4 first in the coelomic epithelium on the ventromedial surface of the mesonephros at 19 dpc (37). By day 22 to 25, GATA-4 immunoreactivity was localized to most of the somatic cells of the bipotential gonad of both sexes. After ovarian differentiation around 33 dpc, porcine GATA-4 could clearly be identified in the somatic follicular cells surrounding egg nests (37, 38). GATA-2 has been detected in germ cells of the XX gonad in mouse embryos between days 11.5 and 14.5 dpc (39). Collectively, the data in mouse, human, and pig suggest a role for GATA-4 in somatic follicular cell differentiation, and data in mouse suggest a role for GATA-2 in germ cell differentiation. However, the target genes of GATA-4 and GATA-2 remain unknown.

The follicles of adult ovaries express GATA-4 and GATA-6. In mice, humans, and pigs, GATA-4 mRNA and/or protein is abundant in the granulosa cell layer of all healthy follicles, and present in some thecal cells and interstitial cells (11, 35, 37, 40). GATA-6 is also found in the granulosa cell layer of all these species (35, 40, 41). In humans and pigs, GATA-6 mRNA or protein is present in some thecal cells as well (40, 41), but has not been reported in mouse (35). The localization of GATA-6 in the ovaries of mice was performed using mRNA *in situ* hybridization (35) because GATA-6 specific antiserum was not available, and the lack of detection of GATA-6 in theca may be due to the limitations of resolving weak hybridization signals. Alternatively, the lack of GATA-6 in mice theca may represent a species or rodent specific variation that cannot be explained at this time except to infer that thecal expression of GATA-6 may not be needed for mouse follicular development since GATA-4 is present. Compared with the follicular somatic cells, oocytes are typically negative for GATA-4 immunoreactivity (11, 33–37, 41). One study did report GATA-4 immunostaining of some oocyte nuclei in adult pig ovary (40) whereas another study did not detect immunostaining (37). Both studies utilized similar antigen retrieval techniques, and thus the differences may be due to the specific antisera employed (rabbit anti-GATA-4 versus goat anti-GATA-4, Santa Cruz Biotech). GATA-6 immunoreactivity has been reported in porcine oocytes of adult ovaries (40). In addition, GATA-4 has been localized to some yolk sac, thecal, and granulosa cell tumors (41, 42).

Species-specific differences in GATA-4 and GATA-6 expression occur in corpora lutea. After ovulation, GATA-4 mRNA and protein are dramatically downregulated in the murine ovary, while GATA-6 mRNA is strongly expressed (34, 35). In humans, GATA-4 mRNA was present in luteinized granulosa cells (from IVF patients) and in luteal structures, but the protein was not detected by immunostaining in ovarian sections probed with the goat anti-GATA-4 antibody (41). In pigs, GATA-4 and GATA-6 mRNA and/or protein continue to be expressed in corpora lutea although GATA-4 immunoreactivity in tissue sections was less intense than in antral follicles on the same slides (40). Of particular relevance may be the observation that GATA-4 DNA-binding activity predominates over GATA-6 in nuclear extracts from these tissues expressing both GATA factors (40). Such variations between species may correspond to the steroidogenic capacity (progesterone in particular) of the corpora lutea at the time of isolation, which was not determined in any of the above studies. One might predict that the essential nature of GATA-4 or GATA-6 to luteal function could be deduced from its nuclear presence during periods of steroidogenic gene upregulation and/or

peak progesterone production by the corpus luteum. To date the corpus luteum of pregnancy has not been evaluated in any species, and it will be of particular interest to determine whether both GATA-4 and GATA-6 are present in the highly steroidogenic structure.

In terms of function in the adult ovary, GATA-4 and/or GATA-6 have been implicated in the transcription of gonadotropin-regulated genes, including inhibin, aromatase, and steroidogenic acute regulatory protein (see Table I). Because GATA-4 has been linked to inhibition of apoptosis in cardioblasts and cardiac muscle cells (43–46), one proposed role for GATA-4 in the ovary is inhibition of follicular cell apoptosis. However, the evidence for this is only correlative and stems from observations that granulosa cells in follicles undergoing apoptosis do not express GATA-4 (11, 35, 36, 40). Another study has shown that granulosa cell-specific expression of the GnRH receptor gene requires a GATA family member, but it has not been determined if it is GATA-4 or GATA-6 (47).

Localization of GATA in Fetal and Adult Testis

Testicular GATA-1 localization has been described for the mouse and has not been examined in other species. In 1993, Ito *et al.* (48) detected GATA-1 in the mouse testis. This observation was unexpected since GATA-1 was found predominantly in hematopoietic cell lineages (49). However, it was determined that GATA-1 is transcribed from a testis-specific promoter that resides 8 kb upstream of the erythroid specific exon 1 (48). By immunohistochemistry, GATA-1 was detected in the cytoplasm but not in the nuclei of Sertoli cell precursors in the male genital ridge (13–14.5 dpc) and neonatal mouse testis (50), suggesting it does not influence gene transcription during these periods. GATA-1 is restricted to Sertoli cells (including nuclei) and is evenly distributed in tubules during prepubertal testis development. In one study of the adult mouse, GATA-1 was only found in Sertoli cell nuclei in seminiferous tubules from stages VII to IX of spermatogenesis, suggesting germ cells at particular developmental stages regulate GATA-1 expression (50). Another developmental study in mouse did not detect immunoreactive GATA-1 in testis in embryonic/fetal or newborn animals, but did confirm protein expression in stage VII to IX tubules of the adult, with some weaker expression in stage X to XII tubules (51). Although GATA-1 expression has not been evaluated in the rat, this stage-specific expression overlaps in the rat with follicle-stimulating hormone (FSH) receptor mRNA expression in Sertoli cells during stages VIII to XII (52), and the rat FSH receptor promoter possesses a functional GATA-1 site (53). Other gene promoters activated by GATA-1 that are potentially important to Sertoli cell function are listed in Table I. GATA-1 has been detected in MA-10 Leydig tumor cells (54), and Leydig cell-enriched testis extracts in one study (55). However, another study failed to detect GATA-1 in purified Leydig cells (25), and GATA-1 has not been localized to Leydig cells in tissues sections (50, 51). Thus, there is no conclusive evidence that GATA-1 is expressed in the Leydig cell population *in situ*.

Testicular localization of GATA-4 has been evaluated in mice, humans, and pigs. GATA-4 mRNA was detected in

Table I. GATA Overexpression Studies Employing Gonadal Gene Promoters

Gene promoter	GATA factor(s)	Effect	Cell type	References
MIS	1,4,5,6	↑	CV-1 (kidney)	33, 66
	2,3	—		101
	4	↑	KK-1 (granulosa) 3T3 (fibroblast) 293T (kidney)	34
Inhibin α-subunit	1	↑	MA-10 (Leydig)	54, 89
	4	—		
	4	↑	mLTC-1 (Leydig) KK1	56
	4	↑	CV-1	32
	4,6	↑	Porcine granulosa cells	40
Inhibin/activin β-B-subunit	1,4	↑	MA-10 MSC-1 (Sertoli)	89
StAR	1,4,6	↑	CV-1	32, 70
	4,6	↑	Porcine granulosa cells	40
	4	↑	HEK293 (kidney)	72
17α-hydroxylase	4	↑	CV-1	32
Aromatase	1,4,6	↑	CV-1	32, 70
SF-1	1,4,6	—	CV-1	70
	4	—	L cells (fibroblast)	
	4	—	TM3 (Leydig)	
	4	—	Y-1 (adrenal)	
	4	↑	αT3-1 (gonadotrope)	
	4	↑	MSC-1	

Note. A 1.5- to 2.1-fold increase for GATA-4 and GATA-6 was not statistically significant.

the urogenital ridge of the mouse as early as 10.5 dpc (34). GATA-4 mRNA and protein persist in the developing mouse testis (13.5 dpc) through adulthood and localize to both Sertoli and Leydig cells (33, 34, 51, 56). In humans, immunoreactive GATA-4 protein was evident in 12-week-old fetal testes (earliest sample available) and was continuously expressed in the Sertoli and Leydig cells through adulthood (57). Peak Sertoli cell GATA-4 immunoreactivity was strongest during the period of Sertoli cell proliferation, and Leydig cell GATA-4 expression was strongest during developmental periods associated with testosterone production (week 15 and after puberty). GATA-4 expression was found in a majority of germ cells before puberty, but its expression was not detected in germ cells after puberty (57). GATA-4 was weak or absent in the testis of humans with androgen resistance (57). In pig, GATA-4 appears in the primitive gonad before male differentiation, and persists through all gestational ages evaluated (37). After the onset of testicular differentiation (26 dpc) and through adulthood, GATA-4 immunoreactivity was found in Sertoli, Leydig, some peritubular myoid cells, and cells destined to form the tunica albuginea, and it colocalizes with Müllerian-inhibiting substance (MIS) and 17α-hydroxylase (p450c17) immunoreactivity (37, 38, 58). In addition, GATA-4 is abundant in both Sertoli and Leydig cell tumors (57). Thus, in all species examined so far, GATA-4 is consistently observed in both the Sertoli and Leydig cell populations. The potential functions of GATA-4 in these cells are summarized in part in Table I or presented below.

GATA-6 expression in testis has only been evaluated in the mouse and human. GATA-6 mRNA was abundant in mouse fetal testicular cords (19 dpc), neonatal, prepubertal, and adult testis and localized to Sertoli cells only (25, 56). In humans, GATA-6 mRNA and protein was detected in fetal testis week 16 to 40 in testicular cords and interstitium with highest expression in the second trimester (59). GATA-6 immunolocalized to both Sertoli and Leydig cells, with strongest staining between weeks 16 to 23, yet GATA-4 cells outnumbered GATA-6 immunopositive cells at all stages. In addition, a few peritubular myoid cells were positive for GATA-6. There is little information currently available about the function of GATA-6 in these cells, but some of the possible gene targets are summarized in Table I.

Role of GATA-4 in Sex Determination and Differentiation

Male sex determination and differentiation depends on the SRY gene located on the Y chromosome in mammals (60, 61). Transient expression of the SRY gene product will initiate Sertoli cell differentiation and testis development from the bipotential embryonic gonad (62, 63). The Sertoli cells of the early testes will produce MIS, which leads to regression of the Müllerian ducts unilaterally, and testosterone, produced by the interstitial Leydig cells of the fetal testis will foster the development of the Wolffian duct system. Several of the transcription factors that can regulate MIS have been elucidated by overexpression studies in cultured cells and activators of this gene include SF-1, WT-1, SOX-9, and GATA-4 (64). SOX-9 is upregulated in male gonad and downregulated in female gonad (64). SF-1 and GATA-4 are present in the bipotential mouse gonad when the MIS gene is activated (33). SF-1 directly interacts with SOX-9 to activate the MIS promoter (65), and GATA-4 transcriptionally cooperates with SF-1 to activate MIS promoter-driven reporter gene activity (66). GATA-4 responsive sites mediate MIS-promoter luciferase activity in primary Sertoli cell cultures (67), and overexpression of GATAs 1,4,5,6 can activate MIS promoter reporter constructs in clonal cells (Table I). Only one study with human embryos reported that GATA-4 appears only after sex cord organization, suggesting it is not involved in onset of MIS gene expression (68). However, this does not preclude a role for GATA-4 in ongoing MIS production.

In vivo studies evaluating the involvement of GATA-4 in the developing gonad have not been possible until just recently because GATA-4 null mice die *in utero* at approximately 9 dpc due in part to cardiac defects (69). However, a recent study has utilized two mouse models, GATA-4^{ki} homozygous mice, and $Fog2^{-/-}$ mice, which both survive *in utero* through 13.5 dpc, and allow evaluation of gonadal differentiation between 10.5 to 12.5 dpc (10). The GATA-$4^{ki/ki}$ animals have a GATA-4 knock-in allele, V217G, which abolishes the ability of this factor to interact with co-factor FOG-2. Both of these models exhibited similar defects in gonadal differentiation. In XY mice, testicular cords did not develop. At 13.5 dpc, XY gonads failed to upregulate SF-1 and WT-1, and their expression was similar to XX gonads. In the XY gonads of both models, SRY gene expression was reduced, SOX-9 and MIS were absent, and transcripts for steroidogenic enzymes, p450scc, 3βHSD, and P450c17 were absent also. These gene products are required for the onset of testosterone synthesis. The transcript for Wnt-4, a mediator of ovarian development, was not downregulated in the mutant XY gonad. These findings show that in the male, GATA-4 and its ability to interact with co-factor, FOG-2, is essential for normal determination and differentiation of the male gonad. As noted by the authors of that study, the role of GATA-4 in ovarian development is less clear, because of the few early ovarian markers.

Role of GATA in Gonadal Steroidogenesis

One of the growing areas of research on GATA-4 involves its potential role in steroid hormone production by gonadal cells. The GATA-4^{ki} homozygous mice and $Fog2^{-/-}$ mice failed to turn on XY gonadal expression of genes mediating steroid synthesis, p450scc, 3βHSD, and p450c17 (10). However, it is unclear whether this was a direct effect of GATA-4 inactivity or the result of reduced expression of SRY and SOX-9. Because of the unavailability of tissue-specific knockouts, the role of GATA-4 in steroidogenesis must be inferred from the available cell culture

experiments. The cell culture data support a requirement of GATA-4 for the induction of genes mediating critical biosynthetic steps in steroidogenesis (70). These genes code for proteins transporting cholesterol to the mitochondria, steroidogenic acute regulatory protein (StAR)—those involved in androgen synthesis, p450c17, and those involved in estrogen synthesis, aromatase (see Table I for references). Silverman *et al.* (71), working with rat granulosa cells, were the first to implicate GATA-4 in ovarian steroidogenesis by demonstrating its requirement in the FSH-stimulation of the StAR gene promoter. Whether gonadotropins stimulate increased GATA-4 binding to DNA elements has not been investigated. Subsequently, other studies have shown that overexpression of GATA-4 (or GATA-6) cDNAs in various primary or clonal cell stimulates the activity of StAR promoter gene constructs (40, 70, 72) and other steroidogenic gene promoters (Table I). In heterologous cells, p450c17 gene promoter activity was only modestly increased (i.e., two-fold) even when stimulated by protein kinase A (PKA) (32), suggesting the need for studies in homologous or primary cells in the context of other tissue specific factors. Indeed, studies with primary cells and conditional knockout animals must be performed to determine if such overexpression studies are relevant *in vivo*.

GATA Functions at Multiple Levels of the Reproductive Axis

Hypothalamus and Pituitary. In addition to roles in the developing and adult gonads, GATA family members regulate reproductive gene expression in the hypothalamus and anterior pituitary gland. In studies conducted in mice, GATA-4 is detected in the nasopharyngeal arch at the time of the olfactory placode formation 9.5 dpc (73). Slightly later in development (13.5 dpc), GATA-4 localizes to migrating GnRH neurons, suggesting a role in their differentiation (74). GnRH-secreting neuronal GT1-7 cell nuclear extracts exhibited GATA-4 binding to GnRH gene promoter sequences, and GATA-4 activated GnRH promoter constructs in co-transfection experiments (75). A role for GATA-4 has not been shown in the adult. This is because GATA-4 is not detected in mature GnRH secreting neurons *in vivo* and adult hypothalamic extracts lack GATA-4 binding (74). However, another GATA-binding molecule or another transcription factor may activate the same regulatory region (74).

GATA-2 and GATA-3 are expressed in the developing anterior pituitary gland (76, 77). Both of these mRNAs are detected in mouse at 10.5 dpc, but GATA-3 mRNA disappears by 13.5 dpc, whereas GATA-2 persists (76). In the pituitary gland, BMP2 is a signaling molecule required for the differentiation of four anterior pituitary cell types: lactotropes, somatotropes, thyrotropes, and gonadotropes (78, 79). Overexpression of BMP-2 induces GATA-2 in the ventral portion of the developing pituitary gland (76). PitX2, a homeobox gene critical to pituitary development, also stimulates the production of GATA-2 (77). GATA-2 colocalizes with α-glycoprotein subunit-expressing (α-GSU) pituitary lineages (thyrotropes and gonadotropes). High levels of GATA-2 lead to the gonadotrope lineage, whereas GATA-2 in the presence of Pit1 will determine the thyrotrope lineage (76). Consistent with this cell-restricted expression, GATA-2 is found in most gonadotrope and thyrotrope adenomas (80).

In terms of gene regulation, studies in gonadotrope cells (αT3 and LβT2) implicate GATA in the SF-1 dependent regulation of the human α-GSU and GnRH receptor gene promoters (81, 82). The αT3 cell line expresses GATA-2, in addition to a GATA-4 related mRNA, and overexpression of either GATA-2 or GATA-3 in these cells stimulates the human α-GSU promoter (83).

Placenta/Trophoblasts. GATA-2 and GATA-3 mRNAs and proteins have been localized in the murine placenta, specifically to giant trophoblast cells (84). Their mRNAs peak during mid-gestation (day 10), coincident with the peak in placental lactogen I mRNA. *In vivo*, studies of placentas lacking GATA-2 or GATA-3 exhibited reduced placental lactogen I and proliferin gene expression, with GATA-2 null placentas having greater reductions in proliferin (85). In support of a role of proliferin's angiogenic function, placentas lacking GATA-2 have significantly less neovascularization compared with wild-type placentas in the same uterus. DNase footprinting analysis of the mouse placental lactogen gene promoter showed recombinant GATA-2 and GATA-3 binding to up to 3 sites. Subsequent, co-expression of GATA-2 or GATA-3 expression vectors with murine placental lactogen I gene promoter constructs in rat Rcho-1 choriocarcinoma and fibroblast cell lines stimulated reporter gene activity (84). In agreement with studies in mice, the ovine placental lactogen gene promoter constructs expressed in human BeWo and Rcho-1 cells also revealed a functional GATA site (86). However, gel mobility shift assays using ovine chorionic binucleate or Rcho-1 cell nuclear extracts showed only GATA-2 and not GATA-3 proteins bound DNA. Other genes critical to human placental functions, including the GnRH receptor and α-glycoprotein subunit, were regulated by GATA-2 and/ or GATA-3 in co-transfection studies in choriocarcinoma cells (83, 87).

In addition to activation of genes essential for placental growth and function, GATA may dictate the cell-specific restriction of particular placental genes. For example, mouse placental hormone, prolactinlike protein A (PLP-A), is expressed only in secondary giant trophoblast cells and not in primary giant cells. PLP-A acts to inhibit the activity of natural killer cells at the implantation site. GATA-2 restricts PLP-A to secondary giant trophoblast cells, and elimination of GATA-2 leads to expression of PLP-A in both primary and secondary giant trophoblast cells (88).

Regulation of Gonadal GATA Expression by Hormones. Evidence supports gonadotropin regulation of gonadal GATA gene expression. The most intriguing data implicating FSH (and possibly estradiol) in GATA-4 induc-

tion comes from studies of individuals with inherited Finnish-type inactivating (A189V) mutations of the FSH receptor gene (36). Women with this FSH receptor mutation exhibit little GATA-4 protein in their ovaries, lack ovarian aromatase, and therefore have negligible estradiol. The ovaries of these women also lack significant follicular development. In support of the idea of gonadotropin regulation, immature mice stimulated with PMSG or estradiol enhanced follicular expression of GATA-4 and GATA-6 transcripts (35). In these animals, hCG-induced ovulation reduced GATA-4 mRNA in granulosa cells, but not that of GATA-6. In addition, expression of GATA-4 and GATA-6 messages peak in the porcine preovulatory follicles, which have been exposed to high levels of estrogens as well as gonadotropins *in situ* (40).

Several gonadal cell lines, including MSC-1 Sertoli cells and NT-1 granulosa cells, respond to FSH and/or cyclic AMP (cAMP) agonists with increases in GATA-4 and/or GATA-6 (35). Mouse tumor Leydig cells (mLTC-1) exhibit a modest yet significant increase GATA-4 mRNA accumulation in response to hCG (56). In human granulosa luteal cells, hCG or cAMP agonist could modestly stimulate GATA-6 mRNA accumulation (41). In contrast, in rat primary Sertoli cells, FSH and forskolin decreased GATA-1 mRNA but did not alter GATA-4 mRNA (55). GATA-1 mRNA in MA-10 Leydig cells was also decreased by cAMP agonist and was inversely correlated with inhibin α-subunit mRNA expression (55). These data, however, are inconsistent with another study showing GATA-1 can stimulate inhibin α-subunit gene transcription in these cells (54, 89). Such inconsistencies may be due to cell culture conditions. However, such studies in Leydig tumor cells may not reflect endogenous Leydig cell function, in light of the fact that GATA-1 protein has been immunolocalized only to Sertoli cells and not to Leydig cells *in situ* (51). Collectively, the effect of cAMP on GATAs appears to depend on the cell type but tends to be predominantly stimulatory for GATA-4.

Regulation of GATA-4 (by Kinases). Virtually nothing is known about regulation of GATA-4 activity in the reproductive system. Most of what is known about GATA-4 regulation by upstream signaling pathways is derived from studies in cardiovascular cells. In cardiomyocytes, GATA-4 activity is positively regulated via phosphorylation at serine 105 by mitogen-activated kinases (MAPK), ERK1/ERK2, and p38 MAPK (90, 91). Also in cardiomyocytes, phosphorylation by glycogen synthase kinase 3β within the first 205 amino acids of GATA-4 inhibits its activity by initiating its export from the nucleus (92). Two recent studies using MA-10 Leydig cells have demonstrated a cyclic AMP-PKA-mediated increase in GATA-4 phosphorylation (18, 32). *In vitro* phosphorylation by protein kinase A has implicated Ser261, and mutation of this phosphorylation site decreases the ability of GATA-4 to transactivate the StAR gene promoter in transfected MA-10 cells. Phosphorylation of GATA-4 by PKA is of particular interest for several reasons. First, PKA is the major signaling pathway for gonadotropins FSH and LH (and hCG) in gonads. In addition, GATA-4 transactivates several PKA-responsive gonadal promoters (32). Moreover, GATA-4 has been shown to be present as both phosphorylated and nonphosphorylated isoforms *in vivo* in adult ovarian somatic cells (40). The development of antisera targeting the GATA-4 protein kinase A phosphorylation site(s) and phosphopeptide mapping is needed to verify these events *in vivo*.

Future Directions. It is apparent from this review that our understanding of the roles of the GATA family in reproductive development and function is in its infancy. GATA family members, especially GATAs 1 through 4, have been extensively studied in nonreproductive tissues. From these studies, it would be predicted that GATA-4 in particular has important reproductive roles that expand beyond gonadal steroidogenesis. Perhaps more rapid advances in the field of reproduction can be made by extrapolating from model systems where these molecules have been well studied. For example, in cardiomyocytes, GATA-4 stimulates endothelin production; endothelin, in turn, activates GATA-4 and mediates cellular hypertrophy (93–97). In the ovary, endothelin is produced by the granulosa cell layer of antral follicles and increases with advancing follicular size (98). Granulosa cell hypertrophy is one of the hallmarks of ovulation (99). Studies of the relationship between GATA-4, endothelin, and hypertrophy are needed in the ovary. In another example, GATA-6 has been shown to induce cell cycle quiescence and differentiation in vascular smooth muscle cells (100). Since peaks in GATA-6 mRNA have been observed in periovulatory follicles (40), perhaps GATA-6 helps mediate the terminal differentiation of ovarian cells into luteal cells around ovulation. Although these studies are possible with the current cell culture and animal models, rapid advances are predicted to be made when animals with GATA gene ablation in specific reproductive tissues are generated.

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