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# Oestrogen Dependent Regulation of Gonadal Fate

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Andrew John Pask

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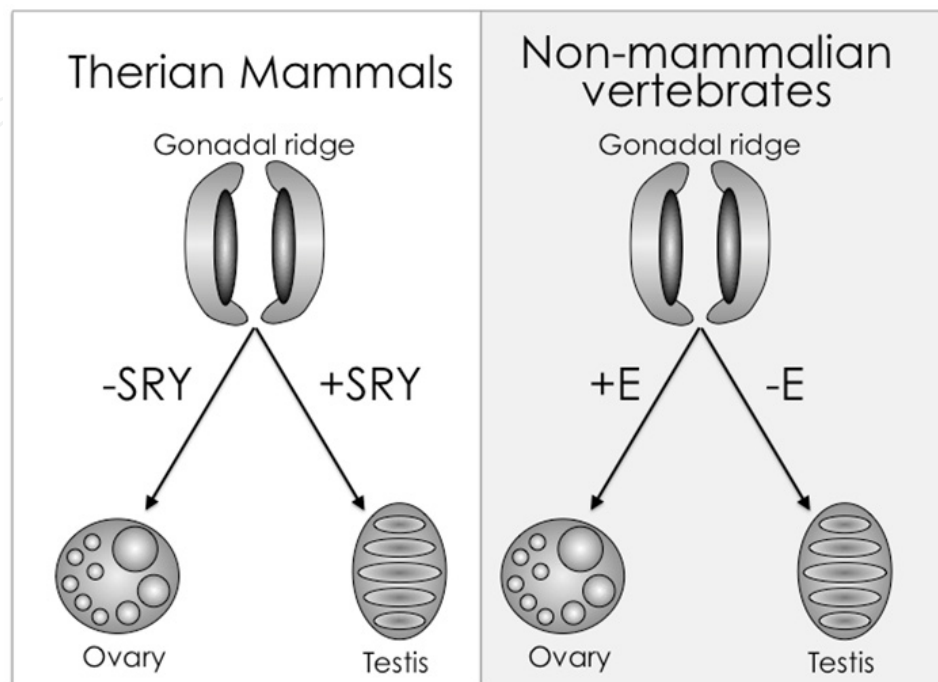
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## 1. Introduction

In mammals, the ovary has been historically viewed as the default gonadal state, such that in the absence of the Y-chromosome and the sex determining switch gene, *SRY*, an ovary would passively form (Wilhelm et al. 2007). This view was in stark contrast to our understanding of gonadal development in non-mammalian vertebrates, where the opposite appears to be true. Ovarian development is the active state, achieved in the presence of estrogen, while development of the testis appears to passively occur in the absence of estrogen signalling (Nagahama 2005) (Figure 1). Despite the different modes of achieving sex determination, recent research suggests that in fact, the role of estrogen may not be so different between non-mammalian and mammalian vertebrates.

Gonads are comprised of two primary cell types: the somatic cell lineages including the supporting cells and the germ cell lineage which gives rise to the haploid gametes. In testes, the supporting cells consist of the Sertoli cells, which support spermatogenesis, the Leydig cells, which produce testosterone, the peritubular myoid cells, which maintain the structure of the testis cord through the secretion of the basal lamina and the endothelial cells that form the vasculature. In the ovary, the supportings consist of the granulosa cells that support oogenesis, the theca cells that secrete hormones, and the stromal cells will form the connective tissue of the ovary. The germ cells will become the spermatozoa in the testes and oocytes in the ovary. The fate of the germ cells is dependent on the somatic cell environment, (ie, whether they are surrounded by Sertoli or granulosa cells) which, in turn, regulates the appropriate development of the gonad (Koubova et al. 2006; Bowles et al. 2006). Germ cells in the developing ovary will enter into meiotic arrest early in development, while testicular germ cells will arrest in mitosis. The regulation of germ cell entry into meiosis in the ovary is induced by retinoic acid (RA), which activates the expression of *Stra8*, a cytoplasmic protein required for pre-meiotic DNA replication

(Koubova et al. 2006). Early entry into meiosis in males is prevented by expression of *Cyp26b1* in the Sertoli cells, an enzyme in the cytochrome P450 family that degrades RA (Koubova et al. 2006; Bowles et al. 2006; Vernet et al. 2006). Thus, establishing somatic cell fate is key to regulating the overall development of the gonad.



**Figure 1.** In most therian mammals (marsupials and eutherians; left panel), sex is determined by the presence or absence of the testis determining factor SRY, located on the Y-chromosome. When SRY is present, the gonad is activated to follow a testis pathway, while in its absence the ovary will develop. This is in contrast to most non-mammalian vertebrates (right panel) where sex appears to be determined by the presence or absence of oestrogen, which drives active ovarian development from the indifferent gonad when present. In the absence of oestrogen, the testis will form.

In the male gonad, it is the activation of *SOX9* (Sry-type HMG box number 9) in the somatic cells that directs Sertoli cell differentiation (Sinclair et al. 1990; Bishop et al. 2000). *SOX9* and its gonadal enhancer, *TESCO* (Testis-specific Enhancer of Sox9 Core element), are highly conserved in the tetrapods, suggesting they play a critical function in vertebrate testis development (Bagheri-Fam et al. 2010). *SOX9* is initially present at low levels in the indifferent gonad and is localized to the cytoplasm of the somatic cell precursors. In developing testes, *SOX9* translocates to the nucleus and is subsequently dramatically upregulated (de Santa Barbara et al. 2000; El Jamil et al. 2008; Morais da Silva et al. 1996). In mammals, it is the expression of the Y-linked sex-determining gene *SRY* (Sex-determining Region on the Y chromosome) that triggers *SOX9* upregulation in the male gonad (Sekido and Lovell-Badge 2008). *SRY* has been shown to bind directly to *TESCO*, leading to *SOX9* activation. *SOX9* then acts as a transcriptional activator of the testis differentiation pathway. The nuclear translocation of *SOX9* is both necessary and sufficient for Sertoli cell development in mice (Qin et al. 2004; Bishop et al. 2000), and is the most critical step in the initiation of the testis pathway. However, even after testicular fate is established, the Sertoli

cell phenotype remains plastic. In mice, expression of *Dmrt1* (Doublesex and mab-3 related transcription factor 1) is essential to maintain Sertoli cells (Matson et al. 2011). Loss of *Dmrt1* even in adult Sertoli cells, leads to upregulation of *FoxL2* (Forkhead box L2) and transdifferentiation into a granulosa cell phenotype. Thus, development of the gonad requires a tightly regulated set of key factors to specify and then maintain gonadal cell identity.

## 2. Molecular control of ovarian differentiation

Since *SRY* is absent from the XX gonad, *SOX9* upregulation is not triggered, and *SOX9* protein levels remain low and cytoplasmic in the somatic cells of the indifferent gonad. In the absence of nuclear *SOX9*, the testis differentiation pathway cannot be initiated and granulosa cell development is activated, leading ultimately to ovarian development. The precise mechanism preventing *SOX9* from entering the nucleus and activating the Sertoli cell program in female gonads is unknown, but recent data suggest that oestrogen may play a key role in this process (Pask et al. 2010). The potential effect of estrogen on sex determination in mammals, including humans, is of great interest due to a recent increase in male reproductive abnormalities in humans and wildlife, resulting in lower sperm counts and quality and increased rates of hypospadias and testicular dysgenesis. The increase in these disorders is too rapid to be accounted for genetic factors, and instead has been attributed to an increased exposure to synthetic environmental endocrine disrupting compounds found in the environment (Giwerzman et al. 1993; Carlsen et al. 1992). Defining how endogenous and exogenous estrogen affects gonadal development in mammals is essential for understanding the aetiology of such disorders.

The sex determining *SRY* gene was discovered in 1990 (Sinclair et al. 1990) and much of the subsequent research has focused on how it mediates testicular development. It is only in the past decade, that key ovary-promoting genes have been identified in mice and humans, which include the *WNT4* (Wingless-type MMTV Integration Site Family, Member 4), *RSPO1* (R-spondin-1) and *FOXL2* genes. Mutations in each of these genes is associated with a failure of normal ovarian formation in mice and humans (Chassot et al. 2008a; Chassot et al. 2008b; Heikkila et al. 2001; Uda et al. 2004; Vainio et al. 1999). In mice, *Rspo1* activates the canonical beta-catenin signalling pathway required for female somatic cell differentiation (Chassot et al. 2008a; Chassot et al. 2008b). *WNT4* suppresses the development of Leydig cells in the developing ovary and may act through follistatin (*Fst*) since mutations in both these genes result in a failure of the coelomic vessel to form (a key event in murine testis development) in XY mouse gonads and a loss of germ cells (Yao et al. 2004). The development of Leydig cells in *WNT4* mutant females results in masculinization and when the female germ cells are lost, seminiferous-like cords form (Heikkila et al. 2001; Vainio et al. 1999). Thus the germ cells play a central role in the development of a normal ovarian morphology (reviewed in (Whitworth 1998; Capel 2000; Brennan and Capel 2004)). While the loss of XX either mitotic or meiotic germ cells results in the formation of seminiferous-like cords in a developing ovary, loss of male germ cells has no effect on testicular formation

(Whitworth 1998; Burgoyne 1988; McLaren 1991; Whitworth et al. 1996). These findings suggest that XX germ cells actively participate in maintaining ovarian histology by inhibiting cord formation and highlight the importance of somatic cell-germ cell interactions in gonadal development.

*FoxL2* is another gene that plays a central role in ovarian development by regulating female somatic cell fate. Ablation of *FoxL2* in adult mouse ovaries leads to a loss of granulosa cell identity and instead the somatic cells develop a Sertoli cell phenotype and an show the upregulation of Sertoli cell markers such as *SOX9* (Uhlenhaut et al. 2009). *FoxL2* appears to mediate somatic cell fate in the ovary by suppressing the male developmental program. It achieves this role through directly binding to the *SOX9* enhancer element, *TESCO*, suppressing *SOX9* transcription. Interestingly, *FoxL2* achieves *TESCO* suppression in conjunction with activated oestrogen receptors (Uhlenhaut et al. 2009). The function of *FOXL2* and activated oestrogen receptors in suppressing *SOX9* appears to be highly conserved as the binding sites for both proteins are highly conserved in *TESCO* across mammals, including in the marsupials which last shared a common ancestor with the mouse over 160 million years ago (Luo et al. 2011) (Figure 2). Furthermore, *FOXL2* has been shown to play a direct role in the upregulation of *CYP19* (Cytochrome P450 Aromatase; required for the synthesis of oestrogen from testosterone) in both the fish brain (Sridevi et al. 2011) and indifferent XX goat gonad, where it initiates the synthesis of oestrogen, promoting ovarian development (Pannetier et al. 2004).

### 3. Oestrogenic control of ovarian cell fate

Non-mammalian vertebrates trigger sex of the developing fetus in a variety of different ways. These can largely be grouped into either genetic sex determining mechanisms, where a sex specific gene triggers sex, or environmental sex determination, where extrinsic cues determine sex. Oestrogen is known to play an essential role in female sex determination in nonmammalian vertebrates regardless of the sex determining mechanism (Solari 1994; Nakamura 2010). The production of oestrogen in the indifferent gonad is controlled by the expression of *CYP19*, which encodes the aromatase enzyme and causes oestrogen production. In the presence of oestrogen, the indifferent gonad will follow an ovarian development pathway, while in its absence the gonad will become a testis (Solari 1994). As a result, exogenous oestrogen exposure to developing fish, reptile, amphibian and bird fetuses will trigger ovarian development, while exposure to oestrogen inhibitors causes testis development (Solari 1994; Ramsey and Crews 2009). This is in contrast to mammals where *SRY* triggers testis development and the ovary is the default state. However, in nonmammalian vertebrates, oestrogen appears to be the master regulator of ovarian development and in its absence the gonad will default to a testicular fate.

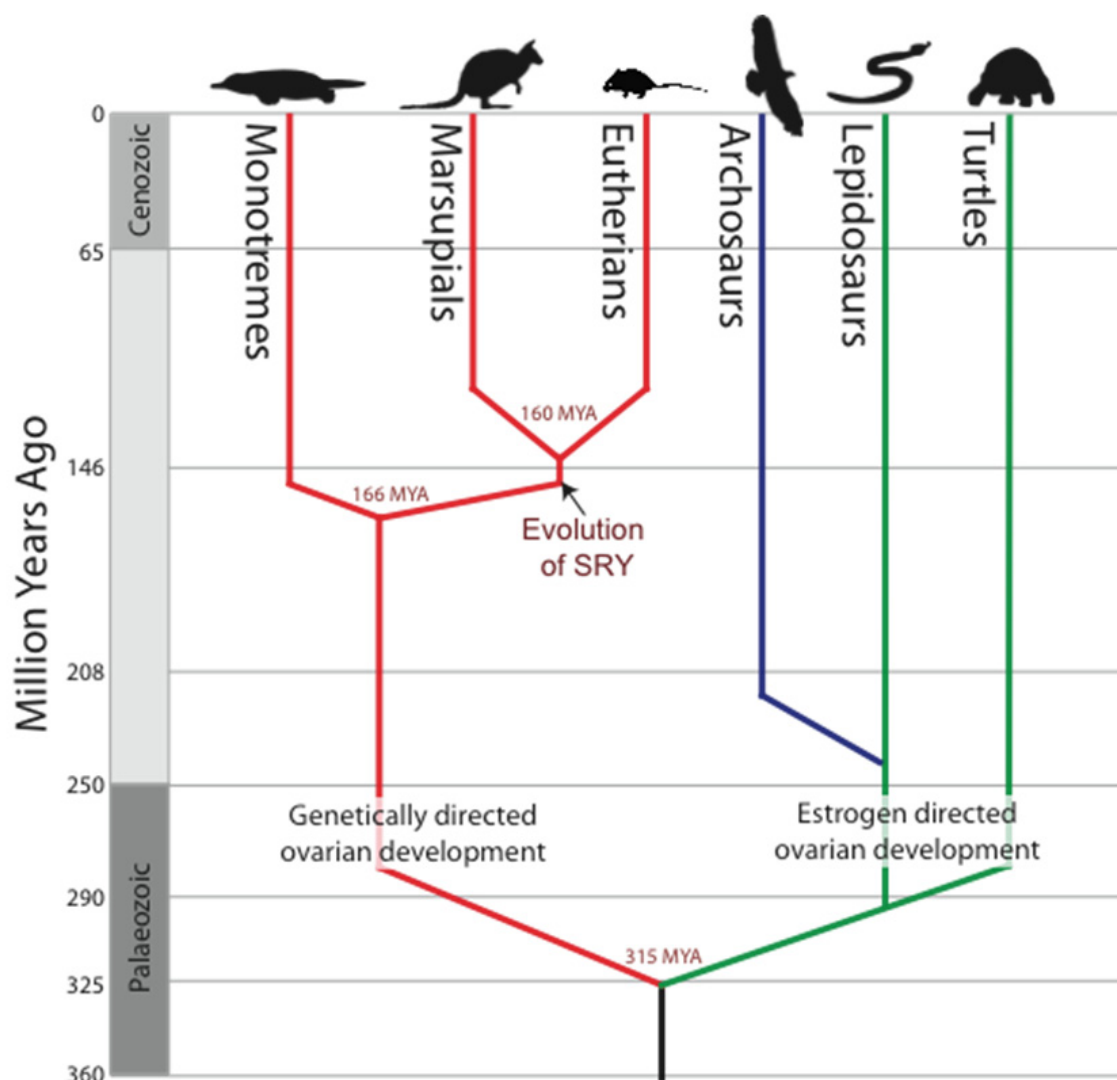
Despite the highly conserved role of oestrogen in nonmammalian vertebrates, its function in the development of the mammalian ovary remains less clear. Interestingly, expression of the oestrogen receptors, which mediate oestrogen actions within the cell, is maintained in the somatic cells of the indifferent gonads of mice, humans, goats, sheep and marsupials



indicative of a highly conserved role for oestrogen in the early mammalian gonad (Calatayud et al. 2010). It was a surprising finding then, that oestrogen was not required for initial ovarian development in mice (Couse and Korach 1999). Mice deficient for both the alpha and beta oestrogen receptors or *CYP19*, have normal early ovarian differentiation (Britt and Findlay 2003; Britt et al. 2001). However, shortly after birth, germ cells are lost and the somatic cells take on a Sertoli cell phenotype (Fisher et al. 1998; Toda et al. 2001). These Sertoli-like cells express *SOX9* and show a characteristic Sertoli cell morphology, with tight junctions, and arrangement (Britt and Findlay 2003). Upon administration of oestrogen to aromatase deficient mice, ovarian histology is restored and *SOX9* levels are significantly decreased, along with several other testis markers, to normal female levels (Britt et al. 2004). Together these data show that the somatic cells of the ovary also retain a plasticity that, along with the genes regulating somatic cell differentiation, is directly responsive to oestrogen.

While mouse studies have been fundamental in developing a basic understanding of gonadal differentiation, there are differences in gene expression, responses to haploinsufficiency of critical genes and, most importantly, in the role of oestrogen in the fetal gonad between mice and other mammals (Wilhelm et al. 2007). Comparative analyses across multiple species can be particularly helpful in isolating critical regulatory networks required for developmental events from those that show species specific variations (Sanchez et al. 2011; Pounds et al. 2011; Crozat et al. 2010; Lu et al. 2009). Outside of the rodent lineage, upregulation of *CYP19* has been reported in the fetal ovary of many eutherian species including goats (Pannetier et al. 2004), sheep (Quirke et al. 2001) and cows (Garverick et al. 2010), suggesting oestrogen may play a central role in its early differentiation. Similarly, in humans, exposure of the developing fetus to potent synthetic oestrogenic compounds can dramatically affect male gonadal differentiation (Toppari 2008; Arai et al. 1983). Thus, it appears that gonadal development in rodents may be unusually resistant to a loss of oestrogen.

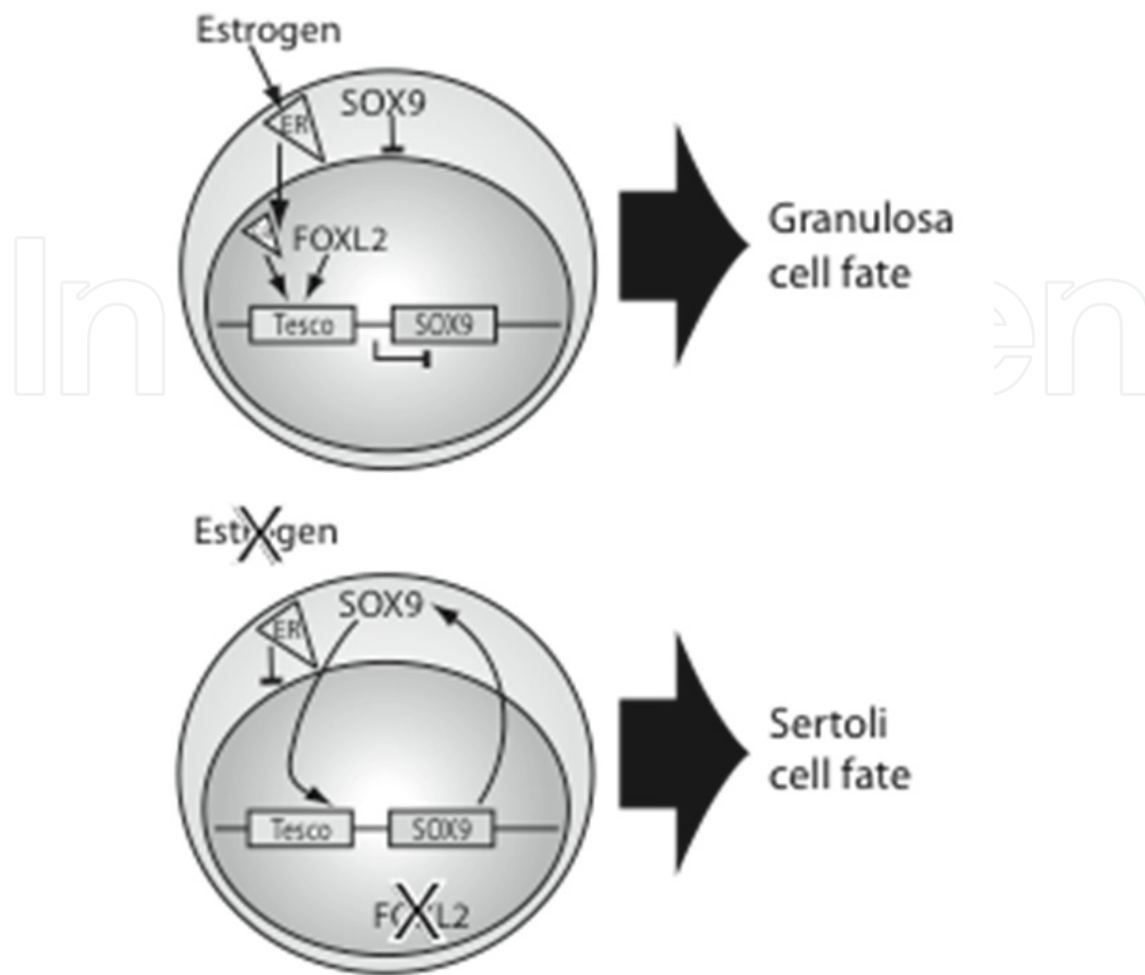
The ability for oestrogen to direct ovarian development in mammals has been demonstrated in marsupials (Pask et al. 2010; Coveney et al. 2001; Burns 1955). Marsupials have been evolving independently of humans and mice for around 160 million years (Figure 2) (Luo et al. 2011). Sexual differentiation occurs around the time of birth in marsupial, unlike in eutherian mammals where this process occurs *in utero*. Marsupials develop gonads that are identical in structure to human and mouse gonads and determine sex based on the presence/absence of the *SRY* bearing Y chromosome (Pask and Graves 2001). Development of the somatic cell lineages and germ cell entry into either meiotic or mitotic arrest is separated by several days in the tammar wallaby, similar to the developmental timing seen in human, goat, sheep and cow gonads, whereas in the mouse these events occur concurrently (Harry et al. 1995; Renfree et al. 1996). Thus in marsupials it is possible to examine the effects of exogenous oestrogen on the differentiation of the somatic cell lineages *ex utero*, uncomplicated by changes in germ cell development or the *in utero* environment.



**Figure 2.** Alternative control of sex determination in amniotes. Amniotes split into the sauropsids (leading to birds and reptiles) and synapsids (leading to mammal-like reptiles). Both lineages have fundamentally different control of gonadal development. In the mammals (at least in marsupial and eutherian lineages) sex is controlled by the presence of the SRY gene on the Y. In non-mammalian amniotes, sex is primarily dependant on whether the gonad is exposed to estrogen or not in early development.

#### 4. Oestrogen blocks male development by modulating SOX9

Administration of oestrogen to genetically male marsupial neonates causes ovarian development of the gonad (Pask et al. 2010; Coveney et al. 2001; Burns 1955). In the presence of oestrogen, key male differentiation genes fail to be up-regulated in the XY gonad and instead, key ovary-promoting genes are upregulated leading to ovarian development (Pask et al. 2010). Oestrogen appears to trigger sex reversal through the exclusion of SOX9 from entering the nucleus in the somatic cells of the developing gonad (Pask et al. 2010). In the absence of nuclear SOX9, Sertoli cell development cannot be initiated and the somatic cells follow a granulosa cell fate (Figure 3).



**Figure 3.** A potential model for the role of oestrogen in somatic cell determination and maintenance. In the presence of oestrogen (top panel), the activated oestrogen receptors direct gonadal somatic cells towards the granulosa cell pathway. Activated ERs (Oestrogen Receptors) work together with FOXL2 to suppress *TESCO* and *SOX9* transcription. Any *SOX9* protein already produced within the cell fails to enter the nucleus. In the absence of nuclear *SOX9*, *AMH* fails to upregulate and ovarian genes are activated. Exogenous oestrogen retains the ability to direct XY bipotential somatic cells towards a granulosa cell fate. Oestrogen may act in a similar manner to maintain granulosa cell fate in mature eutherian ovaries, preventing basal levels of *SOX9* protein from translocating to the nucleus and propagating its own upregulation. In normal XY gonads (bottom panel), the somatic cells upregulate *SRY*, which in turn upregulates *SOX9*. *SOX9* is translated and *SOX9* protein can then translocate to the nucleus and activate the expression of *AMH* and direct Sertoli cell development.

A conserved role for oestrogen mediating *SOX9* action is consistent with several observations in mammals. In mice, *Sox9* is able to autoregulate by binding to its own promoter (Sekido and Lovell-Badge 2008). However, despite *Sox9* expression in the somatic cells of the adult mouse ovary, it does not become upregulated (Notarnicola et al. 2006). High levels of oestrogen could prevent the nuclear translocation of *SOX9* in adult female gonads, preventing its own upregulation. Conversely, *Sox9* is upregulated in the absence of oestrogen in aromatase-deficient mice ovaries, suggesting it can translocate to the nucleus to propagate its own transcription. However, when these mice are exposed to exogenous



oestrogen the effect is reversible, and *Sox9* is repressed (Britt et al. 2002; de Santa Barbara et al. 2000). Data from marsupials would suggest this repression occurs by trapping SOX9 in the cytoplasm preventing its autoregulation. Furthermore, activated oestrogen receptors, in conjunction FoxL2, could directly suppress SOX9 transcription through binding to TESCO (Uhlenhaut et al. 2009). Either way, in mammals oestrogen still remains a critical factor in maintaining ovarian somatic cell fate. This fundamental role of oestrogen is also consistent with observations in nonmammalian vertebrates. In the presence of oestrogen SOX9 remains cytoplasmic in the early developing gonads of many nonmammalian vertebrates permitting granulosa cell development (de Santa Barbara et al. 2000). However, in the absence of oestrogen, SOX9 becomes nuclear and Sertoli cell development is initiated (Sim et al. 2008). Therefore, the ability of oestrogen to mediate the subcellular localization of SOX9 and directly mediate its transcription, could explain the primary mechanism by which oestrogen establishes sex in nonmammalian vertebrates.

Further investigations are needed to determine how oestrogen mediates the subcellular localization of SOX9 within the somatic cells. SOX9 contains two defined nuclear localization signals (NLS) found in the C- and N-termini that are 100% conserved between mouse, human and the wallaby (Pask et al. 2002). Active transport through nucleopore complex is facilitated in part by importin- $\beta$ , binding directly to the C-terminal NLS (Sim et al. 2008). This binding is enhanced by phosphorylation of SOX9 by phosphokinase A, facilitating increased nuclear import (Malki et al. 2005). The N-terminal NLS binds calmodulin, another factor that facilitates nuclear transport of SOX9 (Argentaro et al. 2003). SOX9 is also subject to SUMOylation and ubiquitination (Sim et al. 2008). SUMOylation has been shown to regulate nucleocytoplasmic trafficking of several proteins while ubiquitination marks proteins for degradation. SUMOylation of SOX9 in COS7 cells has been shown to alter its subnuclear localisation and transcriptional activity (Hattori et al. 2006). Oestrogen may affect one or many of these different pathways to regulate the subcellular localization and activity of SOX9.

## 5. Conclusions

### 5.1. A conserved model for determining vertebrate somatic cell fate

While the switch mechanisms that trigger the development of the ovary or testis pathways vary widely among vertebrates, the fundamental control mechanisms regulating somatic cell fate share many commonalities. This suggests a highly conserved and antagonistic relationship between SOX9 and oestrogen driving Sertoli cell and granulosa cell differentiation respectively. In mammals, the somatic cell decision is initially determined by the presence or absence of SRY. When SRY is present, SOX9 is upregulated and can translocate to the nucleus to activate Sertoli cell differentiation. In females, in the absence of SRY, SOX9 is not upregulated and the granulosa cell program is initiated. While it is yet to be shown if oestrogen plays a critical role in early mammalian ovary formation outside of the rodent lineage, oestrogen is essential for maintaining granulosa cell fate in the mature gonads, possibly by ensuring that any SOX9 protein produced remains trapped in the

cytoplasm. In nonmammalian vertebrates, the primary sex determining mechanism, be it genetic sex determination or environmental sex determination, leads to either the presence or absence of *CYP19* expression. In the presence of aromatase and oestrogen, basal SOX9 cannot enter the nucleus and the Sertoli cell program is blocked. In the absence of aromatase and oestrogen, SOX9 can translocate to the nucleus, trigger its own upregulation and initiate Sertoli cell development. More work is needed to confirm this model and determine the precise mechanism by which activated oestrogen receptors mediate the subcellular localization of SOX9. However, these findings provide a simple explanation for the dramatic switch in vertebrate sex determination mechanisms from primarily hormonal control to primarily genetic control, converging through the modulation of SOX9.

## Author details

Andrew John Pask

*Department of Molecular and Cell Biology, The University of Connecticut, Storrs, USA*

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