Focus on TGF- β signalling

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Transforming growth factor- β (TGF- β) is the index member of a large family of multifunctional growth factors. They were named originally for their ability to induce normal rat kidney fibroblasts to grow in soft agar in the presence of Epidermal Growth Factor (EGF) (De Larco & Todaro 1978, Roberts *et al.* 1981). There are 5 subtypes, all products of separate genes, three of which, TGF- β 1, β 2 and β 3, have been shown to be expressed in mammalian ovarian cells (Derynck *et al.* 1988, Hernandez *et al.* 1990, Mulheron & Schomberg 1990). These factors are synthesized in inactive precursor forms that undergo cleavage to produce monomers, which can dimerize to 25 kDa forms through the conserved cysteine regions. The active regions of the TGF- β monomers share 98–100% identity.

The isolation and cloning of inhibin and erythroid differentiation factor (subsequently called activin), and Mullerian inhibiting substance (MIS) led to the observation that these peptides are also members of the TGF- β superfamily. The family has grown to consist of more than 40 members (for a review see Chang *et al.* 2002), including the growth differentiation factors (GDFs) and bone morphogenetic proteins (BMPs) (Fig. 1). Members of the family are related by sequence homology (30–40%) and conservation of the cysteine residues. Many also share a similar signal transduction mechanism involving serine–threonine kinase receptors with downstream Smad signalling pathways (for reviews see Miyazawa *et al.* 2002, Shi & Massague 2003, Lin *et al.* 2006).

The concept that TGF- β superfamily members function as local regulators, either paracrine or autocrine, gained focus after a review on the topic was published by Sporn and Todaro (1980). Further to this, it had been realized that 'there are events of gametogenesis and endocrine function ...which do not necessarily have a direct relationship to the known hormonal milieu being determined by pituitary secretion rates and the afferent blood supply' (Findlay & Risbridger 1987), supporting the concept of local regulation. It very quickly became apparent that many family members were acting as local regulators in reproductive tissues.

In this issue of Reproduction, TGF- β signalling in reproductive tissues is reviewed. This focus issue begins with a chapter on the signal transduction systems that

underlie the actions of TGF- β family members in reproductive tissues. As defined by its title, Lin *et al.* (2006) cover the structural basis of TGF- β , BMP and activin ligand binding. A discussion of ligand-receptor interactions and the inhibition of TGF- β superfamily signaling by extracellular antagonists (noggin, follistatin, chordin/SOG etc) or membrane bound inhibitors (BAMBI, betaglycan etc), are included.

Phil Knight and Claire Glistler (2006) review the role that members of the TGF- β superfamily play in ovarian follicle development, across a range of species. They address the contribution of the three major cell types of the follicle (oocytes, granulosa and theca cells) to the local milieu within the ovary, which might regulate the transition from primordial to antral follicles, selection of the dominant follicle and ovulation.

Bilezikjian *et al.* (2006) have reviewed the effects of the TGF- β superfamily of ligands on the pituitary, with emphasis on the inhibin/activin/follistatin nexus and the regulation of gonadotrope function.

Jones *et al.* (2006) summarize the roles that TGF- β superfamily members play in the uterus and placenta, with particular reference to the processes of endometrial cycling, menstruation, implantation and pregnancy.

Testicular development is addressed in a review by Itman *et al.* (2006). The roles that the TGF- β superfamily members play in the specification of germ cells and their subsequent proliferation or death during embryonic development, in spermatogonial proliferation, differentiation and during adult spermatogenesis, are addressed.

Several outstanding issues arise from these reviews. They include:

- The diversity of the members of the family that can influence reproductive tissues
- The importance of the actions of these members for normal reproductive function
- The redundancy of actions and promiscuity of the receptors and Smads
- The similarities in conformations of receptor/ligand binding
- The important roles of modifying proteins such as follistatin, betaglycan, inhibitory and stimulatory Smads, and nuclear co-activators and co-repressors

Figure 1 Dendrogram of the TGF- β superfamily modified from Chang *et al.* (2002). Cysteine rich, carboxy terminal, polypeptide sequences of mouse TGF- β superfamily members, were aligned using PILEUP software.

The actions of the TGF- β superfamily members in reproductive tissues represents a very complex set of interactions that are context and spatio-temporally specific, and will require much more research before we can fully understand and appreciate the diversity and necessity of their actions.

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