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Plenary lecture

## **New Insights into Inhibins and Activins**

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The TGF $\beta$  superfamily arose millions of years ago and co-opted a transmembrane receptor with serine-threonine kinase properties. The modern family consists of forty-two encoded subunits, five binding receptors (RII) that are constitutively active serine-threonine kinases, and seven signaling receptors (RI) that are RII substrates. The ligands in this family are dimers that are disulfide linked in most, but not all cases. A large number of ligands can be produced from the subunit family and interact with a limited array of receptor partners. Therefore, the evolutionary pressure for the TGF $\beta$  superfamily was to build regulatable ligands rather than to expend energy on a larger set of receptors. The three activin isoforms [activin A ( $\beta$ A- $\beta$ A), activin B ( $\beta$ B- $\beta$ B) and activin AB ( $\beta$ A- $\beta$ B)] are regulated independently and have distinct biological functions. Activin is a unique ligand within the TGF $\beta$  superfamily because it has a naturally occurring antagonist called inhibin. Inhibin is the only endocrine hormone in the TGF $\beta$  superfamily and blocks the paracrine acting activin in a classically defined negative feedback loop.

One of the reasons that the ligands act as functional antagonists is their structural similarity. Activin is a dimer of two TGF-like  $\beta$  subunits, while inhibin is assembled from a  $\beta$ A- or  $\beta$ B-subunit and a dissimilar  $\alpha$  subunit. Inhibin is known to bind the activin receptor ActRIIB, with the aid of an accessory protein known as betaglycan. Mammalian  $\alpha$ -subunits are not able to homo-dimerize and regulation of  $\alpha$ - $\beta$  heterodimers vs.  $\beta$ - $\beta$  homodimers is just one of the major cellular problems that had to be solved. The ovarian granulosa cell produces both ligands, whereas inhibin B is the dominant form produced by Sertoli cells. Loss of inhibins at the time of menopause in women, following Sertoli damaging chemotherapy in men, or by experimental interventions leads to a prodigious increase in FSH production, indicating that these ligands are central to FSH restraint in an endocrine manner. Our studies are expected to provide insight into the control of inhibin and activin action and to a more complete understanding of normal fertility and the mechanisms that underlie reproductive diseases in women resulting from inappropriate hormone action.

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