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Review

Regulation of activin and inhibin in the adult testis and the evidence for functional roles in spermatogenesis and immunoregulation

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ABSTRACT

Activin A provides a unique link between reproduction and immunity, which is especially significant in the adult testis. This cytokine, together with inhibin B and follistatin acting as regulators of activin A activity, is fundamentally involved in the regulation of spermatogenesis and testicular steroidogenesis. However, activin A also has a much broader role in control of inflammation, fibrosis and immunity. In the Sertoli cell, activin A is regulated by signalling pathways that normally regulate stress and inflammation, signalling pathways that intersect with the classical hormonal regulatory pathways mediated by FSH. Modulation of activin A production and activity during spermatogenesis is implicated in the fine control of the cycle of the seminiferous epithelium. The immunoregulatory properties of activin A also suggest that it may be involved in maintaining testicular immune privilege. Consequently, elevated activin A production within the testis during inflammation and infection may contribute to spermatogenic failure, fibrosis and testicular damage.

Contents

1. Background/historical

Activin and inhibin were first identified and isolated in gonadal fluids and extracts, based on their opposing abilities to regulate the production and secretion of follicle-stimulating hormone (FSH) by the anterior pituitary (Ling et al., 1986; Robertson et al., 1986). While gonadotrophin regulation is still considered to be the principal physiological role of inhibin, it is now widely recognised that activin is produced in many different cell types and tissues, where it exerts control of several fundamental biological processes. These processes include the control of inflammation and immunity and the development of the foetal and prepubertal testis (Hedger et al., 2011; Itman et al., 2006; Loveland et al., 2007). However, it is equally apparent that activin possesses important roles in the

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control of mature testicular function that have received much less attention, hence this review.

2. Biology of activin and inhibin

Activin and inhibin are structurally-related members of the much larger, pleiotrophic and ubiquitous transforming growth factor β (TGFβ) superfamily. When first isolated from ovarian extracts, based on the ability to inhibit FSH production, inhibin was found to be composed of two subunits, a single α-subunit and one of two homologous β-subunits, A and B, encoded by separate genes (Table 1). These heterodimers were named inhibin A and inhibin B, respectively. However, homodimers and heterodimers of the β-subunits were also quickly found to be present in ovarian and testicular extracts and, because these molecules opposed the actions of inhibin (i.e. they stimulated FSH production), were named activin A, activin B and activin AB (Ling et al., 1986).

The best studied of the activins is activin A, which, apart from stimulating FSH synthesis by pituitary gonadotrophs, plays critical roles in the regulation of embryogenesis, stem cell development, cell growth and cell survival, inflammation and fibrosis, immune cell development and immunoregulation. Activin B appears to be a weaker agonist of activin A, although there is evidence that it may also express its own range of actions (Brown et al., 2000; Mathews and Vale, 1991; Thompson et al., 2004). Activin AB has received almost no scrutiny, and it is uncertain at this time whether this molecule is simply a by-product of differential subunit dimerisation in cells which express both β-subunits. Like other members of the TGFβ superfamily, the activins act by binding to one of two specific type 2 activin receptors on the cell surface (ACVR2A or ACVR2B), which then dimerises with an activin-specific type 1 receptor serine/threonine kinase (activin receptor-like kinase, ALK) (Tsuchida et al., 2009). This involves ALK4 (ACVR1B) in the case of activin A and ALK4 or ALK7 (ACVR1C) in the case of activin B and activin AB (Bernard et al., 2006; Tsuchida et al., 2004). The activins also bind to ALK2 (ACVR1), but binding does not transmit a signal, and this molecule appears to act as a negative regulatory subunit in relation to activin activity (Renlund et al., 2007; ten Dijke et al., 1994) (Table 1). Differences in activins A and B activity have been attributed to different affinities for the type 1 and type 2 activin receptors (Mathews and Vale, 1991). Subsequent phosphorylation of the SMAD proteins 2 and 3, leads to formation of a heteromeric transcription factor with SMAD4, thereby activating SMAD-responsive gene transcription; however, other signalling pathways may also be activated, most notably inflammation and stress-mediated pathways via the adapter protein, tumour necrosis factor receptor associated factor 6 (TRAF6), and downstream mitogen-activated protein kinases (MAPK): p38, c-Jun N-terminal protein kinases (JNK), and extracellular-signal-regulated kinases (ERK) (Heldin et al., 2009).

In spite of considerable effort, a distinct receptor for inhibin has not been identified. Inhibin is able to interact with the activin receptor, through the mediation of a third receptor subunit, or co-receptor, called transforming growth factor, beta receptor III (TGFBR3) or betaglycan (Lewis et al., 2000). Betaglycan enhances the binding of the inhibins to the type 2 activin receptors, thereby blocking activin binding, and preventing dimerisation with the type 1 receptors. In fact, the ability of inhibin to suppress FSH is due to the blockade of endogenous activin activity within the anterior pituitary itself (Bilezikjian et al., 2004). In a reversal of the apparent relative activities of the activin subunit homodimers, data indicate that inhibin B is a more effective antagonist of activin activity than inhibin A (Makanji et al., 2009).

Inhibin is just the best characterised and most specific regulator of activin activity, and there are several other regulators with significant physiological roles (Table 1). Follistatin is a highly selective activin-binding protein, which was initially identified in ovarian extracts, but, like activin itself, is produced in many tissues (Michel et al., 1990; Nakamura et al., 1990). The bone morphogenetic protein and activin membrane-bound inhibitor (BAMBI) is a transmembrane protein, related to the activin type 1 receptor,

Table 1
Activin-related genes and protein products relevant to testis biology, and their known functions in activin biology.

Gene name	Gene product/trivial name	Abbreviation	Known functions
Inhibin, alpha	Inhibin α-subunit	INHA	Inhibin A (heterodimer with βA-subunit) Inhibin B (heterodimer with βB-subunit) Antagonist of activins A and B
Inhibin, beta A	Inhibin/activin βA-subunit	INHBA	Activin A Activin AB (heterodimer with βB-subunit) Inhibin A
Inhibin, beta B	Inhibin/activin βB-subunit	INHBB	Activin B Activin AB (heterodimer with βA-subunit) Inhibin B
Inhibin, beta C	Activin βC-subunit	INHBC	Activin C Activin AC (heterodimer with βA-subunit) Antagonist of activin A
Activin A receptor, type IIA	Activin receptor type 2	ACVR2A	Activin receptor subunit
Activin A receptor, type IIB	Activin receptor type 2B	ACVR2B	Activin receptor subunit
Activin A receptor, type I	Activin-like kinase 2 (Alk2)	ACVR1	Activin receptor subunit (non-activating)[a] Blocks activin signalling
Activin A receptor, type IB	Activin-like kinase 4 (Alk4)	ACVR1B	Activin receptor subunit Transduces signalling (activins A, AB and B)
Activin A receptor, type IC	Activin-like kinase 7 (Alk7)	ACVR1C	Activin receptor subunit Transduces signalling (activins AB and B only)
Transforming growth factor, beta receptor III	Betaglycan	TGFBR3	Activin co-receptor Facilitates binding of inhibin to activin receptor type 2
Bone morphogenetic protein and activin membrane-bound inhibitor homolog		BAMBI	Activin pseudoreceptor Blocks activin signalling
Follistatin		FST	High-affinity activin-binding protein Prevents activin activity and targets for degradation

[a] N.B.: although ACVR1 cannot mediate activin signalling, it is activated by other TGFβ family members, most notably the bone morphogenetic proteins.