A New Compass for Activin Research—A Triumph for Systems Biology

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The last decade of biomedical research has witnessed an explosion of new information with the advent of the genomic and proteomic eras. Array technology has literally swamped bench and translational/clinical researchers with such an overabundance of data that highly innovative approaches are required to determine relevance to development and disease. One such approach is the development of the field of systems biology. Strictly speaking, systems biology refers to the all-encompassing approach that begins with detailed knowledge of gene and protein structure, together with cell-specific information for protein function; integrates this knowledge into organ and/or pathway functions; and culminates in translational applications in medicine. The overall goal of the systems biologist/medical researcher is the development of a biologically holistic understanding and approach to human health. The study by Makanji *et al.* (1) in this issue presents an excellent example of the value of a systems biology approach.

In practice, a common beginning step in applying a systems biology approach is the use of powerful software programs, which organize raw data from gene or protein arrays into networks of interrelated biological pathways. It is then the task of researchers to identify important foci of interactions and functions that provide context and meaning to these networks. The challenge is not unlike trying to navigate a complex maze without map or compass. Success is achieved by developing specific reagents that the medical scientist can use to establish orientation and identify medically relevant interactive mechanisms.

The endocrinologist is by nature traditionally familiar with the challenge of understanding interrelated biological pathways. Hormones, by their very nature, have a multitude of effects on numerous organ systems. Evolution has provided complex systems of checks and balances through interrelated pathways such that hormonal actions are precisely controlled. An excellent example of such interrelated pathways is presented by the hormone activin. Activin is a member of the TGFβ superfamily of peptide growth factors and shares many characteristics of this superfamily, including mechanisms of ligand-receptor interactions, signaling mechanisms, and of particular interest here the ability of the propeptide to regulate the synthesis and secretion of the mature peptide (2, 3). Activin has significant roles in the regulation of a number of biological systems plus a multitude of apparent interactive relationships with other members of the TGFβ superfamily as well as other hormones/peptides (reviewed in Ref. 2). Underlying the motivation for this study by Makanji *et al.* (1) is activin's apparent role in promoting cachexia in patients with a variety of tumors and promoting development of gonadal tumors, however the value of this study is much broader.

A challenge in studies of activin and other members of the TGFβ superfamily is the frequent occurrence of nonspecific interactions with the regulation and signaling of other family members. This makes both the identification of specific actions and the development of specific agonists and antagonists highly challenging. Approaches using genetic manipulations (transgenic animals or *in vitro* small interfering RNA gene knockdown) are useful but have limitations that could be overcome by development of ag-

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Abbreviation: AT propetide, Activin propetide.

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onistic and antagonistic compounds that are highly specific for the peptide of interest. In this issue, Makanji *et al.* (1) report the use of a systems biology framework to create a highly specific activin antagonist [activin propetide (AT propetide)] that suppresses activin A (and at a modestly lesser potency, activin B) stimulation of FSH release. Systems biology contributed significantly to the development of the AT propeptide. Makanji *et al.* (1) drew on studies of the molecular two- and three-dimensional structures of both the TGFβ1 propeptide and the activin propeptide to determine specific domains involved in protein folding that, for the TGFβ1 propeptide, create a structure that binds and thereby inhibits mature TGFβ1. By linking the C-terminal activin portion with the N-terminal TGFβ1 portion, a chimeric peptide (AT propeptide) was created that binds mature activin with high affinity and blocks its action with high specificity, such that the actions of related molecules are not affected.

The elegance of this approach lies in the specificity of the AT propeptide. Existing activin antagonists display cross-reactivity with other members of the TGFβ superfamily, limiting their utility both for probing the specific actions of activin and for development of clinical therapies in conditions in which blockade of activin activity may confer significant health benefits. One may predict that the AT propeptide will generate significant and otherwise unavailable insights into the many functions of activin and mechanisms of interactions with other related TGFβ1 family members such as inhibin. It is also likely that this chimeric propeptide will lead to development of novel therapies for cancer and other diseases. This study is a model example of the value and rewards that may be expected from properly applied systems biology thinking in the 21st century.

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References

1. **Makanji Y, Walton KL, Chan KL, Gregorevic P, Robertson DM, Harrison CA** 2011 Generation of a specific activin antagonist by modification of the activin A propeptide. Endocrinology 152:3758–3768
2. **Xia Y, Schneyer AL** 2009 The biology of activin: recent advances in structure, regulation and function. J Endocrinol 202:1–12
3. **Stenvers KL, Findlay JK** 2010 Inhibins: from reproductive hormones to tumor suppressors. Trends Endocrinol Metab 21:174–180