

Computational Design of Inhibitors of Activin-Follistatin Interaction

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ABSTRACT

The pituitary gonadotropins, FSH, play a pivotal role in a normal reproductive function. Activin is produced in various tissues and stimulates synthesis of FSH by direct action on gonadotrope cells. Many other functions have been found to be exerted by activin, including their roles in cell proliferation, differentiation, apoptosis, metabolism, homeostasis, immune response, wound repair and endocrine function. Activins (25 kDa) are the members of the TGF-beta superfamily, have powerful actions on erythropoiesis, liver proliferation, immune function, bone formation, angiogenesis, neuronal survival, skin morphogenesis, and wound repair.

The ability of activins to assemble their receptor complex, however, is regulated by a number of extracellular binding proteins, chief among them is Follistatin. Follistatin is a monomeric protein, structurally unrelated to TGF- β superfamily and acts primarily by binding to activin and preventing its interaction with its receptor. Designing inhibitor that block binding of Follistatin to Activin will promote the activin, TGF- β and/or BMP responsiveness.

Crystal structure of Activin β A - Follistatin and Activin β A - Activin Receptor type IIB extracellular domain are known. There is no crystal structure available for activin-A bound to activin-like kinase-4. From the structures we computed surface accessibility in presence and in absence of the complexed partner and identified the region of Follistatin that binds to receptor and also involved in binding to Activin there by antagonizing the Follistatin interaction with the receptors and with Activin. We have used the interaction site of the Follistatin with Activin to screen millions of small molecules in the CAP and ZINC databases. We have used LUDI *de novo* design method for screening the small molecules that bind to Activin and also against Follistatin binding site. We have then selected molecules unique to Follistatin binding. We present our results in obtaining Follistatin binding ligands along with various theoretical binding scores obtained. We further analyzed various binding scores to select a manageable number of these molecules for experimental binding assay.