Activins and Inhibins

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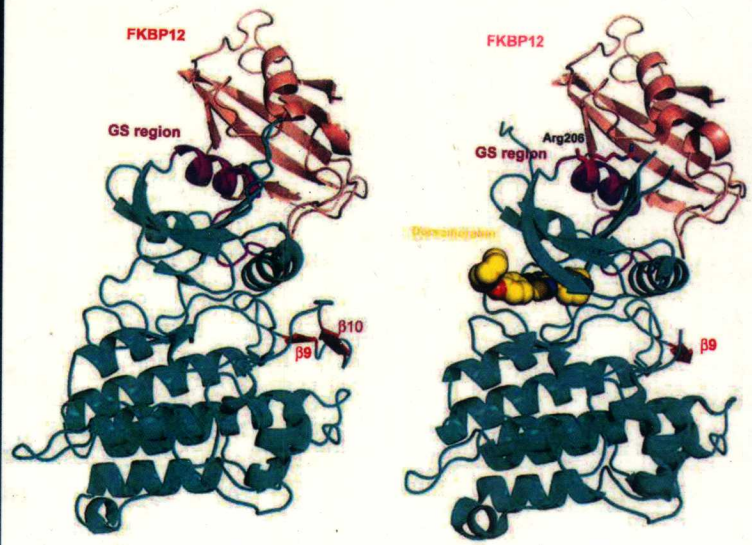
Gerald Litwack



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VITAMINS AND HORMONES

Activins and Inhibins

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PREFACE

Activin and inhibin are dimeric proteins. There are three possible activins, based on the content of β_A and β_B subunits, and two inhibins, based on the content of α and β_A or β_B subunits. β_A subunit is $\sim$32 kDa, and activin A (β_A–β_A) is about 100 kDa. Activin is synthesized in the gonads, pituitary, and placenta, and its action is to stimulate the synthesis and secretion of follicle-stimulating hormone (FSH) from the anterior pituitary. Inhibin inhibits the synthesis of FSH as well as the secretion of gonadotropic-releasing hormone (GnRH) from the hypothalamus. GnRH acts on the gonadotropic cell of the anterior pituitary to cause the release of FSH. Besides its effect on FSH, activin has activities in cell proliferation, metabolism, differentiation, apoptosis, and others. Inhibin's effect on FSH is known, but less is known about its functions and the mechanism by which it can inhibit the actions of activin. In this volume, these features of the two hormones are reviewed and the latest information on their characteristics and activities is recorded.

Chapter 1, entitled "Activin receptor-like kinase and the insulin gene," is by R. Watanabe. Chapter 2, an important structural chapter, is entitled "Crystal structure of activin receptor type IIB kinase domain" and authored by S. Han. Chapter 3, entitled "Activin/Nodal signaling and pluripotency," is authored by Z. Chng, L. Vallier, and R. Pedersen. Chapter 4 is entitled "Intracrine signaling mechanisms of activin A and TGF-β" and is by O. A. Gressner. Chapter 5, "Negative regulation of activin signal transduction," is offered by S.-C. Choi and J.-K. Han. This is followed by Chapter 6, "Antagonism of activin by activin chimeras," by U. Muenster, R. Korupolu, R. Rastogi, J. Read, and W. H. Fischer. Chapter 7, "Activins and cell migration," is authored by H.-Y. Kang and C.-R. Shyr. K. L. Walton, Y. Makanji, D. M. Robertson, and C. A. Harrison contributed Chapter 8, "The synthesis and secretion of inhibins." Regarding the central nervous system, H. Ageta and K. Tsuchida introduce "Multifunctional roles of activins in the brain." Following along with the biological functions of activin, C. Payne, J. King, and D. Hay report on "The role activin/nodal and Wnt signaling in endoderm formation." "Activin in glucose metabolism" is covered by O. Hashimoto and M. Funaba, and K. Ogawa and M. Funaba discuss "Activin in humoral immune responses." "The regulation and functions of activin and follistatin in inflammation and immunity" is a report by M. P. Hedger, W. R. Winnall, D. J. Phillips, and D. M. de Kretser. Y. Makanji, C. A. Harrison, and D. M. Robertson contribute "Feedback regulation by inhibins A and B of the pituitary secretion of

follicle-stimulating hormone." Chapter 15 describes "Activin A in nonalcoholic fatty liver disease" by A. Yndestad, J. W. Haukeland, T. B. Dahl., B. Halvorsen, and P. Aukrust.

The figure on the book cover is Fig. 2.1. It shows the type I receptor kinase domain structures. (A) The structure of TβRI in complex with FKBP12. (B) ActRI kinase domain in complex with FKBP12 and dorsomorphin.

I appreciate the cooperation of Narmada Thangavelu, Lisa Tickner, and Delsy Retchagar, all of Elsevier, in aspects of the production of this volume.

Gerald Litwack
October 13, 2010

Contents

CHAPTER ONE

Activin Receptor-Like Kinase and the Insulin Gene

Rie Watanabe[1]

Contents

Abstract

The biological responses of the transforming growth factor-β (TGF-β) superfamily, which includes Activins and Nodal, are induced by activation of a receptor complex and Smads. A type I receptor, which is a component of the complex, is known as an activin receptor-like kinase (ALK); currently seven ALKs (ALK1–ALK7) have been identified in humans. Activins signaling, which is mediated by ALK4 and 7 together with ActRIIA and IIB, plays a critical role in glucose-stimulated insulin secretion, development/neogenesis, and glucose homeostatic control of pancreatic endocrine cells; the insulin gene is regulated by these signaling pathways via ALK7,

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which is a receptor for Activins AB and B and Nodal. This review discusses signal transduction of ALKs in pancreatic endocrine cells and the role of ALKs in insulin gene regulation.

I. Introduction

The transforming growth factor-β (TGF-β) superfamily, which includes TGF-βs, Activins, Nodal, Inhibins, the bone morphogenetic proteins (BMPs), and growth and differentiation factors (GDFs), regulates a wide variety of cellular processes involving proliferation, differentiation, adhesion, apoptosis, and migration. All TGF-β family members are synthesized as precursor proteins and form dimeric ligands, some of which remain inactive as latent forms by binding to their propeptides, for example, TGF-βs and some GDFs, or as trapped forms by extracellular antagonists, for example, follistatin, which inhibits Activins and noggin and chordin which inhibit some BMPs (Moustakas and Heldin, 2009). On release from these inactive states, the dimeric ligands bind to pairs of membrane receptor serine/threonine kinases, type I (activin receptor-like kinases, ALKs) and type II receptors, promoting the formation of heterotetrameric receptor complexes (Fig. 1.1). Ligand binding induces a link between the constitutively active type II receptors and the dormant type I receptors; when the type II receptor phosphorylates a serine/threonine-rich region, called the GS region, in the cytoplasmic domain of the type I receptor, kinase activity of the type I receptor is stimulated, and ligand-dependent signal transduction then advances. Currently, five type II and seven type I receptors have been identified in mammals. In addition, the TGF-β family ligands also interact with type III receptors: epidermal growth factor–Cripto–FRL1–Cryptic (EGF–CFC)/Cripto, endoglin, and the proteoglycan betaglycan, which are coreceptors and either facilitate or limit the signaling of the receptor kinase. In the absence of the ligand, the small proteins FKBP12 and FKBP12.6 bind to the GS region and maintain the inactive conformation of TGF-β type I receptor by occluding the site of phosphorylation under the TGF-β signaling.

The activated type I receptor phosphorylates receptor-regulated Smads (R-Smads) in the cytoplasm; phosphorylated R-Smads associate with common-mediator Smad (Co-Smad), Smad4, and the resulting Smad oligomer is then shuttled into the nucleus. In nucleus, the Smad complexes bind to target genes and regulate their expression together with other transcription factors (Fig. 1.1; Lönn *et al.*, 2009; Massague and Gomis, 2006, Massague *et al.*, 2005; Moustakas and Heldin, 2009; Schmierer and Hill, 2007; Zhang, 2009).