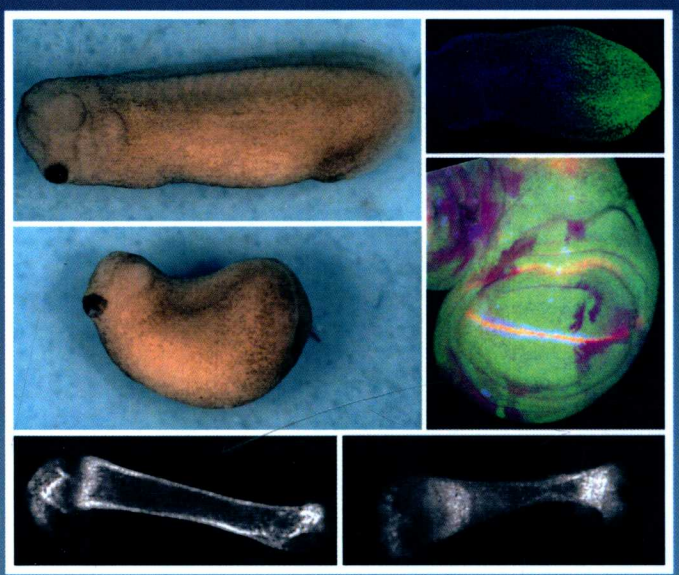
# PROTEIN KINASES IN DEVELOPMENT AND DISEASE



Edited by

Andreas Jenny

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# CURRENT TOPICS IN DEVELOPMENTAL BIOLOGY

## Protein Kinases in Development and Disease

Edited by

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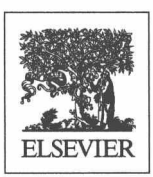


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## Protein Kinases in Development and Disease

# CURRENT TOPICS IN DEVELOPMENTAL BIOLOGY

*"A meeting-ground for critical review and discussion of developmental processes"*
**A.A. Moscona and Alberto Monroy (Volume 1, 1966)**

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# PREFACE

As the ancient Greek word κινειν (kinein; to move) suggests, kinases are true movers (or blockers) in a cell and are broadly grouped into protein, lipid, and carbohydrate kinases (plus a few others such as nucleoside-phosphate kinases). The roughly 518 human protein kinases comprise seven major subfamilies and represent roughly 2% of the genome (Manning, Plowman, Hunter, & Sudarsanam, 2002; Manning, Whyte, Martinez, Hunter, & Sudarsanam, 2002; Taylor & Kornev, 2011; Ubersax & Ferrell, 2007).

Posttranslational phosphorylation likely is the most widespread way of regulating protein function. Phosphorylation state affects every basic process in a cell including transcription, translation, cell division, inter- and intracellular communication, differentiation, metabolism, and so on. Not surprisingly, kinases and their counterparts, phosphatases, are crucial for normal development of multicellular organisms and aberrant kinase function or regulation can cause diseases.

The first kinase to be discovered in the 1950s by Fischer and Krebs was Phosphorylase kinase, which converts Phosphorylase B to the more active Phosphorylase A that mediates degradation of glycogen. This discovery paved the way forward for this previously unappreciated mode of regulation (Krebs, 1998; Krebs, Graves, & Fischer, 1959). Over the years, work in many labs has contributed to the identification, and biochemical, structural, and physiological characterization of a variety of kinases (reviewed in Taylor & Kornev, 2011; Ubersax & Ferrell, 2007). All kinases are characterized by the presence of a kinase domain, the activity of which is tightly regulated by intra- and intermolecular interactions. Kinase domains span about 250 amino acids and consist of a smaller N-terminal lobe composed of mostly β-sheets and a larger α-helical C-lobe (Knighton et al., 1991; reviewed in Taylor & Kornev, 2011; Ubersax & Ferrell, 2007). Sandwiched between these lobes is the hydrophobic ATP-binding site with the γ-phosphate oriented toward the substrate that binds in the cleft. Auto- or transactivation of a protein kinase generally occurs via phosphorylation of an activation segment within the C-lobe. Phosphorylation orders and moves the loop structure to allow access of the substrate to the binding cleft (Adams, 2003; Taylor & Kornev, 2011). This off/on switch type of regulatory mechanism thus allows for tight control of kinase activity and offers the opportunity for intricate regulation of cellular signaling networks.

The 13 chapters of this issue of *Current Topics in Developmental Biology* highlight the roles of some familiar and some less well-known kinases in development and disease.

This volume begins with WNK kinases that are characterized by an atypical placement of a critical lysine residue in the catalytic domain (Rodan and Jenny; Chapter 1) and have recently been shown to have developmental functions in addition to their role in ion transport regulation in the kidney. Activation of PI3 (Phosphoinositide 3)-kinase is central to many physiological and pathological processes including growth control, motility, and differentiation. Although Akt (aka Protein kinase B) has long been thought to be the key mediator of PI3K effects, Di Cristofano in Chapter 2 highlights a more recently discovered PI3K effector, serum, and glucocorticoid-regulated kinase 1 (SGK1), and emphasizes both roles shared with Akt and effects that are mediated exclusively by SGK1.

Blaquiere and Verheyen shed light on the diverse and sometimes conflicting roles of Homeodomain-interacting protein kinases (Hipk; Chapter 3) and discuss involvement of these kinases in the regulation of a variety of signaling pathways. Chapters 4 and 7 by Stricker et al. and Chitu and Stanley, respectively, discuss regulatory roles of the tyrosine kinases Ror (Receptor tyrosine kinase-like orphan receptor) and CSF1-R (Colony-stimulating factor-1 receptor) during embryonic development in vertebrates, the former affecting gastrulation and the latter fulfilling macrophage-dependent and -independent functions.

In Chapter 5, Keira *et al.* summarize current knowledge of Four-jointed, an intriguing kinase originally identified in *Drosophila* that acts in the Golgi lumen where it phosphorylates extracellular receptors involved in growth and epithelial planar polarity. In addition to Four-jointed, the Hippo/Salvador/Warts kinase module also affects cell and tissue growth. Recent advances toward the mechanistic basis of the evolutionarily conserved Hippo signaling pathway and functions of Hippo to prevent aberrant cell growth are illustrated by Pfleger in Chapter 6.

GSK3s (Glycogen synthase kinases) are two largely redundant kinases originally identified as regulators of glycogen metabolism that intersect with most signaling pathways in multicellular organisms. Given that most roads apparently converge upon these kinases, Patel and Woodgett (Chapter 8) discuss the puzzling matter of how two kinases that are—unusually—chiefly regulated by their inhibition can lead to pathway-specific output and functional specificity. They also outline possible utility and risks associated with application of GSK inhibitors for disease treatment. In Chapter 9, Jiang explains that Casein kinases 1 (CK1s) not only serve as priming kinases

for GSK3 during Wnt signaling but are also critical for Hedgehog signaling during development.

Once rooted, plants spend their entire life at the same location and therefore rely on unique mechanisms to adapt to their environment, for example, by adjusting growth rate. In Chapter 10, Haruta and Sussman discuss plant hormones, their receptors, and functions with a particular emphasis on FERONIA tyrosine kinase that may play a role in the transduction of a mechanosensory signal during growth.

Establishment of cell and organismal polarity is highly reliant on the function of Par1 (Partitioning defective 1) in *C. elegans*, *Drosophila*, and vertebrates, as becomes evident from the contribution by Wu and Griffin (Chapter 11). Continuing with polarity, Oliva and Hassan (Chapter 12) review the functions of tyrosine kinases and phosphatases, some of which have lost catalytic activity, in neuronal wiring. The issue closes with a review by Álvarez-Aznar et al. in Chapter 13 of the functions of Vascular Endothelial Growth Factor (VEGF) receptors during the development of the mammalian vascular system.

Collectively, this series of reviews aims to provide an overview of the remarkable recent advances in our understanding of protein kinase (and phosphatase) functions during development. A mission of this collection of articles written by experts in their fields is to demonstrate the persisting utility and merit of traditional model organisms in the "omics" era.

I am indebted and grateful to all of the authors for their hard work and dedication that allowed compilation of this set of very interesting and high-quality reviews. I also would like to thank the reviewers for critically and quickly reading the manuscripts. I would like to take the opportunity to thank my mentors, collaborators, and past and present lab members, all of whom continue to be important for the research in my lab. Last, but not least, I am grateful to Paul Wassarman for giving me the opportunity to assemble this volume for *Current Topics in Developmental Biology* and to Shellie Bryant and the production team for their assistance.

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## REFERENCES

Adams, J. A. (2003). Activation loop phosphorylation and catalysis in protein kinases: Is there functional evidence for the autoinhibitor model? *Biochemistry*, *42*, 601–607.

Knighton, D. R., Zheng, J. H., Ten Eyck, L. F., Ashford, V. A., Xuong, N. H., Taylor, S. S., & Sowadski, J. M. (1991). Crystal structure of the catalytic subunit of cyclic adenosine monophosphate-dependent protein kinase. *Science*, *253*, 407–414.

Krebs, E. G. (1998). An accidental biochemist. *Annual Review of Biochemistry*, *67*, xii–xxxii.

Krebs, E. G., Graves, D. J., & Fischer, E. H. (1959). Factors affecting the activity of muscle phosphorylase b kinase. *The Journal of Biological Chemistry*, *234*, 2867–2873.

Manning, G., Plowman, G. D., Hunter, T., & Sudarsanam, S. (2002). Evolution of protein kinase signaling from yeast to man. *Trends in Biochemical Sciences*, *27*, 514–520.

Manning, G., Whyte, D. B., Martinez, R., Hunter, T., & Sudarsanam, S. (2002). The protein kinase complement of the human genome. *Science*, *298*, 1912–1934.

Taylor, S. S., & Kornev, A. P. (2011). Protein kinases: Evolution of dynamic regulatory proteins. *Trends in Biochemical Sciences*, *36*, 65–77.

Ubersax, J. A., & Ferrell, J. E., Jr. (2007). Mechanisms of specificity in protein phosphorylation. *Nature Reviews. Molecular Cell Biology*, *8*, 530–541.

# CONTENTS

CHAPTER ONE

# WNK Kinases in Development and Disease

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## Contents



## Abstract

WNK (With-No-Lysine (K)) kinases are serine–threonine kinases characterized by an atypical placement of a catalytic lysine within the kinase domain. Mutations in human WNK1 or WNK4 cause an autosomal dominant syndrome of hypertension and hyperkalemia, reflecting the fact that WNK kinases are critical regulators of renal ion transport processes. Here, the role of WNKs in the regulation of ion transport processes in vertebrate and invertebrate renal function, cellular and organismal osmoregulation, and cell migration and cerebral edema will be reviewed, along with emerging literature demonstrating roles for WNKs in cardiovascular and neural development, Wnt signaling, and cancer. Conserved roles for these kinases across phyla are emphasized.

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