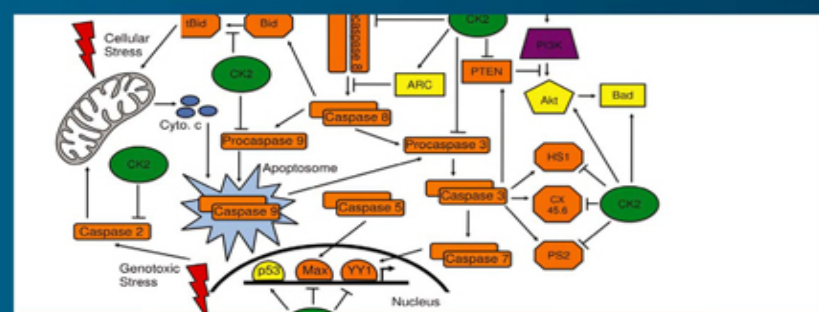
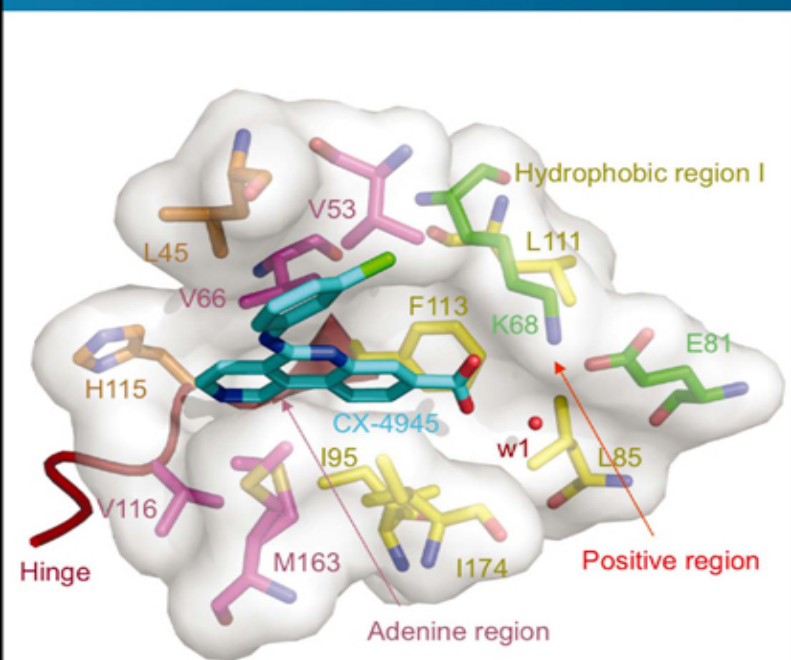


The Wiley-IUBMB Series on Biochemistry and Molecular Biology

# Protein Kinase CK2

Edited by **Lorenzo A. Pinna**



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# Table of Contents

[Cover](#)

[Title page](#)

[Copyright page](#)

[CONTRIBUTORS](#)

[PREFACE](#)

[THE WILEY-IUBMB SERIES ON  
BIOCHEMISTRY AND MOLECULAR BIOLOGY](#)

## [Part I: Molecular and Structural Aspects](#)

### [1 Structural Bases of Protein Kinase CK2 Function and Inhibition](#)

[INTRODUCTION](#)

[BASIC STRUCTURE/FUNCTION RELATIONSHIPS OF  
CK2](#)

[CK2 INHIBITORS](#)

[CONCLUSIONS AND OUTLOOK](#)

[ACKNOWLEDGMENTS](#)

### [2 The Interactome of Protein Kinase CK2](#)

## INTRODUCTION

FROM THE OUTSIDE TO THE INSIDE: INTERACTION OF CK2 WITH MEMBRANE PROTEINS

REGULATING GENE EXPRESSION: INTERACTION OF CK2 WITH COMPONENTS OF SIGNALING CASCADES, TRANSCRIPTION FACTORS AND DNA MODIFYING ENZYMES

MASTERING NUCLEIC ACID FUNCTIONS: INTERACTION OF CK2 WITH PROTEINS OF THE REPLICATION, TRANSCRIPTION, AND TRANSLATION MACHINERY OF THE CELL

LET IT ROLL: INTERACTION OF CK2 WITH CELL CYCLE REGULATORY PROTEINS

GUARDIAN ANGELS: INTERACTION OF CK2 WITH PROTEINS THAT MAINTAIN THE CELLULAR INTEGRITY

LIVE AND LET DIE: INTERACTION OF CK2 WITH PROTEINS OF THE APOPTOTIC PATHWAY

HIGHWAYS IN THE CELL: INTERACTION OF CK2 WITH THE CYTOSKELETON AND MOTOR PROTEINS

COLLABORATING WITH THE ENEMY: INTERACTION OF CK2 WITH PROTEINS IMPLICATED IN VIRAL INFECTIONS

LAST BUT NOT LEAST: MISCELLANEOUS CONCLUDING REMARKS

## 3 CK2 Contribution to the Generation of the Human Phosphoproteome

KINASES CONTRIBUTION TO THE HUMAN PHOSPHOPROTEOME

CK2 SUBSTRATE SPECIFICITY  
SUBPHOSPHOPROTEOMES OF PROTEINS WITH  
SPECIFIC FUNCTIONS  
SUBPHOSPHOPROTEOMES OF CELLULAR  
COMPARTMENTS  
ABSOLUTE QUANTIFICATION OF YEAST  
PHOSPHOPROTEOME REFLECTS THE  
CONSTITUTIVE ACTIVITY OF CK2  
CONCLUSIONS  
ACKNOWLEDGMENTS

## Part II: Functional Aspects

### 4 CK2 in Embryonic Development

CK2 IN YEAST BIOLOGY  
CK2 IN INVERTEBRATE DEVELOPMENT  
CK2 IN VERTEBRATE DEVELOPMENT  
CK2 IN PLANT DEVELOPMENT  
CK2 IN ANIMAL DEVELOPMENTAL SIGNALING  
PATHWAYS  
DISCUSSION  
OUTLOOK  
ACKNOWLEDGMENTS

### 5 Protein Kinase CK2: At the Crossroads of Pathways Controlling Cell Proliferation and Survival

GENERAL INTRODUCTION  
PROTEIN KINASE CK2

CK2 IN CANCER  
INVOLVEMENT OF CK2 IN SIGNALING PATHWAYS  
CONTROLLING PROLIFERATION AND DEATH  
CONCLUDING REMARKS  
ACKNOWLEDGMENTS

## 6 The Role of Protein Kinase CK2 in the p53 Response

PROTEIN KINASE CK2  
THE p53 NETWORK  
THE INTERACTION BETWEEN p53 AND CK2  
REGULATION OF p53 BY PHOSPHORYLATION OF Ser392  
PROPOSED MECHANISM FOR REGULATION OF p53 PHOSPHORYLATION AT Ser392 (THE "CK2" SITE)  
PHOSPHORYLATION OF p53 BY CK2 IN A PHYSIOLOGICAL CONTEXT?  
A BROADER ROLE FOR CK2 IN REGULATING THE p53 NETWORK?

## 7 The Pivotal Role of CK2 in the Kinome-Targeting Hsp90 Chaperone Machinery

PROTEIN KINASE CK2  
Hsp90: A MAJOR MOLECULAR CHAPERONE  
CO-CHAPERONES THAT REGULATE Hsp90 FUNCTION  
Hsp90 AND SIGNALING PROTEIN KINASES  
PHOSPHORYLATION AND THE REGULATION OF Hsp90 BY CK2

PHOSPHORYLATION OF Cdc37 BY CK2  
A CRUCIAL ROLE OF CK2-DEPENDENT  
PHOSPHORYLATION IN THE FUNCTIONAL  
REGULATION OF Cdc37  
REGULATION OF THE Cdc37 PHOSPHORYLATION  
CYCLE  
REGULATORY PHOSPHORYLATION OF FKBP52 BY  
CK2  
PHOSPHORYLATION OF p23 BY CK2  
TARGETING THE CK2-Cdc37-Hsp90 TRINITY FOR  
CANCER CHEMOTHERAPY  
CONCLUSION

## 8 CK2: A Global Regulator of Cell Survival

CK2 AND CELL SURVIVAL: STRATEGIES,  
METHODS, AND TECHNIQUES FOR EXPLORING ITS  
ROLE  
CK2 AND CELLULAR DEATH  
ROLE OF CK2 IN DNA DAMAGE  
ROLE OF THE INDIVIDUAL CK2 SUBUNITS IN CELL  
SURVIVAL  
CK2 STATUS IN NON-NEOPLASTIC CELLS  
CK2 ACTIVITY AND EXPRESSION IN NEOPLASIA  
CK2 IN HETEROTRANSPLANTED TUMORS IN NUDE  
MICE  
CK2 HOLOENZYME AND ITS SUBUNITS  
TUMOR HYPOXIA  
CONCLUSION

## 9 Specific Features of Plant CK2

INTRODUCTION

CK2 $\alpha$  CATALYTIC SUBUNITS

CK2 $\beta$  REGULATORY SUBUNITS

CK2 HOLOENZYME

PHYSIOLOGICAL ROLE OF CK2 IN PLANTS

## Part III: CK2 and Neoplasia

### 10 The Oncogenic Potential of CK2

INTRODUCTION

CK2 OVEREXPRESSION IN HUMAN CANCER

CK2 OVEREXPRESSION IN ANIMAL MODELS OF  
CANCER

ONCOGENIC ACTIVITY OF CK2 IN TRANSGENIC  
MICE

POTENTIAL TARGETS OF CK2 IN CANCER: Wnt,  
NF- $\kappa$ B, AND PI3-KINASE PATHWAYS

CONCLUSIONS

ACKNOWLEDGMENTS

### 11 Addiction of Cancer Cells to CK2: Survival at All Costs or Achilles' Heel?

MANY SUBSTRATES, ONE MAJOR ROLE

A LATERAL PLAYER

"MORE NECESSARY" FOR SOME CELLS

TO SURVIVE AT ALL COSTS

A NOVEL ACHILLES' HEEL OF CANCER CELLS

THE RIGHT WEAPONS

ACKNOWLEDGMENTS

## 12 CK2 Suppression of Apoptosis and Its Implication in Cancer Biology and Therapy

INTRODUCTION

CK2 DYNAMICS IN CELL GROWTH AND CELL DEATH

CK2 AND HALLMARKS OF CANCER

CK2 AS TARGET OF CANCER THERAPY

ACKNOWLEDGMENTS

## 13 Protein Kinase CK2 in Normal and Malignant Hematopoiesis

HEMATOPOIESIS AND BLOOD TUMORS: GENERAL CONCEPTS

CK2 ROLE IN MOUSE EMBRYONIC DEVELOPMENT: INSIGHTS INTO CK2 INVOLVEMENT IN BLOOD DEVELOPMENT

CK2-DIRECTED REGULATION OF HEMATOPOIESIS-ASSOCIATED MOLECULES AND SIGNAL TRANSDUCTION PATHWAYS

ROLE OF CK2 IN HEMATOLOGIC MALIGNANCIES

CK2 IN BLOOD TUMORS ARISING FROM LYMPHOCYTES

CK2 IN BLOOD TUMORS ARISING FROM MYELOID CELLS

CONCLUSIONS

## 14 Role of CK2 in the Control of Cell Plasticity in Breast Carcinoma Progression

INTRODUCTION



DYSREGULATION OF CK2 IN MAMMARY  
TUMORIGENESIS

CK2 AS A GUARDIAN OF EPITHELIAL CELL  
INTEGRITY

UNBALANCED EXPRESSION OF CK2 SUBUNITS IS  
CORRELATED WITH HYPOXIA AND EMT-RELATED  
MARKERS

CK2 $\beta$  SUBUNIT SILENCING INDUCES EMT-LIKE  
MORPHOLOGICAL CHANGES

GENE EXPRESSION PROFILING

CK2 $\beta$  SILENCING TRIGGERS Snail1 INDUCTION

OVEREXPRESSION OF SIX1 IN CK2 $\beta$ -DEPLETED  
CELLS

CONCLUSIONS

ACKNOWLEDGMENTS

## 15 CK2 as a Logical Target in Cancer Therapy: Potential for Combining CK2 Inhibitors with Various Classes of Cancer Therapeutic Agents

INTRODUCTION

SUPPRESSION OF APOPTOSIS

PI3K-Akt-mTOR SIGNALING

PROMOTION OF ANGIOGENESIS

Hsp90 MACHINERY

NF- $\kappa$ B TRANSCRIPTION

Wnt SIGNALING

EPITHELIAL-MESYNCHEMAL TRANSITION

DNA DAMAGE REPAIR

OTHER PATHWAYS  
CONCLUDING REMARKS  
ACKNOWLEDGMENTS

Appendix: CK2 and Its False Sisters: The  
Recent Solution of a Very “Cold Case”

Index

# PROTEIN KINASE CK2

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*Edited by*

**Lorenzo A. Pinna**

Department of Biomedical Sciences  
University of Padua  
Padua, Italy

 **WILEY-BLACKWELL**  
A John Wiley & Sons, Inc., Publication





This edition first published 2013 © 2013 by John Wiley & Sons, Inc.

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

Editorial offices: 2121 State Avenue, Ames, Iowa 50014-8300, USA

The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

9600 Garsington Road, Oxford, OX4 2DQ, UK

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*Library of Congress Cataloging-in-Publication Data*

Protein kinase CK2 / edited by Lorenzo A. Pinna.

pages cm. - (The Wiley-IUBMB series on biochemistry and molecularbiology)

Includes bibliographical references and index.

ISBN 978-0-470-96303-6 (hardback : alk. paper) 1. Protein kinase CK2.

I. Pinna, Lorenzo A.

QP606.P76P73546 2013

612'.015756-dc23

2012028574

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Cover image: The cover figure provides examples of CK2 peculiar properties by showing, clockwise, starting from left upper corner: the unique butterfly shape of CK2 holoenzyme, composed of two catalytic subunits bound to a dimer of the noncatalytic subunit; the CK2 catalytic subunit pharmacophore occupied by an inhibitor now in clinical trials as an anticancer drug; the convergence of CK2 with caspase pathways; the dorsal axis duplication induced by injecting *Xenopus laevis* embryos with CK2 mRNAs. Figures are drawn from Chapters 1, 5, and 4, respectively.

Cover design by Modern Alchemy LLC

# CONTRIBUTORS

KHALIL AHMED

Research Service, Minneapolis V.A. Health Care System  
Department of Laboratory Medicine and Pathology  
Masonic Cancer Center  
and Department of Urology  
Department of Otolaryngology  
University of Minnesota  
Minneapolis, MN, USA

ROBERTO BATTISTUTTA

Department of Chemical Sciences  
University of Padua  
Padua, Italy

LUCA CESARO

Department of Biomedical Sciences  
University of Padua  
Padua, Italy

CLAUDE COCHET

INSERM, UJF, CEA, DSV/iRTSV  
Biology of Cancer and Infection  
Grenoble, France

ALEXANDRE DESHIERE

INSERM, UJF, CEA, DSV/iRTSV  
Biology of Cancer and Infection  
Grenoble, France

ISABEL DOMINGUEZ

Hematology Oncology

Department of Medicine  
Boston University School of Medicine  
Boston, MA, USA

DENIS DRYGIN  
Cylene Pharmaceuticals  
San Diego, CA, USA

ODILE FILHOL  
INSERM, UJF, CEA, DSV/iRTSV  
Biology of Cancer and Infection  
Grenoble, France

MICHELLE GABRIEL  
Department of Biochemistry  
Schulich School of Medicine and Dentistry  
The University of Western Ontario  
London, Ontario, Canada

CLAUDIA GÖTZ  
Medical Biochemistry and Molecular Biology  
University of the Saarland  
Homburg, Germany

BARBARA GUERRA  
Department of Biochemistry and Molecular Biology  
University of Southern Denmark  
Odense, Denmark

OLAF-GEORG ISSINGER  
Department of Biochemistry and Molecular Biology  
University of Southern Denmark  
Odense, Denmark



BETSY T. KREN

Research Service, Minneapolis V.A. Health Care System  
Masonic Cancer Center  
Department of Medicine  
Minneapolis, MN, USA

ESTHER LANDESMAN-BOLLAG

Section of Hematology-Oncology  
Department of Medicine  
Boston University School of Medicine  
and Boston Medical Center  
Boston, MA, USA

TOMMASO LEGNAIOLI

Center for Research in Agricultural Genomics  
Molecular Genetics Department  
Parc de Recerca UAB  
Edifici CRAG, Campus UAB  
Bellaterra (Cerdanyola del Vallés)  
Barcelona, Spain

DAVID W. LITCHFIELD

Departments of Biochemistry and Oncology  
Schulich School of Medicine and Dentistry  
The University of Western Ontario  
London, Ontario, Canada

LAURA MACIAS ALVAREZ

Hematology Oncology  
Department of Medicine  
Boston University School of Medicine  
Boston, MA, USA

DAVID W. MEEK

Division of Cancer Research

Medical Research Institute  
The University of Dundee  
Ninewells Hospital  
Dundee, Scotland, United Kingdom

YOSHIHIKO MIYATA  
Department of Cell and Developmental Biology  
Graduate School of Biostudies  
Kyoto University  
Kyoto, Japan

MATHIAS MONTENARH  
Medical Biochemistry and Molecular Biology  
University of the Saarland  
Homburg, Germany

KARSTEN NIEFIND  
University of Cologne  
Department of Chemistry  
Institute of Biochemistry  
Cologne, Germany

MONTSERRAT PAGÈS  
Center for Research in Agricultural Genomics  
Molecular Genetics Department  
Parc de Recerca UAB  
Edifici CRAG, Campus UAB  
Bellaterra (Cerdanyola del Vallés)  
Barcelona, Spain

FRANCESCO PIAZZA  
Department of Medicine  
Haematology and Clinical Immunology Branch  
University of Padua School of Medicine  
and Venetian Institute of Molecular Medicine

Haematological Malignancies Unit  
Padua, Italy

LORENZO A. PINNA  
Department of Biomedical Sciences  
University of Padua  
Padua, Italy

JESUS REVUELTA-CERVANTES  
Hematology Oncology  
Department of Medicine  
Boston University School of Medicine  
Boston, MA, USA

MARTA RIERA  
Center for Research in Agricultural Genomics  
Molecular Genetics Department  
Parc de Recerca UAB  
Edifici CRAG, Campus UAB  
Bellaterra (Cerdanyola del Vallés)  
Barcelona, Spain

MARIA RUZZENE  
Department of Biomedical Sciences  
and Venetian Institute of Molecular Medicine  
University of Padua  
Padua, Italy

MAURO SALVI  
Department of Biomedical Sciences  
University of Padua  
Padua, Italy

DAVID C. SELDIN  
Section of Hematology-Oncology

Department of Medicine  
Boston University School of Medicine  
and Boston Medical Center  
Boston, MA, USA

JANEEN H. TREMBLEY  
Research Service, Minneapolis V.A. Health Care System  
Department of Laboratory Medicine and Pathology  
Masonic Cancer Center  
Minneapolis, MN, USA

GRETCHEN M. UNGER  
GeneSegues  
Chaska, Minnesota

ISABEL CRISTINA VÉLEZ-BERMÚDEZ  
Center for Research in Agricultural Genomics  
Molecular Genetics Department  
Parc de Recerca UAB  
Edifici CRAG, Campus UAB  
Bellaterra (Cerdanyola del Vallés)  
Barcelona, Spain

JING JIANG WU  
Research Service, Minneapolis V.A. Health Care System  
Department of Laboratory Medicine and Pathology  
Minneapolis, MN, USA

# PREFACE

## A KINASE FOR ALL SEASONS

In the twilight of his scientific life, the Nobel laureate Edwin G. Krebs became more and more attracted by protein kinase CK2. In a 1999 paper (Mol. Cell. Biochem. 191: 3-12), tellingly entitled “CK2, a protein kinase of the next millennium,” he wrote that such a title was “intended to emphasize the fact that CK2 is such a rich topic for investigation that research involving this enzyme will continue for decades to come.” This statement is one of the justifications for devoting an entire book to an individual member of the human “kinome,” a huge gene family including more than 500 enzymes.

Indeed the long history of CK2, from its early—and in some ways “premature”—discovery in 1954 to the present day, is unique and paradoxical in several respects. CK2 activity was the first example of an enzymatic phosphorylation reaction affecting a protein rather than a small metabolite, leading Eugene Kennedy to coin the term “protein (phospho) kinase” (J. Biol. Chem. 211:: 969-980, 1954). For decades, however, and at variance with other protein kinases discovered between 1955 and 1980, notably phosphorylase kinase, PKA, PKG, and PKC, which were immediately recognized to participate in signal transduction pathways, the biological role of CK2 remained obscure. Indeed, its physiological targets remained entirely unknown for many years, its activity being measured *in vitro* with proteins that were not its physiological target, such as casein, leading to it being “misnamed” “casein kinase 2,” a historical name still hinted at by its current acronym of CK2.

The first physiological targets of CK2 were discovered in the late 1970s, causing CK2 to be independently “re-discovered” by a number of researchers working in different areas, for example as a “glycogen synthase kinase 5” (GSK-5) (Cohen P et al. *Eur. J. Biochem.* 124: 21-35, 1982) and a “Troponin-T kinase” (Villar-Palasi C et al. *J. Biol. Chem.* 256:7409-7415, 1981), as has been discussed elsewhere (Pinna LA *Cell. Mol. Biol. Res.* 40:391-399, 1994). Later, by a remarkable “snowballing” effect, the pleiotropy of CK2 eventually came to surpass that of any other individual protein kinase, with more than 300 substrates identified by 2003 (Meggio F and Pinna LA *FASEB J.* 17:349368, 2003). However, even this number is a huge underestimate of the total number of CK2 substrates that undoubtedly exist, bearing in mind that recent proteomic analyses have revealed that a large proportion of naturally occurring phosphorylation sites in proteins display the unique acidic motif C-terminal to the phosphorylated residue that is recognized specifically by CK2. This suggests that more than 20% of the entire human phosphoproteome may be generated by this individual protein kinase (see Salvi and Cesaro’s discussion in Chapter 3 of this book).

The pleiotropy of CK2 is now considered to be just one facet of this remarkable enzyme, its unique feature being its “constitutive” activity, an intriguing property whose structural basis is discussed by Niefind and Battistutta in the first chapter of this book. This is in contrast to many other protein kinases, which are silent under basal conditions and only become active in response to specific stimuli. CK2 seems to always be present in cells in an active conformation, without the need of phosphorylation events to sustain its activity. In this respect, it is therefore quite different from kinases that participate in signaling “cascades.” However, to exclude CK2 from participation in signaling pathways would be an incorrect inference,

contradicted by the overwhelming evidence that CK2 impinges on many signaling pathways, but in a unique “lateral” fashion rather than a “vertical” linear manner (see Chapter 5 by Gabriel and Litchfield and Chapter 11 by Ruzzene in this book).

Constitutive activity also underlies another paradox of CK2: many oncogenes encode protein kinases endowed with inappropriate activity or a gain of function mutation. Although this might appear to exclude CK2 from being an oncogene, since no gain of function mutations have ever been reported, nonetheless CK2 is clearly implicated in many cell biology phenomena that are associated with cancer, and the expression and activity of this protein kinase is invariably high in malignant cells compared to untransformed cells. This issue is dealt with in several chapters of this book. An attractive explanation for this apparent contradiction seems to be that diverse neoplastic cells become “addicted” to abnormally high levels of CK2 to such an extent that pharmacological downregulation of CK2 can reverse the tumorigenic phenotype. There are two important consequences of this situation. Firstly, cells where CK2 is abnormally high are “predisposed” to malignant transformation, thus deserving the neologism “oncophilic” cells (Ruzzene et al. *Mol. Cell. Biochem.* 356: 5–10, 2011). Secondly, CK2 may represent a pharmacological target for the treatment of a wide range of neoplastic diseases. The structures and mode of binding of several inhibitors in complex with CK2 are described in the first chapter of this book, and a potent and selective CK2 inhibitor is now undergoing clinical trials for the treatment of different kinds of tumors as discussed in detail by Drygin in the last chapter of this book.

Another consequence of the constitutive activity of CK2 is that many viruses and other infectious agents have learned how to exploit its presence in the host cell for the

phosphorylation of proteins that are essential to their life cycle. Therefore, CK2 also represents an attractive target for anti-infectious therapies although in contrast to cancer, where a partial downregulation of abnormally high CK2 activity may suffice, the suppression of host cell CK2 activity may have undesired consequences that still have to be evaluated. Other pathologies where an involvement of CK2 is suspected, mostly based on the scrutiny of its protein targets, are neurodegenerative syndromes, cardiovascular diseases, inflammation, and cystic fibrosis as reviewed by Guerra and Issinger (*Curr Med Chem.* 15:1870–86, 2008). In these cases, however, the roles of CK2 still need to be unravelled, and it is unclear whether any beneficial effects will come from downregulation or upregulation of CK2 activity.

The widespread and continuously increasing interest in CK2 in the scientific community is obvious from even a cursory scrutiny of the literature, the number of paper mentioning “CK2” in their title rising from 94 in 2000, to 159 in 2005, and 329 in 2011. This mainly reflects the increasing numbers of investigators who are inevitably coming across this kinase in the course of their studies. Although the “love affair” of most scientists with CK2 is transient, there remains a hard core group of “CK2 addicted” labs where this topic has been studied for decades, and this community of CK2 investigators meets periodically to discuss their most recent findings and to try to delineate new perspectives in the field. The first conference was held in Heidelberg, Germany, in 1994, followed by other conferences in Villard de Lans, near Grenoble, France (1997), in San Esteban, Chile (2001), in London, Ontario, Canada (2004), in Padua, Italy (2007), and in Cologne, Germany (2010). These international conferences on CK2 have been sponsored and generously supported by IUBMB. It is therefore not



surprising that a book of the Wiley-IUBMB series is now devoted to CK2.

The first part of this book will deal with structural aspects underlying the unique properties of CK2, its specific susceptibility to pharmacological inhibition, and its extraordinary pleiotropy. In the second part, the fundamental role of CK2 in a wide number of biological functions will be illustrated, and the third part will be devoted to the potential roles of CK2 in malignancy, which is providing new strategies and tools to treat neoplasia.

Chapter 1 by Karsten Niefind and Roberto Battistutta provides a thorough and detailed overview of present knowledge about structural features that underlie the enigmatic mode of regulation of CK2 and its susceptibility to a wide spectrum of potent, selective, and cell permeable inhibitors that are invaluable in helping to dissect the cellular functions of this kinase, as well as to counteract its oncogenic role. This theme will be exemplified throughout the book.

Chapters 2 and 3, by Mathias Montenarh and Claudia Götz and by Mauro Salvi and Luca Cesaro, respectively, deal with the pleiotropic nature of CK2 function, by presenting an updated repertoire of its interacting partners and a proteomic analysis that supports the concept that a substantial proportion of the whole human phosphor-proteome is generated by this single kinase.

A global view of the biological role of CK2 from both an embryogenetic and phylogenetic standpoint is provided by Isabel Dominguez and collaborators in Chapter 4, where the phenotypes of CK2 deregulation in model organisms, with special reference to yeast, *C. elegans*, *Drosophila*, and mouse are described.

Chapter 5 by Michelle Gabriel and David Litchfield mainly focuses on the unusual mode of operation of CK2 in signaling pathways and on devices by which the apparent

“lack of control” of CK2 can be overcome. In this connection, special reference is made to “substrate level regulation” mediated by hierarchical phosphorylation.

The next three chapters by David Meek, Yoshihiko Miyata, and Olaf-Georg Issinger and Barbara Guerra, respectively, deal with specific and relevant aspects of CK2 functionality, namely its potential role in the regulation of the tumor suppressor protein p53 (Chapter 6), its role in the Hsp90 chaperone machinery, which is essential for the survival of the “onco-kinome” (Chapter 7), and its involvement in cell survival (Chapter 8).

Chapter 9 by Montserrat Pagès and collaborators is entirely devoted to the distinctive properties of CK2 in plants, where unique structural features of the kinase may reflect roles in a variety of specialized functions.

Chapter 10 is an introduction to the implied involvement of CK2 in neoplasia, where David Seldin and Esther Landesman-Bollag summarize studies that have proved that CK2 has the capability to act as an oncogene. They also show that the overexpression of CK2 is associated with reduced survival and with invasiveness of cancer cells.

In a similar vein, albeit from a different angle, Maria Ruzzene provides evidence in Chapter 11 for a “vicious circle” whereby cells sporadically expressing abnormally high levels of CK2 are predisposed to malignancy if an oncogenic mutation occurs, leading to the selective increase of these cells, which in turn are more susceptible than “normal” cells to the cytotoxic efficacy of CK2 inhibitors.

The concept that malignant cells are more susceptible to loss of CK2 activity than normal cells is also dealt with by Khalil Ahmed and collaborators in Chapter 12, whose important message is that CK2 is deregulated in all cancers examined and that its downregulation results in potent induction of apoptosis. The authors also describe recent

progress in targeting CK2 cancer cells in a specific manner, leading to eradication of the cancer.

An overview of the role of CK2 in normal and malignant hematopoiesis is presented by Francesco Piazza in Chapter 13, showing that CK2 is upregulated in a variety of acute and chronic lymphoid and myeloid malignancies and suggesting that this protein kinase could be a suitable therapeutic target in these cases.

The role of CK2 in the progression of breast carcinoma through its control of epithelial cell plasticity is the topic addressed by Claude Cochet, Alexandre Deshiere, and Odile Filhol in Chapter 14, where the authors describe an unbalanced expression of CK2 subunits in a subset of breast tumor samples providing a detailed explanation for the molecular events underlying this process.

In Chapter 15, Denis Drygin provides a thorough and stringent survey of arguments supporting the concept that CK2 is a “logical target” in cancer therapy, especially if its inhibition is combined with chemotherapeutic agents. In that chapter, the efficacy of CK2 inhibitors whose mode of action is detailed at the molecular level in Chapter 1, is highlighted by showing how the “first-in-class” CK2 inhibitors have entered clinical trials. This has demonstrated for the first time that CK2 can be safely and extensively inhibited in humans without unacceptable side effects.

Needless to say, I am enormously grateful to all of the authors for having participated in this editorial enterprise and for having provided such an excellent series of contributions.

I also wish to thank Professor Angelo Azzi, President of the IUBMB Executive Committee, Professor Willy Stalmans, Chairman of the IUBMB Publication Portfolio, and Professor William J. Whelan, Editor-in-Chief, IUBMB Life, for having given me the opportunity to crown my academic career by editing a book devoted entirely to my “favorite” enzyme,

which has monopolized my attention for decades and I hope will continue to keep me busy scientifically in the future.

Special thanks also to Justin Jeffryes, Wiley's Executive Editor, for his encouragement and continuous support, to Anna Ehler for her invaluable help in editorial matters, and to Luca Cesaro for his help in collecting and assembling the authors' contributions and for preparing the cover figure of the book.

Lorenzo A. Pinna

# THE WILEY-IUBMB SERIES ON BIOCHEMISTRY AND MOLECULAR BIOLOGY

*Protein Kinase CK2*

**Editor:** Lorenzo A. Pinna

# Part I

## Molecular and Structural Aspects