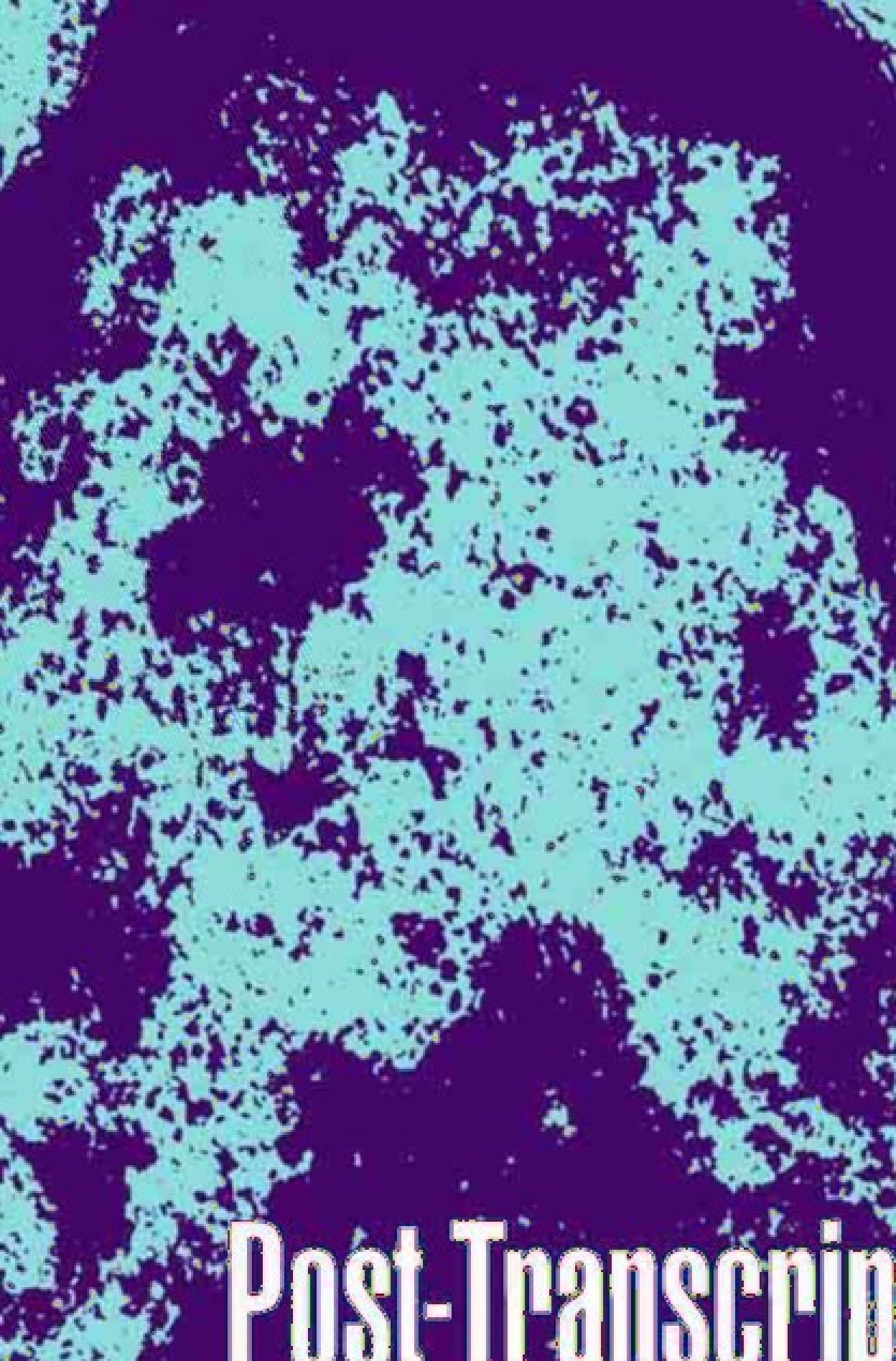

Post-Transcrip

Post-Transcriptional Regulation by STAR Proteins

ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

Editorial Board:
NATHAN BACK, *State University of New York at Buffalo*
IRUN R. COHEN, *The Weizmann Institute of Science*
ABEL LAJTHA, *N.S. Kline Institute for Psychiatric Research*
JOHN D. LAMBRIS, *University of Pennsylvania*
RODOLFO PAOLETTI, *University of Milan*

Recent Volumes in this Series

Volume 685
DISEASES OF DNA REPAIR
Edited by Shamim I. Ahmad

Volume 686
RARE DISEASES EPIDEMIOLOGY
Edited by Manuel Posada de la Paz and Stephen C. Groft

Volume 687
BCL-2 PROTEIN FAMILY: ESSENTIAL REGULATORS OF CELL DEATH
Edited by Claudio Hetz

Volume 688
SPHINGOLIPIDS AS SIGNALING AND REGULATORY MOLECULES
Edited by Charles Chalfant and Maurizio Del Poeta

Volume 689
HOX GENES: STUDIES FROM THE 20TH TO THE 21ST CENTURY
Edited by Jean S. Deutsch

Volume 690
THE RENIN-ANGIOTENSIN SYSTEM: CURRENT RESEARCH PROGRESS IN THE PANCREAS
Edited by Po Sing Leung

Volume 691
ADVANCES IN TNF FAMILY RESEARCH
Edited by David Wallach

Volume 692
NEUROPEPTIDE SYSTEMS AS TARGETS FOR PARASITE AND PEST CONTROL
Edited by Timothy G. Geary and Aaron G. Maule

Volume 693
POST-TRANSCRIPTIONAL REGULATION BY STAR PROTEINS
Edited by Talila Volk and Karen Artzt

A Continuation Order Plan is available for this series. A continuation order will bring delivery of each new volume immediately upon publication. Volumes are billed only upon actual shipment. For further information please contact the publisher.

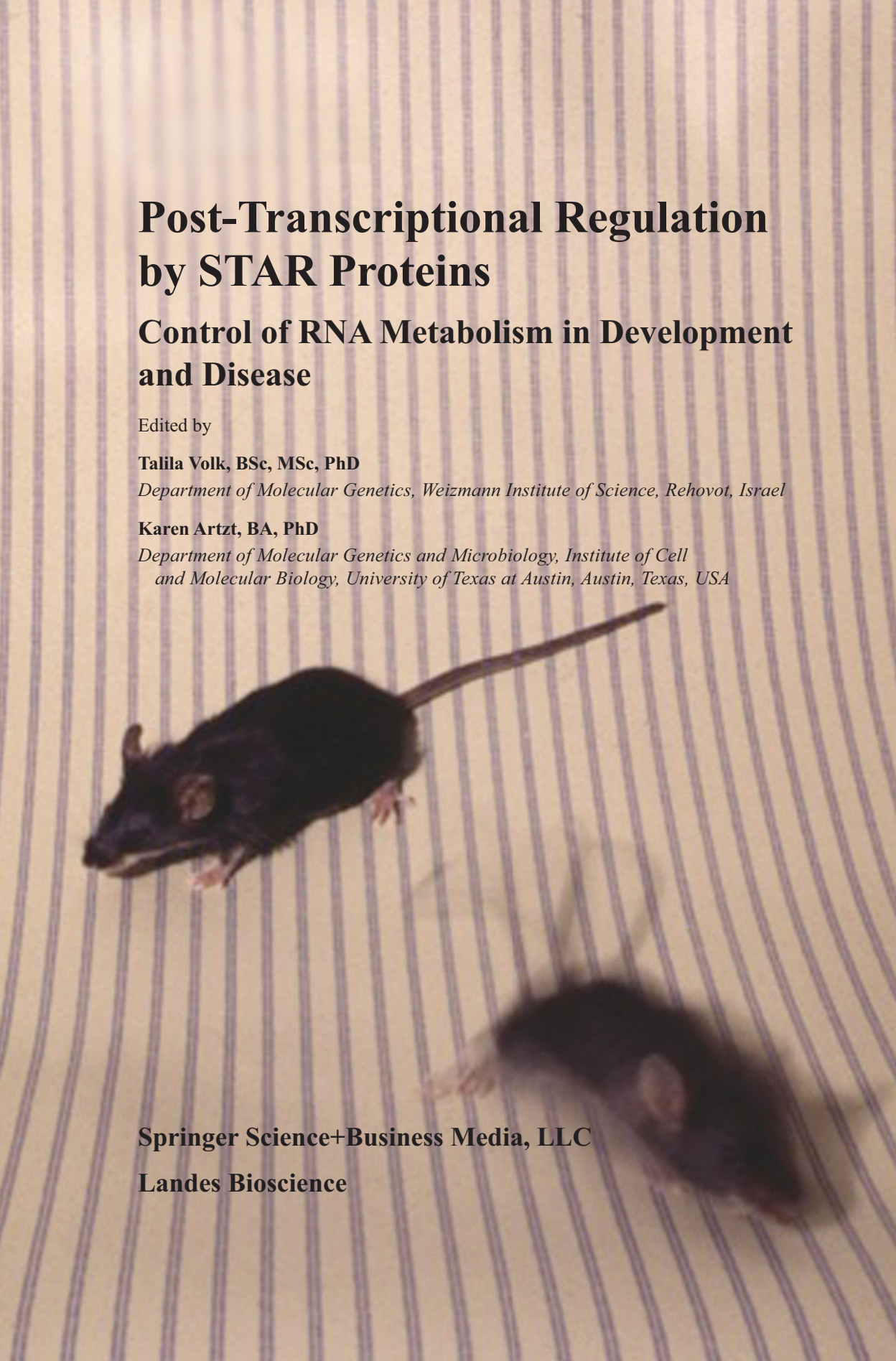
Post-Transcriptional Regulation by STAR Proteins

Control of RNA Metabolism in Development and Disease

Edited by

Talila Volk, BSc, MSc, PhD
Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel

Karen Artzt, BA, PhD
Department of Molecular Genetics and Microbiology, Institute of Cell and Molecular Biology, University of Texas at Austin, Austin, Texas, USA



Springer Science+Business Media, LLC

Landes Bioscience

Springer Science+Business Media, LLC
Landes Bioscience

Copyright ©2010 Landes Bioscience and Springer Science+Business Media, LLC

All rights reserved.
No part of this book may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the publisher, with the exception of any material supplied specifically for the purpose of being entered and executed on a computer system; for exclusive use by the Purchaser of the work.

Printed in the USA.

Springer Science+Business Media, LLC, 233 Spring Street, New York, New York 10013, USA
http://www.springer.com

Please address all inquiries to the publishers:
Landes Bioscience, 1002 West Avenue, Austin, Texas 78701, USA
Phone: 512/ 637 6050; FAX: 512/ 637 6079
http://www.landesbioscience.com

The chapters in this book are available in the Madame Curie Bioscience Database.
http://www.landesbioscience.com/curie

Post-Transcriptional Regulation by STAR Proteins: Control of RNA Metabolism in Development and Disease, edited by Talila Volk and Karen Artzt. Landes Bioscience / Springer Science+Business Media, LLC dual imprint / Springer series: Advances in Experimental Medicine and Biology.

ISBN: 978-1-4419-7004-6

Title page image: Two littermates, the right one is *quaking*.

While the authors, editors and publisher believe that drug selection and dosage and the specifications and usage of equipment and devices, as set forth in this book, are in accord with current recommendations and practice at the time of publication, they make no warranty, expressed or implied, with respect to material described in this book. In view of the ongoing research, equipment development, changes in governmental regulations and the rapid accumulation of information relating to the biomedical sciences, the reader is urged to carefully review and evaluate the information provided herein.

Library of Congress Cataloging-in-Publication Data

Post-transcriptional regulation by STAR proteins : control of RNA metabolism in development and disease / edited by Talila Volk, Karen Artzt.
p. ; cm. -- (Advances in experimental medicine and biology ; v. 693)
Includes bibliographical references and index.
ISBN 978-1-4419-7004-6
1. RNA-protein interactions. 2. RNA--Metabolism--Regulation. 3. Cellular signal transduction. I. Volk, Talila. II. Artzt, Karen Jane. III. Series: Advances in experimental medicine and biology ; v. 693. 0065-2598
[DNLM: 1. RNA-Binding Proteins--metabolism. 2. Embryonic Development--physiology. 3. RNA Processing, Post-Transcriptional. 4. Signal Transduction. 5. Transcriptional Activation. W1 AD559 v.693 2010 / QU 55.2 P857 2010]
QP623.8.P75P67 2010
572.8'8--dc22

2010021544

DEDICATIONS

This book is dedicated to my family. —Talila Volk

Dedicated to my mentors: Dorothea Bennett, 1929-1990 and L.C. Dunn, 1893-1974. —Karen Artzt

PREFACE

This book aims to bring to the forefront a field that has been developing since the late 1990s called the STAR pathway for Signal Transduction and Activation of RNA. It is a signaling pathway that targets RNA directly; in contrast to the canonical signal—kinase cascade—transcription factor—DNA—RNA. It is proposed to allow quick responses to environment changes such as those necessary in many biological phenomenona such as the nervous system, and during development. The pathway is diagramed in Chapter 1, Figure1. This chapter is a historical introduction and general review with some new data on theoretical miRNAs binding sites and STAR mRNAs. In Chapter 2, Feng and Banks address the accumulating evidence that the RNA-binding activity and the homeostasis of downstream mRNA targets of STAR proteins can be regulated by phosphorylation in response to various extracellular signals. Then Ryder and Massi review the available information on the structure of the RNA binding STAR domain and provides insights into how these proteins discriminate between different RNA targets. Next Claudio Sette offers an overview of the post-translational modifications of STAR proteins and their effects on biological functions, followed by two chapters dedicated to in depth review of STAR function in spermatogenesis and in mammalian embryonic development. Chapters 7 and 8 discuss what can be learned from STAR proteins in non-mammalian species; in Drosophila and Gld-1 and Asd-2 in *C. elegans*. Next Rymond discusses the actual mechanics of splicing with mammalian SF1. Lastly Richard reviews what is known about STAR proteins and human disease including osteoporosis, schizophrenia, cancer, infertility and ataxia. The general intention of the editors is that basic researchers and clinicians will be stimulated to join the "Enterprise" studying the role of STAR proteins in other relevant diseases including dysmyelination and remyelination in multiple sclerosis and disorders of the neural and immune synapse.

Talila Volk, BSc, MSc, PhD
Karen Artzt, BA, PhD

ABOUT THE EDITORS...

TALILA VOLK is an Associate Professor in the field of Developmental Biology and the incumbent of the Sir Ernest B. Chain Professional Chair. Her major research interests are tissue morphogenesis and organogenesis during embryonic development. She has been studying the function and activity of the STAR family member Held Out Wing (HOW) in the fruit fly Drosophila since 1999. She served as the chairwoman for the Society of Developmental Biology in Israel (ISDB). Dr. Volk has gained her BSc from Tel-Aviv University, and her MSc and PhD degrees from the Weizmann Institute of Science, Rehovot, Israel.

ABOUT THE EDITORS...

KAREN ARTZT is an Ashbel Smith Professor Emeritus at the University of Texas at Austin where she directed a research laboratory for 20 years, where she was a member of the Section of Molecular Genetics and Microbiology. Prior to that she was an associate Member of the Memorial Sloan Kettering Cancer Center in New York. Her main research interests include developmental genetics with an emphasis on cancer biology. In collaboration with Tom Ebersole she identified and cloned the mouse gene *quaking* that was one of the founding members of the STAR family. Dr. Artzt received her academic degrees from Cornell University; a BA from the Ithaca campus and a PhD from the Medical College School of Graduate Sciences in New York City. In 1972 she spent a year as a Postdoctoral Fellow at the Pasteur Institute in Paris under the direction of the Nobel Prize winner, Francois Jacob.

PARTICIPANTS

Karen Artzt
Department of Molecular Genetics
and Microbiology
Institute of Cell and Molecular Biology
University of Texas at Austin
Austin, Texas
USA

Andrew Bankston
Feng Laboratory
Department of Pharmacology
Emory University School of Medicine
Atlanta, Georgia
USA

Ingrid Ehrmann
Institute of Human Genetics
Newcastle University
International Centre for Life
Newcastle
UK

David J. Elliott
Institute of Human Genetics
Newcastle University
International Centre for Life
Newcastle
UK

Yue Feng
Feng Laboratory
Department of Pharmacology
Emory University School of Medicine
Atlanta, Georgia
USA

Karen K. Hirschi
Department of Pediatrics
Baylor College of Medicine
Houston, Texas
USA

Monica J. Justice
Departments of Molecular and Human
Genetics and Molecular Physiology
and Biophysics
Baylor College of Medicine
Houston, Texas
USA

Min-Ho Lee
Department of Biological Sciences
University at Albany
State University of New York
Albany, New York
USA

Francesca Massi
Department of Biochemistry and Molecular Pharmacology
University of Massachusetts Medical School
Worcester, Massachusetts
USA

Stéphane Richard
Terry Fox Molecular Oncology Group
Bloomfield Center for Research on Aging
Lady Davis Institute for Medical Research
Departments of Oncology and Medicine
McGill University
Montréal, Québec
Canada

Sean P. Ryder
Department of Biochemistry and Molecular Pharmacology
University of Massachusetts Medical School
Worcester, Massachusetts
USA

Brian C. Rymond
Biology Department
University of Kentucky
Lexington, Kentucky
USA

Tim Schedl
Department of Genetics
Washington University School of Medicine
St. Louis, Missouri
USA

Claudio Sette
Department of Public Health and Cell Biology
University of Rome "Tor Vergata"
and
Institute for Neuroscience IRCSS Fondazione Santa Lucia
Rome
Italy

Talila Volk
Department of Molecular Genetics
Weizmann Institute of Science
Rehovot
Israel

Jiang I. Wu
Department of Physiology and Developmental Biology
University of Texas Southwestern Medical Center
Dallas, Texas
USA

CONTENTS

CHAPTER 1

STAR TREK

An Introduction to STAR Family Proteins and Review of Quaking (QKI)

Karen Artzt and Jiang I. Wu*

Abstract: The STAR family has an extremely diverse role during development and in RNA metabolism. We have concentrated on QKI as an example of this pleiotropic activity and also presented some new data on the role of its conserved 3′UTRs gleaned from bioinformatics analysis of theoretical miRNA binding sites. We review the concept of a direct pathway from signal transduction to activation of RNA, how this pathway could be the cell's quick response to developmental and physiological changes and how it must be tightly regulated.

HISTORY OF THE STAR FAMILY

The first member of the signal transduction and activation of RNA (STAR) family analyzed in detail was mammalian Src associated in mitosis (*SAM68* now also known as *KHDRBS1*).[1,2] It was identified for its role in transducing cell signals. *SAM68* was shortly joined by a subfamily of three conserved genes distinguished by their diverse and interesting mutant developmental phenotypes: the tumor suppressor gene *gld-1* in *C. elegans*,[3] the dysmyelinating gene *quaking* (*Qk*) in mouse[4] and a *Drosophila* gene *held out wings* (*how*) important for muscle development.[5,6] In 1996 the family was completed with a more distant relative human *splicing factor 1* (*SF1*)[7] (Fig. 1).

Later, additional members of the three subfamilies were characterized; among them were mammalian orthologs of *Sam68*: *Slm1* (now known as *Khdrbs2*) and *Slm2/T-Star* (now called *Khdrbs3*).[8,9] Very recently identified was *asd-2*,[10] (Table 1), a closer relative

*Corresponding Author: Jiang I. Wu—Department of Physiology and Developmental Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA. Email: jiang9.wu@utsouthwestern.edu

Post-Transcriptional Regulation by STAR Proteins: Control of RNA Metabolism in Development and Disease, edited by Talila Volk and Karen Artzt.
©2010 Landes Bioscience and Springer Science+Business Media.

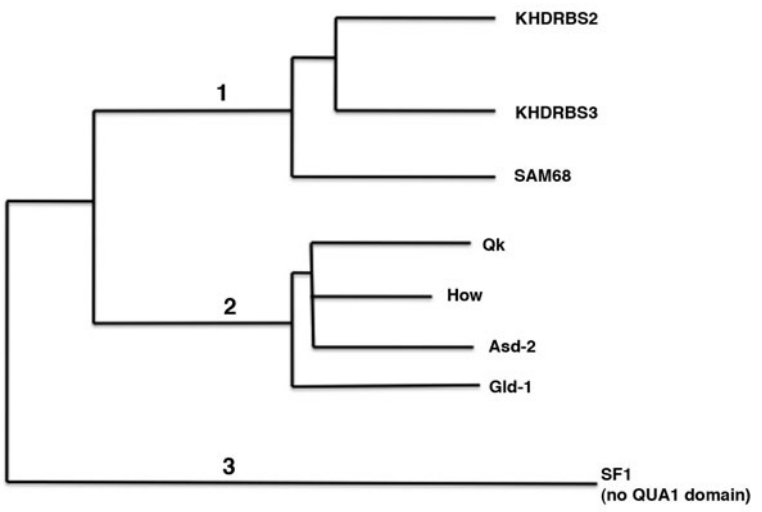


Figure 1. Highly simplified family of STAR proteins. The tree was redrawn from treefam accession numbers TF314878 and TF319159.[80] The three sub branches are numbered.

to *Qk* than *gld-1* in *C. elegans* based on its having three alternative spliced isoforms, two different 3′UTRs, a tyrosine tail and a closer phylogenic distance to *Qk* than *gld-1*. Members of STAR family are now defined from yeast to mammals and plants. The more distant relatives in plants have not been studied except for *SPL11-INTERACTING PROTEIN 1* (*SPIN1*) in rice. SPIN 1 negatively regulates programmed cell death and disease resistance. It is a member of the SF1 Family branch. In total, seven STAR paralogs including *SPIN1* were found in rice.[11] In some species it is hard to determine exact homologs because the species has expanded different family members; thus the blanks in Table 1. What is shared by all of the STAR proteins except SF1, is an uncommon single expanded KH RNA binding domain (Maxi-KH) that was flanked by two new conserved domains: an amino terminal QUA1 and a carboxyl terminal QUA2 domain. This triple domain

Table 1. STAR family members in different species

Mammals	*Drosophila*	*C. elegans*	Yeast	Plants
QKI	*How*	*Asd-2* and *Gld-1*		*AT1G09660, (Arabidopsis thaliana)*
Sam68/*Khdrbs1*	*Sam68* and *Kep1*			*AT2G38610, (Arabidopsis thaliana)*
T-star/*Slm2*/*Khdrbs3*	*qkr58E-1* or *qkr54B (flymine)*			
Slm1/*Khdrbs2*	*qkr54B (flymine)*			
SF1	*SF1*	*sfa-1*	*BBP (pombe), MSL5 (cerevisiae)*	*SPIN1,* rice *(Oryza sativa), RIK [At5g51300] (Arabidopsis thaliana)*

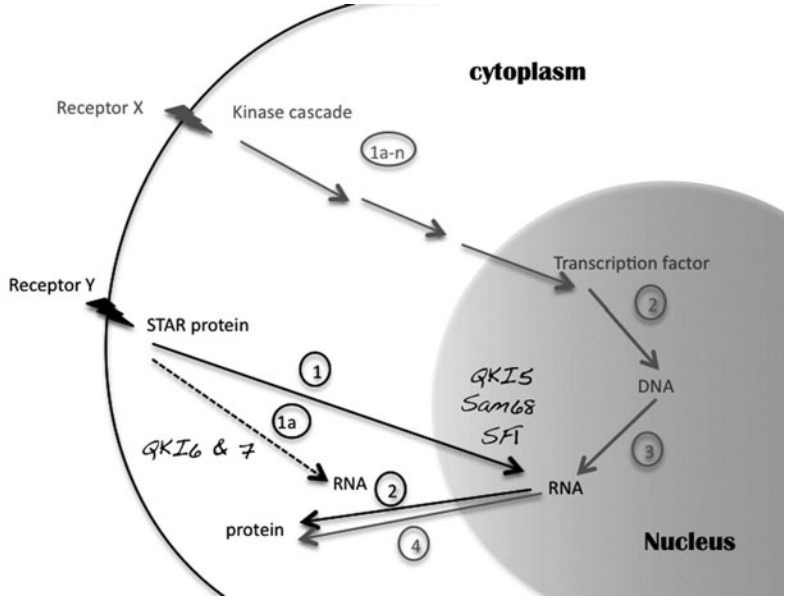


Figure 2. Theoretical schema of a more direct STAR pathway. Instead of the canonical pathways for signal transduction (red arrows) that requires at least four steps from receiving signals to protein production, the STAR pathway requires a minimum of two steps (blue arrows). QKI5, Sam68 and SF1 are for regulation of splicing and RNA metabolism in the nucleus; QKI6 and 7 are for RNA transport, stability and translational regulation in the cytoplasm. It is possible that heterodimers between different isoforms participate in some of the above functions. A color version of this image is available at www.landesbioscience.com/curie.

structure came to be called the STAR domain.[12] It is also known as the GSG domain.[3] The problem in the late 1990s was to make biological and molecular sense of this diverse and highly conserved family.

At the time, the most characterized family member was mammalian SAM68. By virtue of its KH domain, it was thought to bind RNA. There was also ample experimental evidence suggesting that it plays an important role in signal transduction because of its proline-rich regions, SH3- and WW-binding sites, RGG boxes and a prominent string of tyrosines in the C-terminal tail.[13,14] SAM68 is a substrate of SRC and FYN tyrosine kinases during mitosis.[1,2,15] Its tyrosine-phosphorylation can also be regulated by many signals and kinases including the activated insulin receptor and leptin receptor (refs. 13,16 and references within); additionally it is an ERK Ser/Thr kinase target.[17] Phosphorylation of SAM68 not only enables its interactions with many SH2/SH3-containing proteins to activate downstream signaling pathways, but also modulates its RNA regulating activities.[13,14] In addition to phosphorylation, post-translational modifications that regulate SAM68 function in RNA metabolism also include arginine methylation[18] and sumoylation.[19] All of the above suggest a direct connection between signal transduction and RNA regulation (Fig. 2). (See Feng and Bankston chapter for more detail.)

Because of the extreme conservation of QKI from *Drosophila* to mammals, it was noticeable that the tyrosine-rich tail was also present in the QKI subfamily members. Whereas little is conserved between the end of the STAR domain and the tyrosine tail, depending on which alignment is used, from 3 to 5 out of the 6 C-terminal tyrosines and