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Post-Transcriptional Regulation by STAR Proteins

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Post-Transcriptional Regulation by STAR Proteins

Control of RNA Metabolism in Development and Disease

Edited by

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

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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 phenomena such as the nervous system, and during development. The pathway is diagramed in Chapter 1, Figure 1. 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
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ABOUT THE EDITORS...



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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 mouse⁴ 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

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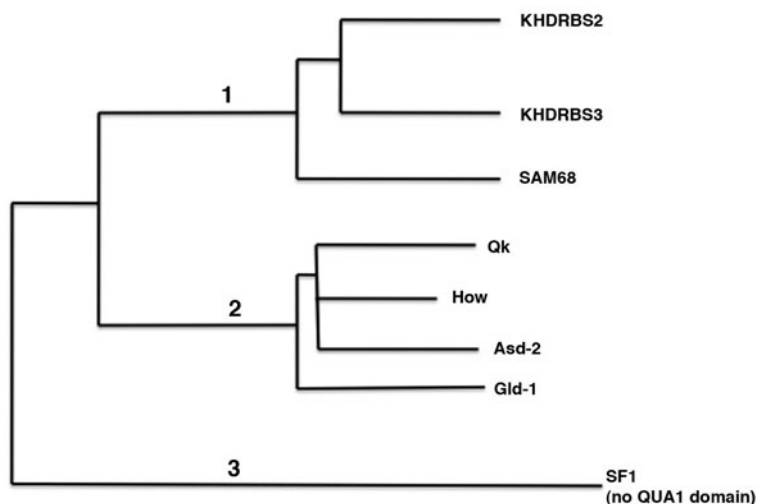


Figure 1. Highly simplified family of STAR proteins. The tree was redrawn from treefam accession numbers TF314878 and TF319159.⁸⁰ The three sub branches are numbered.

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

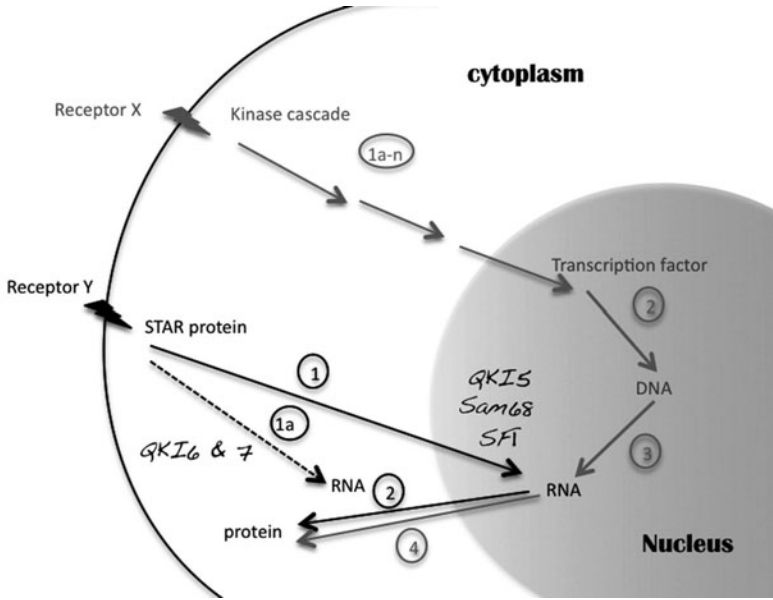


Figure 2. Theoretical schema of a more direct STAR pathway. Instead of the canonical pathways for signal transduction (red arrows) that requires at least four steps from receiving signals to protein production, the STAR pathway requires a minimum of two steps (blue arrows). QKI5, Sam68 and SF1 are for 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 methylation¹⁸ 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