Received: 1 April 2021 | Revised: 11 May 2021 | Accepted: 18 May 2021

DOI: 10.1002/bies.202100092

BioEssays

REVIEW ESSAY

Prospects & Overviews

Keeping the balance: The noncoding RNA 7SK as a master regulator for neuron development and function

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Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Numbers: BR4910/1–1, BR4910/2–1, SE697/4–1, SE697/5–1

Abstract

The noncoding RNA 7SK is a critical regulator of transcription by adjusting the activity of the kinase complex P-TEFb. Release of P-TEFb from 7SK stimulates transcription at many genes by promoting productive elongation. Conversely, P-TEFb sequestration by 7SK inhibits transcription. Recent studies have shown that 7SK functions are particularly important for neuron development and maintenance and it can thus be hypothesized that 7SK is at the center of many signaling pathways contributing to neuron function. 7SK activates neuronal gene expression programs that are key for terminal differentiation of neurons. Proteomics studies revealed a complex protein interactome of 7SK that includes several RNA-binding proteins. Some of these novel 7SK subcomplexes exert non-canonical cytosolic functions in neurons by regulating axonal mRNA transport and fine-tuning spliceosome production in response to transcription alterations. Thus, a picture emerges according to which 7SK acts as a multi-functional RNA scaffold that is integral for neuron homeostasis.

KEYWORDS
7SK, heterogeneous nuclear ribonucleoprotein (hnRNP), positive transcription elongation factor b (P-TEFb), survival motor neuron (SMN)

INTRODUCTION

Gene expression is a highly organized process, which helps cells to maintain their functional state and allows them to achieve a coordinated physiological response to changes in environmental conditions. Additionally, erasure and activation of specialized gene expression programs underlies the functional specialization of cells along developmental trajectories. Gene expression itself is regulated at multiple levels. Transcription factor binding at promoters of individual genes is modified by enhancer and silencer elements, the combination of which determines the transcriptional outcome at these genes. Moreover, modulation of transcription kinetics in conjunction with post-transcriptional processes such as splicing and polyadenylation contributes to the production of mRNAs. In addition to these regulatory events at individual sites of gene transcription, it has emerged that 'master regulators' of gene expression modulate transcriptional outcomes at the global level. Among these, the noncoding RNA 7SK acts as a scaffold for the coordinated regulation of transcriptional modifiers and RNA-binding proteins.

7SK is a highly structured RNA with a length of 331 nucleotides.[1] It folds into four stem-loops that act as interaction sites for proteins (Table 1). The 'core' 7SK ribonucleoprotein particle (RNP) consists of 7SK and the interactors methyl phosphate capping enzyme (MePCE) and La-related protein 7 (LARP7).[2,3] These two proteins protect the ends of 7SK from exonucleolytic degradation (Figure 1A). MePCE adds a methyl group to the γ-phosphate of the 5′ guanosine of 7SK.[4] Following methylation, MePCE remains bound to the 5′ end of 7SK and provides protection from degradation.[3,5] At the 3′ end of

TABLE 1 7SK-interacting proteins and their functions

Component	Name	Function
LARP7	La-related protein 7	Stabilization of 7SK[2]
MePCE	methyl phosphate capping enzyme	Methylation of the 5′ end of 7SK[3]
HEXIM1	hexamethylene bisacetamide-induced protein 1	Binding of P-TEFb to 7SK[16]
CDK9 Cyclin T1	Cyclin-dependent kinase 9 Cyclin T1	Components of the positive transcription elongation factor b (P-TEFb) complex; Transcription pause release through phosphorylation of RNA polymerase II[9]
hnRNP A1, A2/B1, Q and R	heterogeneous nuclear ribonucleoprotein A1, A2/B1, Q and R	RNA binding[22,23]
BAF complex	BRG1/BRM-associated factor	Chromatin remodeling[20]
KAP1 SRSF2 DDX21	Kruppel-associated box (KRAB)-interacting protein 1 Serine/arginine-rich splicing factor 2 DEAD box protein 21	Promoter recruitment of 7SK/P-TEFb[17,18,26]
JMJD6 Brd4	jumonji C-domain-containing protein 6 bromodomain-containing protein 4	Enhancer-mediated P-TEFb release from 7SK[19]
SMN	Survival motor neuron	Spliceosome biogenesis[24]

7SK, LARP7 binds to the fourth stem-loop and the terminal uridines for stabilization.[5–7] The resulting 7SK/MePCE/LARP7 core RNP provides a landing platform for various transcriptional and RNA regulators.

At many genes, RNA polymerase II pauses just downstream of the transcription initiation site.[8] The conversion of stalled RNA polymerase II into elongation-competent polymerase is controlled by the positive transcription elongation factor b (P-TEFb) complex composed of Cyclin-dependent kinase 9 (CDK9) and Cyclin T1. The P-TEFb complex achieves this task by phosphorylating Serine 2 of the C-terminal domain (CTD) of RNA polymerase II.[9,10] Targeting of P-TEFb to the CTD involves a histidine-rich domain of low complexity located at the C-terminus of Cyclin T1.[11] This domain is intrinsically disordered and induces the formation of liquid-like nuclear speckles containing P-TEFb and the CTD through phase separation.[11] This process is thought to enhance the efficiency of phosphorylation by increasing the local concentration of P-TEFb and the CTD. Additionally, P-TEFb phosphorylates the negative transcriptional regulators DRB sensitivity-inducing factor (DSIF) and negative elongation factor (NELF).[12] Together, these events release promoter-proximally paused polymerase II, allowing productive elongation to continue.[13]

Under steady state conditions, approximately half of nuclear 7SK is associated with P-TEFb and inhibits its kinase activity (Figure 1A).[14,15] This interaction between P-TEFb and 7SK is mediated by hexamethylene bisacetamide-induced protein 1 (HEXIM1).[16] The 7SK/P-TEFb complexes are tethered to promoter and enhancer regions of many genes allowing local release of P-TEFb and induction of transcription elongation.[17–20] This way, 7SK provides regulatory support for fine-tuning global transcription and there is evidence that such mechanisms are implicated in neuronal differentiation.[21] The other half of 7SK core RNPs that is not associated with P-TEFb interacts with a diverse range of RNA-binding proteins (Table 1).[22–24] While considerably less is known about these 7SK subcomplexes, research over the past years has revealed that they play important roles for neuronal development and function, such as axon growth and regulation of spliceosome formation.[24,25] Therefore, through regulation of several important RNA-binding proteins and chromatin effectors, 7SK exerts a key intermediary role for transcriptional and post-transcriptional regulatory processes in neurons. Disruption of such 7SK signaling pathways through mutation or aggregation of 7SK-interacting proteins might contribute to neuronal dysfunction in neurological diseases.

7SK PROVIDES REGULATORY SUPPORT FOR AXON GROWTH DURING NEURON DEVELOPMENT

Proteomics analyses have revealed a complex and dynamic protein interactome of 7SK.[22,23] In addition to the core interactors MePCE and LARP7, and the P-TEFb complex, the heterogeneous nuclear ribonucleoproteins (hnRNPs) A1, A2/B1, Q and R were identified as 7SK binders through pull-down experiments followed by mass spectrometric analysis (Figure 1A; Table 1).[22,23] These hnRNPs use stem loop 3 of 7SK as interaction site and thus differ from P-TEFb, which associates with stem-loop 1 via HEXIM1.[22,25,27,28]

Importantly, binding of hnRNPs and P-TEFb to 7SK is mutually exclusive and the balance between these 7SK subcomplexes is determined by the transcriptional activity of a cell (Figure 1A).[22,23] At high levels of transcription, hnRNPs associate with nascent RNA, which promotes sequestration of P-TEFb by 7SK, thereby limiting its kinase activity. Under conditions of low transcription, lack of nascent RNA enables hnRNP interactions with 7SK. As a result, P-TEFb is released and can activate paused RNA polymerase II through phosphorylation. This feedback mechanism ensures a balanced transcriptional output in response to transcriptional deviations from the status quo.

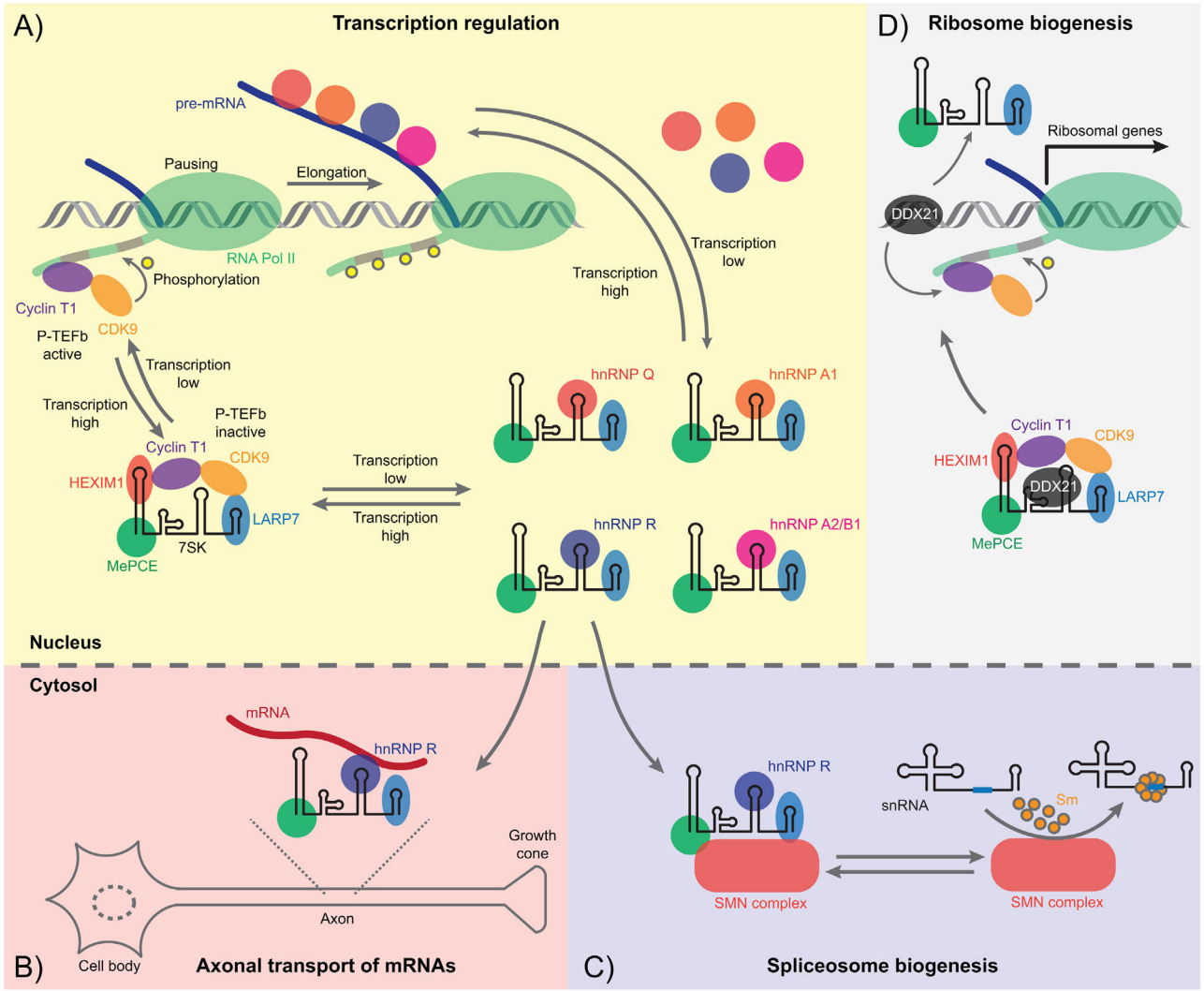

FIGURE 1 Schematic representation of 7SK subcomplexes and their functions in the nucleus and cytosol. (A) 7SK RNA is protected at the 5′ and 3′ end by the core interactors MePCE and LARP7, respectively. In the nucleus, 7SK interacts with the P-TEFb complex composed of CDK9 and Cyclin T1 and inhibits their kinase activity. Upon release from 7SK, P-TEFb is recruited to paused RNA polymerase II to phosphorylate its C-terminal domain, which triggers productive elongation. The fraction of 7SK not associated with P-TEFb binds to the hnRNP proteins A1, A2/B1, Q and R. The relative amounts of 7SK/P-TEFb and 7SK/hnRNP complexes are determined by transcriptional activity. At high levels of transcription, hnRNP proteins are associated with nascent RNA, allowing P-TEFb sequestration by 7SK. At low levels of transcription, 7SK is captured by hnRNP proteins, which releases and activates P-TEFb. (B) In motoneurons, 7SK/hnRNP R complexes regulate the axonal transport of mRNAs during development. (C) Transcriptional inhibition enhances the interaction of 7SK/hnRNP R with SMN complexes in the cytosol, inhibiting their function in snRNP biogenesis. SMN facilitates the assembly of Sm proteins at a uridine-rich sequence (blue box) on snRNAs. (D) Through interaction with the RNA helicase and chromatin interactor DDX21, 7SK regulates transcription of ribosomal genes

While this mechanism of 7SK action has been investigated in detail and is likely to exist across many cell types, research over the past years has revealed that 7SK-associated signaling pathways are particularly important for neurons to support their development and function. 7SK is highly expressed in the nervous system during development and into adulthood.[29] During differentiation, 7SK expression is low in progenitor cells but is increased in differentiated neurons.[29] These findings point toward specific functions of 7SK for neuronal differentiation and maintenance. What could these functions be?

The hnRNPs that are associated with 7SK are known to exert post-transcriptional functions related to mRNA metabolism such as splicing, polyadenylation, stabilization, and subcellular mRNA transport. Neurons in particular utilize such mechanisms to establish and maintain their elaborate structural complexity. In motoneurons, hnRNP R is abundant in the nucleus but also localizes to the cytosol including axons and growth cones.[30] In these compartments, hnRNP R binds to the 3′ UTR of mRNAs and facilitates their axonal transport.[25] This has been demonstrated in detail for the mRNA encoding β-actin, a cytoskeletal component that is locally synthesized in growing axons to enable their elongation and navigation.[31,32] The main RNA interactor of hnRNP R is 7SK.[25] Conspicuously, 7SK/hnRNP R complexes were detected not only in the nucleus but also in the cytosolic compartment of

motoneurons, including axons. This indicates that 7SK/hnRNP R complexes are exported from the nucleus and adopt non-canonical functions such as the assembly and transport of messenger ribonucleoprotein particles (mRNPs) (Figure 1B). In support of this notion, depletion of 7SK in motoneurons altered the axonal localization of a subset of transcripts in a manner similar to loss of hnRNP R demonstrating the RNA transport functions of 7SK/hnRNP R particles.[25] Furthermore, knockdown of 7SK in motoneurons impaired axon growth but not survival, which is phenotypically similar to the consequences of hnRNP R depletion.[25,31,32] Additional evidence for a role of 7SK in mRNP metabolism comes from the finding that the 7SK core interactors LARP7 and MePCE bind to β-actin mRNA and thus might be components of such transport mRNPs involving hnRNP R.[24] Apart from hnRNP R, other hnRNPs associated with 7SK are also expressed in the nervous system. Thus, it can be assumed that separate 7SK/hnRNP complexes exist with distinct functions in regulating the RNA composition of different subcellular compartments. Techniques to investigate subcellular transcriptome alterations such as APEX-seq [33] could help to elucidate these mechanisms in future studies.

7SK FACILITATES NEURONAL GENE EXPRESSION

In addition to the regulation of RNA processing mechanisms, 7SK complexes might be directly involved in the induction of gene expression programs that underlie the postmitotic specification of neurons. A recent study has dissected the reprogramming of fibroblasts into motoneurons through combined expression of microRNAs miR-9/9* and miR-124 and the transcription factors ISL1 and LHX3.[21] While the repression of KLF-family transcription factors by miR-9/9* and miR-124 was important for erasure of the fibroblast identity, 7SK played a role for the induction of neuronal gene expression programs at later stages of differentiation. Specifically, 7SK was found to regulate the accessibility of ~ 3,000 chromatin regions that are associated with genes required for induction of the neuronal fate. Upon depletion of 7SK, neuron conversion did not proceed, signifying the importance of 7SK for neuron development. This function of 7SK might depend on its interaction with chromatin-remodeling complexes such as the BAF complex.[20,21]

A distinguishing feature of gene expression in neurons is the transcription of long genes exceeding 100 kbp in length.[34,35] The neuronal RNA-binding protein Sfpq has been identified as a critical factor in this process.[36] To sustain transcription across large distances, Sfpq binds to the long introns of pre-mRNAs of such genes and recruits CDK9 to locally maintain Serine 2 phosphorylation of the CTD of RNA polymerase II. Consequently, Sfpq depletion in cultured cells impaired the RNA polymerase II occupancy along gene bodies. Moreover, the expression of long genes was particularly perturbed in Sfpq knockout brains. Transcription of long genes was also reduced when 7SK was knocked down during neuronal reprogramming of fibroblasts indicating that a functional 7SK/P-TEFb complex is necessary for the delivery of CDK9 to long pre-mRNAs.[21]

Taking these results together, a picture emerges in which 7SK is a multi-faceted RNA that simultaneously controls not only nuclear proteins involved in gene activation and RNA processing but also cytosolic RNA-binding proteins in order to modulate subcellular RNA localization and local translation.

7SK LINKS THE ACTIVITIES OF MACROMOLECULAR MACHINERIES

While the 7SK complex has been studied in detail for its function in regulating the transcriptional machinery, a recent study described a non-canonical role of 7SK in modulating the biogenesis of spliceosomal small nuclear ribonucleoproteins (snRNPs) in neuronal cells.[24] Spliceosomal snRNPs are produced by the SMN complex, which assembles a seven-membered ring of Sm proteins around a uridine-rich region of snRNAs (Figure 1C).[37] This step is essential for snRNP formation and takes place in the cytosol, prior to re-import of snRNPs into the nucleus where they form the spliceosome.[38,39] SMN and several GEMINs, which are key components of the SMN complex, were identified as interactors of 7SK.[24] Notably, this interaction of SMN with the 7SK complex was not mediated through 7SK itself but rather through RNA-independent contacts with LARP7 and MePCE. Transcriptional inhibition of cells by treatment with the antibiotic Actinomycin D enhanced the association of hnRNP R and the SMN complex with 7SK (Figure 1C). This association occurred in the cytosol and was accompanied by reduced assembly of several snRNPs. Given that transcription rates are altered on a global scale during neuronal differentiation and during nervous system development, the regulation of the SMN complex by 7SK provides a mechanism through which the production of snRNPs is adjusted accordingly. This way, the number of spliceosomes produced is linked to the transcriptional demand of a cell such that a surplus of spliceosomes is avoided, which might otherwise cause detrimental effects at the post-transcriptional level. Interestingly, a link between U2 snRNP function in splicing and promoter-proximal pausing of RNA polymerase II has recently been reported, according to which spliceosome assembly on pre-mRNA stimulates productive transcriptional elongation through P-TEFb recruitment.[40] This suggests that spliceosome biogenesis, splicing, and transcription are co-regulated through complex feedback loops.

There is also evidence that 7SK regulates the biogenesis of ribosomes. 7SK interacts with the RNA helicase DDX21 and regulates the expression of ribosomal protein genes (Figure 1D).[26] DDX21 binds to the promoter regions of ribosomal genes and facilitates the local release of P-TEFb from 7SK for transcriptional activation. Additionally, through association with the little elongation complex (LEC), 7SK promotes transcription of small nucleolar RNAs (snoRNAs), which are involved in maturation of ribosomal RNA (rRNA).[41] In neurons, the 7SK core component LARP7 localizes to nucleoli and modulates ribosome production.[42] Thus, neurons might utilize 7SK to crosstalk between major macromolecular machineries involved in transcription, splicing, and translation.

DISTURBED 7SK SIGNALING PATHWAYS IN NEUROLOGICAL DISEASES

Additional evidence for the importance of 7SK complexes for nervous system function comes from observations showing that dysfunction of 7SK interactors leads to neuronal diseases. Mutations in the *LARP7* gene cause Alazami syndrome, an autosomal recessive developmental disorder.[43] Patients show growth retardation and mental disability. Given LARP7's function in 7SK stabilization, 7SK levels are strongly reduced in cells from Alazami syndrome patients suggesting that 7SK signaling is perturbed by *LARP7* mutations. However, more recently, a function for LARP7 in post-transcriptional modification of the U6 snRNA has been identified.[44] LARP7 was shown to guide specific C/D Box snoRNAs to U6, thereby facilitating its 2′-O-methylation. This modification is critical for U6 function as part of the spliceosomal machinery. Consequently, loss of LARP7 function impaired U6 2′-O-methylation, leading to certain splicing defects in cells derived from Alazami syndrome patients.[44]

Not only LARP7, but also MePCE, the other 7SK core component, has been implicated in neurodevelopment. A patient with a de novo nonsense mutation in MePCE has been described who developed motor defects, cognitive impairment and seizures.[45] 7SK levels were reduced in patient cells haploinsufficient for MePCE in line with MePCE's function in 7SK 5′ end modification and protection. As a result of 7SK depletion, reduced inhibition of P-TEFb by the 7SK interactor HEXIM1 and, consequently, enhanced phosphorylation of RNA polymerase II were observed. This, in turn, led to upregulated transcription of RNA polymerase II-controlled genes. Thus, disruption of 7SK signaling due to loss of MePCE function impairs neurodevelopment.

While LARP7 and MePCE exert regulatory functions during neurodevelopment, several of the hnRNPs interacting with 7SK have been implicated in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). These disorders are characterized by the presence of cytoplasmic protein inclusions in neurons in affected brain regions.[46,47] In sporadic forms of ALS, cytoplasmic inclusions containing TAR DNA-binding protein-43 (TDP-43) are a pathological hallmark and mutations in the *TARDBP* gene encoding TDP-43 have been identified in familial forms of the disease.[46,48,49] Among 7SK interactors, mutations in hnRNP A2/B1 and A1 have been identified in patients with multisystem proteinopathy and ALS.[50] In brains of FTLD patients, hnRNP R and Q were found in pathological inclusions alongside the fused in sarcoma (FUS) protein.[51]

In agreement with the functions of RNA-binding proteins in transcription and post-transcriptional processing, widespread alterations in gene expression have been observed in ALS and FTLD.[52,53] Additionally, TDP-43 aggregates in ALS affect the nucleocytoplasmic transport of proteins and mRNA.[54–56] These transcriptome alterations are likely to affect also the balance of 7SK subcomplexes, particularly those containing hnRNPs. As a result, the 7SK signaling axis might be perturbed, further dysregulating the dynamics of transcription. Additionally, genome-wide analysis of binding sites and functions of hnRNPs in alternative splicing has revealed extensive cross- and autoregulation among them.[57] Thus, dysregulation of one hnRNP protein is likely to affect the function of others. Such alterations in RNA processing might not only occur in ALS and FTLD but also in other neurodegenerative conditions such as Alzheimer's disease (AD), in which depletion of certain hnRNPs has been observed.[58]

Many RNA-binding proteins including the hnRNPs interacting with 7SK contain low-complexity domains (LCDs) that are intrinsically disordered.[59] The LCDs facilitate the assembly of hnRNPs into subcellular membraneless structures such as stress granules through a process termed liquid-liquid phase separation.[60] Stress granules are transient repositories of translationally inactive mRNAs and contain a complex repertoire of proteins.[61,62] In familial forms of ALS and other neurodegenerative disorders, mutations in the LCDs of hnRNPs enhance their tendency to aggregate, thereby preventing stress granule disassembly and inducing the formation of insoluble inclusions.[60,63] Sequestration of hnRNPs into such inclusions might further disturb the balance between 7SK subcomplexes containing P-TEFb and those that are associated with hnRNPs. As a result of such an imbalance, 7SK signaling pathways would be altered, which might exacerbate transcriptional defects and neuronal dysfunctions. Conspicuously, besides the aggregation of RNA-binding proteins, cytoplasmic accumulations of spliceosomal snRNPs have also been reported in ALS and AD.[64–66] This suggests the possibility that failure of proper regulatory control of SMN complex activity due to alterations in 7SK/hnRNP levels results in aberrant production of snRNPs in these disorders.

The most common genetic cause of ALS in Europe and the US is expansion of the GGGGCC (G_4C_2) hexanucleotide repeat in the gene *C9ORF72*.[67,68] Production of dipeptide repeat proteins (DPRs) from these repeats through repeat-associated non-ATG (RAN) translation has been identified as a mechanism contributing to the underlying motor pathology.[69,70] Arginine-containing DPRs, which are particularly toxic, sequester many RNA-binding proteins and render them non-functional. Interestingly, not only hnRNP A1, A2/B1, Q and R but also LARP7 and MePCE were detectable in the DPR interactome.[71] This points to the possibility that aggregation of 7SK core and auxiliary components by DPRs disturbs 7SK-regulated transcriptional control in the nucleus. Future research investigating 7SK-mediated regulation of P-TEFb and other complexes in cell and animal models of neurodegeneration will help to identify such dysfunctions.

Taken together, several lines of evidence have implicated 7SK-interacting proteins in neurological diseases. In the case of the 7SK core interactors LARP7 and MePCE, mutations in these factors have been shown to directly disturb 7SK signaling pathways. Beyond that, pathological aggregation of 7SK-associated hnRNPs during neurodegeneration might indirectly affect the dynamics of 7SK assembly as a consequence. Thus, while mutations in 7SK itself have not been implicated in disease contexts so far, it is possible that alterations in 7SK-related mechanisms contribute to the pathophysiological cascade of events leading to neuron dysfunction and loss in neurodegenerative disorders.

CONCLUSIONS AND OUTLOOK

Research over the last years has continuously elucidated novel roles of 7SK in neurons, extending the canonical model of 7SK function in transcriptional regulation. With these new findings a picture emerges according to which 7SK acts as a versatile RNA platform for the coordinated regulation of different RNA-binding proteins and macromolecular machineries. Nevertheless, several open questions remain. First, while 7SK has been shown to associate with a range of hnRNPs in cultured cells it is unclear whether these 7SK/hnRNP complexes exist in a similar manner in vivo and whether their relative abundance and composition differs between tissues and between neuronal subtypes in the nervous system. This question could be addressed by proteomics approaches following 7SK purification from different cell types and at different stages of neuronal differentiation. Second, the importance of 7SK signaling for nervous system development and maintenance in vivo remains to be determined through constitutive and conditional knockout strategies. Third, recent studies have revealed novel functions of 7SK that are related to the control of cytosolic processes such as the assembly and subcellular transport of various RNPs. Investigating the composition of 7SK complexes in different subcellular compartments of neurons could shed further light on these roles. Finally, several of the 7SK interactors, including the core binders MePCE and LARP7, have been detected in neuronal pathological inclusions. It can thus be hypothesized that aberrant 7SK signaling pathways contribute to the etiology of neurodegenerative disorders. To what extent such alterations are cause or consequence of neurodegeneration remains to be determined in future studies. Investigations on disease models will help to understand the degree of 7SK dysregulation in neurodegenerative diseases and reveal whether correcting such imbalances might provide therapeutic approaches towards ameliorating the underlying neuronal dysfunctions.

ACKNOWLEDGMENTS

Work by Michael Sendtner and Michael Briese on 7SK and hnRNP R is supported by the Deutsche Forschungsgemeinschaft priority programs 1738 and 1935 (grant numbers: BR4910/1–1 and BR4910/2–1 to M.B.; SE697/4–1 and SE697/5–1 to M.S.).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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How to cite this article: Briese, M., & Sendtner, M. (2021). Keeping the balance: The noncoding RNA 7SK as a master regulator for neuron development and function. *BioEssays*, *43*, e2100092. https://doi.org/10.1002/bies.202100092