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RNA Biology

ISSN: 1547-6286 (Print) 1555-8584 (Online) Journal homepage: http://www.tandfonline.com/loi/krnb20

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To cite this article: Emanuele Buratti & Francisco Ernesto Baralle (2010) The multiple roles of TDP-43 in pre-mRNA processing and gene expression regulation, RNA Biology, 7:4, 420-429, DOI: 10.4161/rna.7.4.12205

To link to this article: http://dx.doi.org/10.4161/rna.7.4.12205

Published online: 01 Jul 2010.

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RNA Biology 7:4, 420-429; July/August 2010; © 2010 Landes Bioscience

The multiple roles of TDP-43 in pre-mRNA processing and gene expression regulation

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Key words: TDP-43, alternative splicing, microRNA, autoregulation, microarrays

Heterogeneous ribonucleoproteins (hnRNPs) are multifunctional RNA-binding proteins (RBPs) involved in many cellular processes. They participate in most gene expression pathways, from DNA replication and repair to mRNA translation. Among this class of proteins, TDP-43 (and more recently FUS/TLS) have received considerable attention due to their involvement in several neurodegenerative diseases. This finding has prompted many research groups to focus on the gene expression pathways that are regulated by these proteins. The results have uncovered a considerable complexity of TDP-43 and FUS/TLS functions due to the many independent mechanisms by which they may act to influence various cellular processes (such as DNA transcription, pre-mRNA splicing, mRNA export/import). The aim of this chapter will be to review especially some of the novel functions that have been uncovered, such as role in miRNA synthesis, regulation of transcript levels, and potential autoregulatory mechanisms in order to provide the basis for further investigations.

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Introduction

The heterogenous nuclear ribonucleoproteins (hnRNPs) play crucial roles in many and varied gene expression steps such as DNA replication/repair, gene transcription, pre-mRNA splicing, mRNA export/retention and stability and protein translation.[1-5] Furthermore, hnRNPs have been described to be involved in microRNA maturation,[6] snoRNP composition[7] and mRNA transport and translation[3,8] (the classical and novel roles played by these proteins are schematically summarized in **Figs. 1 and 2**). The functional role played by each individual factor belonging to this class depends on individual characteristics (single-stranded or double-stranded RNA binding specificities, protein-protein interactions etc.,) that at their basic levels are mostly determined by their structure. However, it should also be noted that hnRNPs are seldom "fixed" in a single role within a single cellular process. Rather, it is very often seen that hnRNPs participate in different processes depending on a variety of factors such as cellular localization, relative abundance, binding context, and the interactions with themselves or other cellular components.[5,9,10] Originally, the term hnRNP was coined to define all those abundant proteins that were found to be associated with heterogeneous RNA (hnRNA) populations in rapidly dividing cells.[11] As this first definition did not discriminate between primary or secondary RNA-protein interaction, it was later restricted to the proteins that were binding directly to heterogeneous RNA (hnRNA) molecules in vivo. The RNA-protein complexes formed in this way occur by a combination of various interactions (stacking, electrostatic and hydrogen bonding) between the hnRNP protein and selected nucleotides of an RNA molecule (that often form a loose "consensus" sequence for the binding of each particular factor). In the greatest majority of hnRNP proteins, the region responsible for the direct interaction and RNA binding sequence specificity is a 60 residues long evolutionary conserved motifs that folds in a conserved three dimensional conformation. This motif is commonly known as an RNA Recognition Motifs (RRM) domain. As a side note, the reader should be aware that RRMs is not the only conserved RNA-binding domain in existence. Although they do not occur as frequently, several other structures have been described to mediate RNA-protein recognition. These include double stranded RNA binding motif (dsRBM), Pumilio homology domain (PUF) and RGG repeats, Zinc-binding domains and KH domains, all of which have been recently reviewed.[12,13] A specific hnRNP, TDP-43, is an example of the multifunctional role of these proteins. **Figure 3A** shows a scheme of its structure with two classical RRM sequences and a Gly rich C terminal domain. Despite its unequivocal hnRNP structure, TDP-43 was first described as a DNA binding protein with a putative role in HIV transcription.[14] In 2006, it was found as the major protein component of the intracellular inclusions occurring in the neuronal tissues of patients affected by a series of neurodegenerative diseases which include Fronto Temporal Lobar Degeneration (FTLD-U), Amyotrophic Lateral Sclerosis (ALS),[15,16] and some cases of Alzheimer disease[17-19] and other neurodegenerative diseases, recently reviewed by Geser et al.[20] The impact of TDP-43 in the neurodegeneration field has caused revisions in disease nomenclatures that are currently being modified to better reflect these new clinical and pathological findings.[20-22] In the beginning, the question was still open regarding the relative importance of this protein: should TDP-43 protein inclusions be considered as a simple pathological curiosity of these diseases or did it really play a role in their origin and progression?.[23] This question was partially solved by several genetic findings that have identified TDP-43 mutations in about

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Submitted: 02/09/10; Revised: 04/29/10; Accepted: 04/30/10
Previously published online:
www.landesbioscience.com/journals/rnabiology/article/12205

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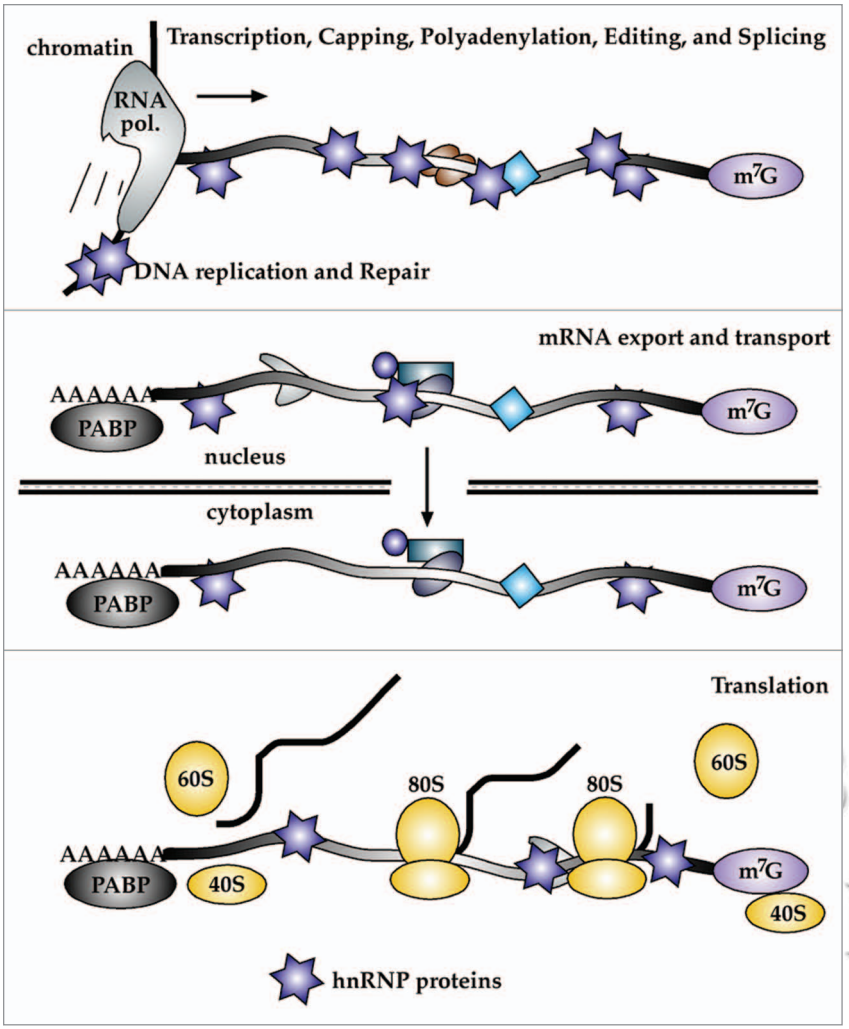

Figure 1. Classical role of hnRNP proteins. The hnRNP proteins function in all classical cellular processes to control pre-mRNA maturation including splicing, editing, proofreading, export and even the translation process itself.

5% of the patients, as recently reviewed by Pesiridis et al.[24] More recently, the development of several animal models has clearly shown the pathological potential of both TDP-43 depletion and overexpression. In this respect, it is worthy to note that the removal of endogenous TDP-43 in Drosophila results in a paralytic phenotype.[25] Consistently, the latest experimental evidences from transgenic mice lines have shown that disruption of TDP-43 expression severely impairs embryonic development when in a homozygous state and also motor functions in heterozygous knockout animals.[26-28] Furthermore, expression of mutant forms of this protein in mice,[29] rat,[30] zebrafish,[31] chicken,[32] yeast[33] and neuronal cell lines[34,35] can reproduce neurodegenerative effects similar to those observed in human disease.

More recently, another hnRNP protein FUS/TLS that possesses several functional and structural analogies with TDP-43 has also been reported to be involved in ALS pathogenesis, and mutations in this gene were found to be responsible for 4–5% of familial ALS cases.[36-39] FUS/TLS inclusions also represent a hallmark of frontotemporal lobar degeneration (FTLD) with neuronal inclusions composed of previously unidentified ubiquitinated protein (also referred to as atypical FTLD-U), which are tau- and TDP-43 negative.[40] In keeping with TDP-43, FUS/TLS possess a RNA Recognition Motifs (wih a different sequence target), several Gly-rich, QGSY-rich and RGG-rich regions (that usually mediate protein-protein interactions), plus a known nuclear export signal (NES) sequence which controls its nuclear/cytoplasmic distribution (**Fig. 3B**).

These parallelisms between TDP-43 and FUS/TLS, have substantially strengthened the hypothesis that in many cases neurodegenerative processes may occur through alterations a the level of RNA metabolism.[41-43] At the moment, of course, disease mechanisms related to these two proteins are still very much in the realm of untested hypotheses. In the patient's affected neurons, TDP-43 and FUS/TLS are abnormally mislocalized in the cytoplasm and TDP-43 can also be ubiquitinated, hyperphosphorylated,[44,45] and cleaved to generate toxic C-terminal fragments (CTFs),[35,46,47] as recently reviewed.[48] It is therefore likely that this mislocalization coupled with post-translational modifications may play a pivotal role in neurodegeneration. These alterations may result in the loss of proper TDP-43 and FUS/TLS functions in the nucleus (loss-of-function effects) and/or, in the case of altered localization, potentially toxic gain-of-function effects (listed at the bottom of **Fig. 3**). These issues, together with the new therapeutic possibilities that they open up, have been the subject of several recent reviews.[41,48-51]

In this work, we aim to provide an updated list of the gene expression events controlled by TDP-43 and FUS/TLS together with emerging trends in their mechanisms of action. The aim will be to hopefully provide the basis for further investigations.

Already known Effects of TDP-43 on Gene Expression

TDP-43 itself was cloned for the first time in 1995 as part of a research aimed at identifying novel HIV-1 inhibitors of transcription in correspondence to the TATA element of the viral LTR.[14] In this work, the binding site of TDP-43 was identified as a polypyrimidine-rich region of the TAR DNA element and was hypothesized to repress the recruitment of transcriptional factors to this promoter. Unfortunately no follow up work has been reported in this system. More recently, a second promoter where TDP-43 has been described to play a functional role is in the mouse *SP-10* gene, which codes for an acrosomal protein, and whose expression is driven by a spermatid specific promoter.[52] Also in this case, TDP-43 seems to mediate transcriptional

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repression in all mouse tissues with the exception of round spermatids. Unlike the HIV-1 system, TDP-43 was described to bind to the antisense strand of the SP-10 promoter that contained two complementary TGTGTG motifs.[53] This binding region was later observed to function as a minimal insulator in transgenic mice.[54] At the moment, however, the exact mechanisms that lead to transcriptional repression remains unclear.

So far, the better characterized functional role of TDP-43 involves pre-mRNA splicing regulation. There are currently four systems in which TDP-43 has been described to play an important role in deciding splicing outcomes. The first two have been extensively reviewed elsewhere[55] and involve the recognition of exon 9 in the *CFTR* gene[56-58] and *Apo AII* exon 3.[59] In both these examples, TDP-43 has been described to act as negative splicing regulator binding to UG-repeated elements, that represents the preferred binding sequence for this protein.[60] From a molecular mechanism point of view, it should be noted that much of the TDP-43 splicing inhibition is dependent on its interaction with several other hnRNPs, such as A1/A2/B1/C, through its terminal tail.[61] Recently, the exact C-terminal region responsible for the binding of these proteins to TDP-43 has been determined in the region spanning residues 321 to 366.[62]

With regards to the other two splicing systems where TDP-43 plays a role, it has been reported by Bose et al. that TDP-43 may also play a positive role in exon inclusion during the splicing regulation of *SMN1/2* exon 7.[63] In their report, these authors have shown that TDP-43 binds specifically to exon 7 sequences (although without any apparent sequence preference) and promotes exon inclusion by either recruiting splicing competent complexes near this exon or antagonizing negative splicing regulatory factors. In the second case, another very recent report investigating the splicing-based, autoregulation mechanism of the SC35 splicing factor has also demonstrated a functional role for TDP-43.[64] In this report, it has been described that TDP-43 together which hnRNP H can antagonize the recognition of the last exon by the splicing machinery[64] (discussed more below).

Finally, in keeping with the characteristics of many other hnRNPs with similar structure, the functional roles of TDP-43 have also been suggested to extend in a variety of functions that include neurofilament stability,[65,66] stress granule formation,[66-69] mRNA translation,[70] and potentially in snoRNA metabolism.[71]

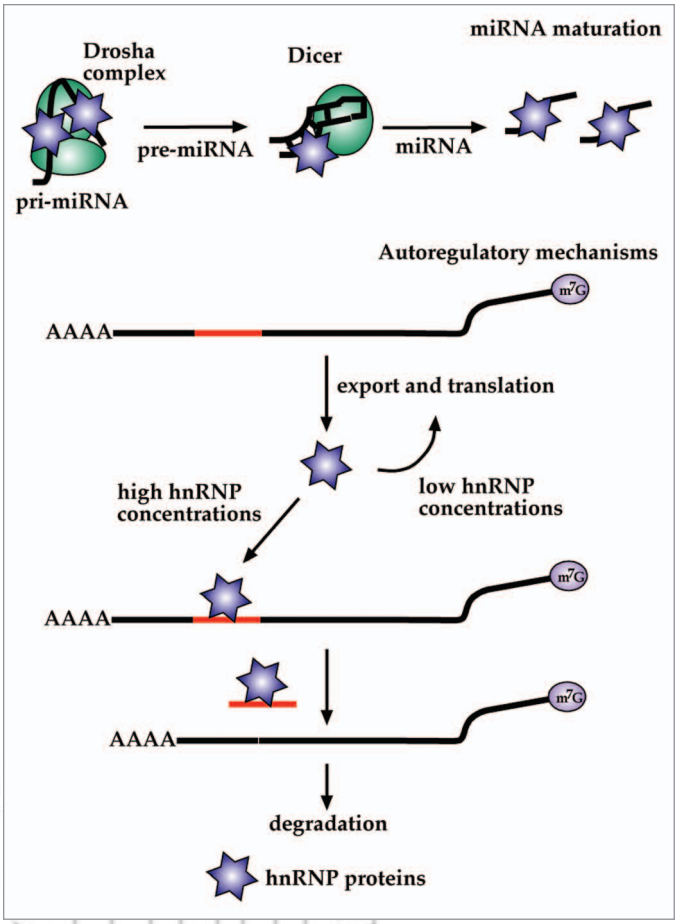

Figure 2. Novel roles of hnRNP proteins. Recently, hnRNP proteins have been described to participate in the maturation microRNA (and various classes of non-coding RNAs). In addition, it is increasingly clear that their cellular levels are often subjected to auto-regulatory mechanisms such as the one shown in this figure. In this case, high levels of a particular hnRNP protein result in the increased recognition of binding sites upon their own pre-mRNAs. As a result, the pre-mRNAs are subjected to additional processing in order to make them degraded more easily by the cellular machinery.

Already Known Effects of FUS/TLS on Gene Expression

Similarly to TDP-43, also the FUS/TLS ("fused in sarcoma" or "translocated in liposarcoma") is an hnRNP protein that was first identified as a transcriptional regulator. Unfortunately, the transcriptional properties of this protein have mostly been studied as a protein fused to other related proteins in some sarcomas.[72] In its natural (unfused) state the FUS/TLS has been reported to be present in the RNA polymerase II (Pol II) transcription complexes,[73] interacting with different transcriptional factors such as various nuclear receptors,[74] Spi-1/PU.1 transcriptional factor,[75] NFκB nuclear factor[76] and the co-transcriptional factor beta-catenin.[77] More recently, Wang et al.[78] have shown that the FUS/TLS protein downregulates the expression of *cyclin D1* gene (*CCND1*) by repressing the acetyltransferase activity of CBP (protein binding CREB) and p300. Interestingly, the recruitment of FUS/TLS to the CCND1 promoter and its CBP/p300 repression activity depends on its binding to particular non coding RNAs (ncRNAs).

Unlike TDP-43, FUS/TLS does not seem to play a prominent role in splicing regulation. However, this possibility should not be discarded if we consider the fact that FUS/TLS has been described to interact with several splicing factors that include SR proteins, especially SC35,[79] and the PTB and SRm160 factors.[80] Moreover, it is known that overexpressing FUS/TLS can induce the preferential usage of the most distal 5' splice site of the artificial E1A pre-mRNA reporter system.[75]

Finally, FUS/TLS at the neuronal level can bind the *Nd1-L* mRNA (encoding the actin-stabilizing protein Nd1-L) and favor its transport to neuron's dendrites.[81]

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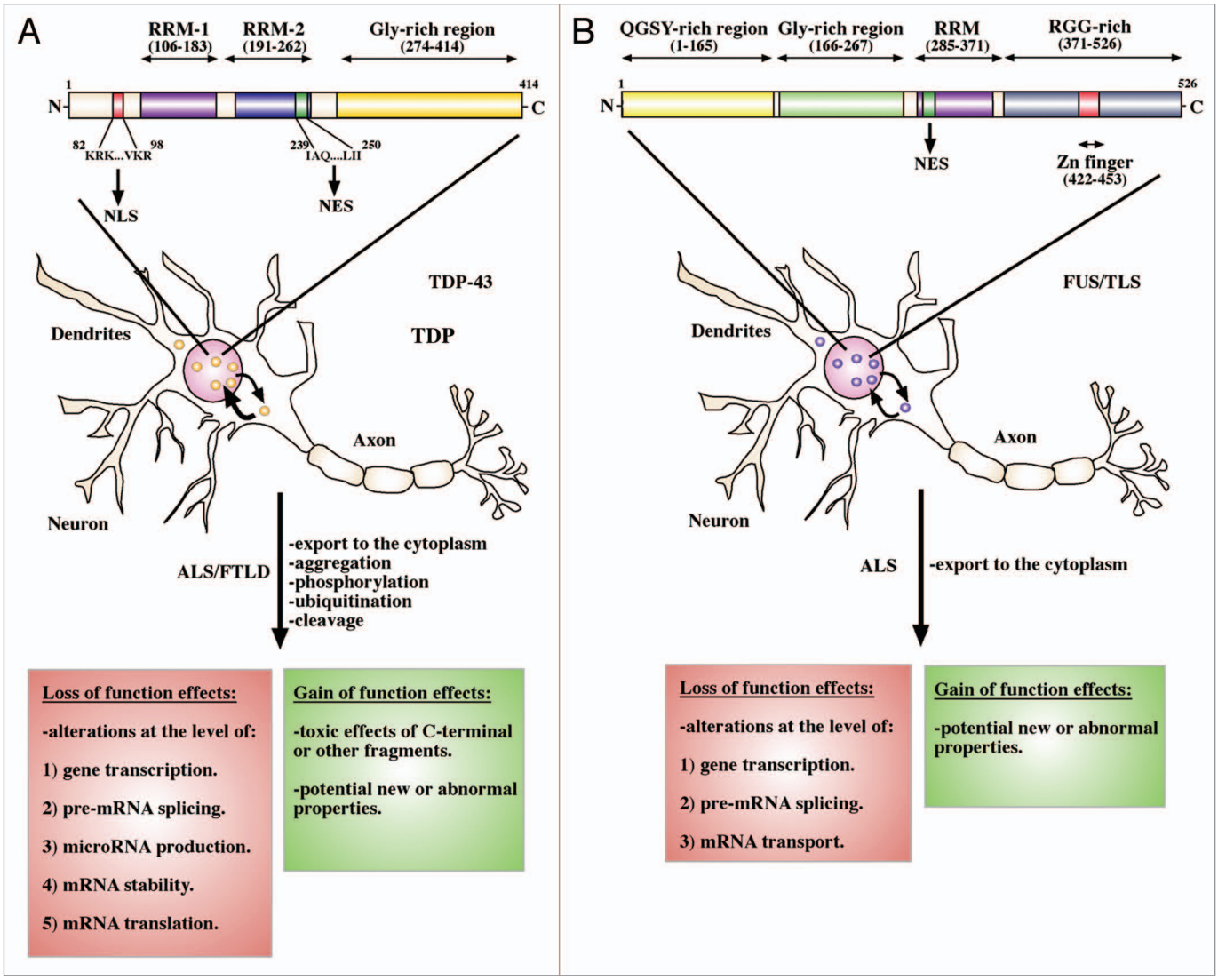

Figure 3. The TDP-43 and FUS/TLS proteins. The upper diagrams show a schematic representation of the TDP-43 and FUS/TLS protein structures reporting the major domain sequences determining nuclear/cytoplasmic localization (NLS and NES) or important for binding to RNA (RRMs and Zinc-fingers (Zn-finger), but also RGG regions), and potential protein-protein interactions (QGSY-rich, RGG-rich and Gly-rich regions). The lower panel shows the normal localizations of these proteins in the cellular environment (normally nuclear). In normal conditions, TDP-43 is continuosly shuttling between the nucleus and the cytoplasm but is predominant in the nuclear compartment. In the disease state, it is ubiquitinated, cleaved, phosphorylated and exported to the cytoplasm to form insoluble aggregates. In the disease state, also FUS/TLS is present in abnormal inclusions in the cytoplasm and nucleus but to a lesser extent than TDP-43. In addition, no signs of hyperphosphorylation or ubiquitination have been detected for this protein. The possible disease mechanisms (gain- or loss-of-functon models) for either protein that may lead to neuronal loss are summarized in the bottom panels.

Novel Aspects of TDP-43 and FUS/TLS Gene Expression Regulatory Mechanisms

Taken together, therefore, it is already quite clear that TDP-43 and FUS/TLS can play several roles in the cellular metabolism. These roles can be perturbed by the changes in the localization/processing/primary sequence (due to mutations) of these proteins and eventually lead to disease. The gain- and loss-of-function effects that could lead to disease depending on each protein are summarized in **Figure 3**. It should be noted, however, that this list of effects is by no means exhaustive and other gene expression pathways controlled by FUS/TLS and TDP-43 may exist that we still know very little about. Of course, it is always difficult to "predict" novel functions for a protein in the presence of very little evidence. However, at least for TDP-43, there is now data that points in two specific directions: a role in specific microRNAs (miRNA) expression and in the potential involvement of TDP-43 itself in autoregulating its expression levels.

TDP-43 and MicroRNA Regulation

In the past, both TDP-43 and FUS/TLS have been found associated with the human and mouse microprocessor complexes.[82,83] This observation has suggested that mis-localization of these

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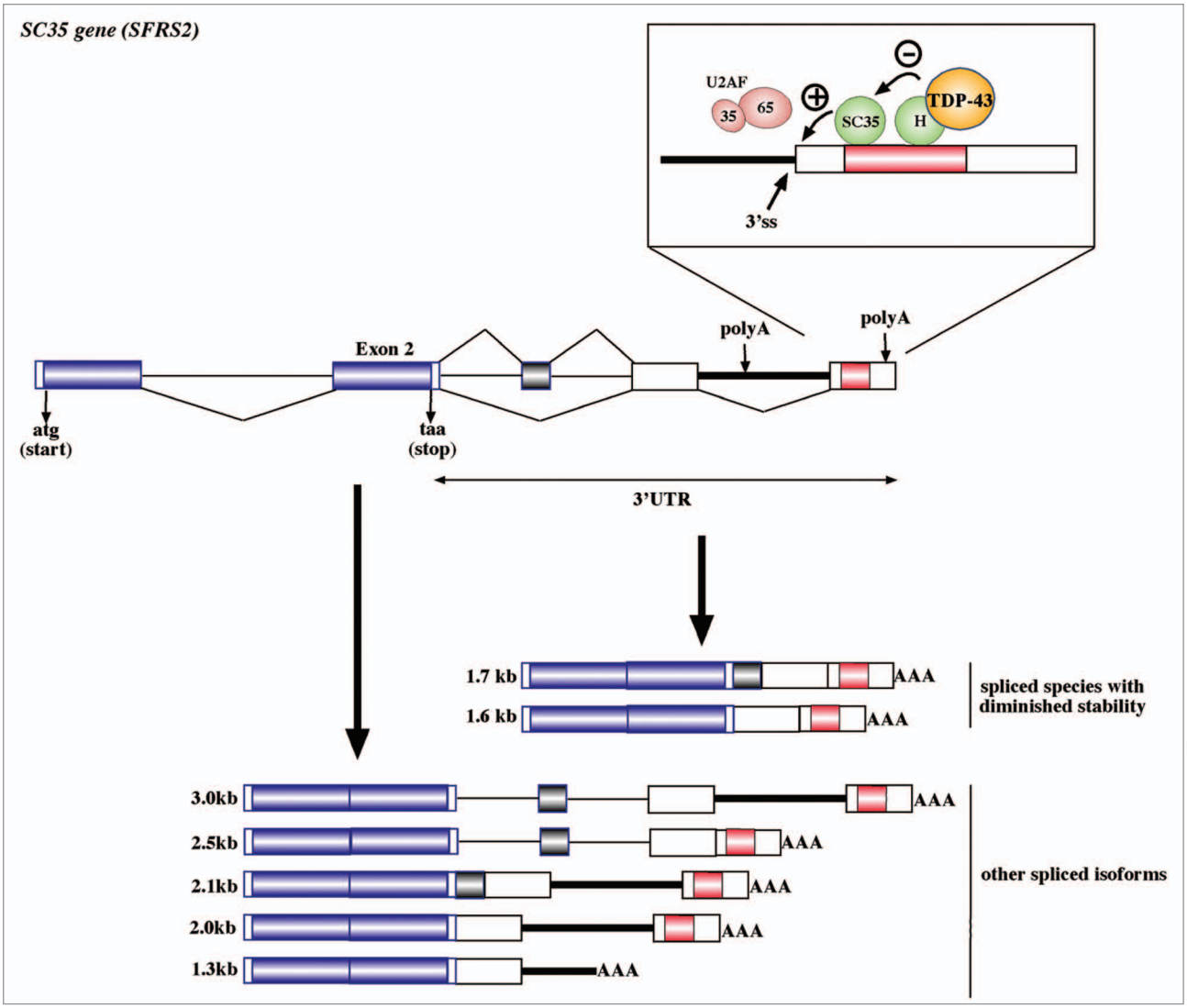

Figure 4. Autoregulatory mechanism. Schematic organization of the SC-35 gene. The open reading frame lies within the first two constitutively spliced exons, wheras the 3′UTR is alternatively spliced and polyadenylated. The SC-35 protein itself has been shown to bind to the last exon and promote 3′ss functioning (see inset). Use of this 3′ss leads to the preferential production of unproductive transcripts that are rapidly degraded by the NMD machinery. Binding of SC-35 to the last exon is inhibited by TDP-43 and hnRNP H, suggesting the existence of a highly complex regulatory mechanism that functions to regulate SC-35 protein cellular levels at the post-transcriptional stage.

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proteins from the nucleus to the cytoplasm can alter the functioning of the Drosha processing enzyme both with regards to the general miRNA cellular population or for selected members. In addition, at least for TDP-43, further support for an eventual role of this protein in miRNA biogenesis comes form the observations that it can also localize in peri-chromatin fibers (PFs),[84] a nuclear region specifically associated with miRNA processing.[85]

In general, Drosha-associated and external factors are now well known to be required to help or inhibit the processing of particular subsets of miRNA molecules. With regards to Drosha-associated factors, this has been shown to be the case for the p68 and p72 helicases,[83] the KSRP protein[86] and the Lin-28 factor.[87-90] Moreover, in a situation that is intriguingly similar to what could be that of TDP-43 and FUS/TLS, microRNA regulatory expression properties have also been described for another well known hnRNP protein, hnRNP A1. This protein, better known as a powerful splicing factor,[2] has been recently shown to regulate the expression of miR-18a by binding to the loop of the pri-miR-18a molecule and inducing a relaxation at the stem, creating a more favorable cleavage site for Drosha.[6,91,92] In this context, it would therefore be not very surprising if either TDP-43, FUS/TLS, or both, could act in a similar manner to hnRNP A1, and regulate the expression levels of at least a subset of microRNA molecules. In keeping with this hypothesis, depletion of TDP-43 has been recently shown to affect the cellular levels of two microRNAs, let-7b and miR-663, in a direct manner and to potentially bind directly other two (miR-558, and miR-574-5p).[93] In this work, it was observed that let-7b and miR-663 expression levels are down and upregulated, respectively, following TDP-43 depletion in a variety of cell lines. Interestingly, binding studies showed that

TDP-43 binds to these miRNAs in different positions, within the miRNA sequence itself (let-7b) or in the hairpin precursor (miR-663) and that downregulation in let-7b levels correlates with changes in the expression levels of several potentially important transcripts involved in neurodegeneration and synapse formation, such as DYRK1A, STX3, VAMP3 and LAMC1. Future experimental studies will hopefully broaden these findings as aberrant miRNA expression seems to be a very promising research field, particularly with regards to a great variety of neurodegenerative diseases.[94-98]

Autoregulatory Mechanisms

Another potentially new TDP-43 property is the existence of autoregulatory mechanisms that maintain stable its cellular protein levels. In fact, with RNA binding proteins (and especially splicing factors) it has been reported the presence of ultraconserved nucleotide sequences within their mRNAs that can act as regulatory elements by triggering particular splicing events that are associated with degradation of the transcript itself through Nonsense Mediated Decay.[99,100] An example of these autoregulatory networks in which TDP-43 is directly involved is represented by the *SC-35* gene. This protein, in fact, can regulate its own expression by stimulating unproductive splicing events in its 3'UTR region.[101] This is achieved by the specific binding of SC-35 to a particular enhancer region in the terminal exon which can promote intron processing by increasing 3'ss recognition. As shown in **Figure 4**, high SC-35 protein concentrations binding near this splice site increase the number of mRNA isoforms which have reduced stability and are degraded by the NMD machinery before they can be exported and translated in the cytoplasm. It follows that when SC-35 is present in low concentrations these unproductive splicing events are less frequent and as a result more protein is produced. As it is obvious, this is a very fast and efficient way of autoregulating a protein's concentration within the cell because it completely bypasses the need to act on the transcriptional machinery. Recently, it has been described that both TDP-43 and hnRNP H can antagonize the binding of SC35 to this terminal enhancer element.[64] Therefore, the levels of intracellular TDP-43 and hnRNP H also contribute to this feedback mechanism.

Do we already have some evidence that, like SC-35, TDP-43 itself might be subjected to this kind of regulation?. As previously mentioned, almost a year ago a report from Baralle's lab initially showed that depletion of the Drosophila TDP-43 protein (TBPH) affected the locomotive behaviour of the flies, reduced life span and presented anatomical defects at the neuromuscular junctions.[25] Most importantly, these phenotypes could be rescued by expression of the human protein in a restricted group of neurons including motoneurons. In a subsequent work by Lu et al.[102] loss of TBPH in Drosophila was observed to decrease dendritic branching and reintroduction of human TDP-43 could restore dendritic branching in neurons. Most importantly, this function was observed to be attenuated if the human protein carried mutations associated with ALS. The results of the model developed by Feiguin et al.[25] were consistent with a pathogenic loss-of-function mechanism whilst several results in the report by Lu et al.[102] are also supportive of a gain-of-function scenario. Of course, the two models do not necessarily exclude each other, and both may well contribute to the particular disease phenotypes in these animal models (as it may be also in the human pathology). Interestingly, however, Lu et al.[102] also reported that overexpression of TBPH in flies significantly increases dendritic branching of sensory neurons in fly larvae. The fact that overexpression of the human TDP-43 protein can be very toxic to neurons has recently been confirmed in subsequent Drosophila models,[103,104] and in a dose-dependent manner also in mice.[105]

Taken together, the major conclusion that can be drawn from these studies is the obvious need by living organisms to tightly control, at least in neuronal tissues, the physiological levels of TDP-43 protein production within a very narrow range. This evident need makes it very likely that TDP-43 levels are probably highly regulated within the cell, possibly in a post-transcriptional manner. In this respect, it should be noted that there are several splicing isoforms of TDP-43 (up to 11 in EST databases) and some are predicted to be susceptible to NMD degradation.[56,65]

All this complexity brings to the fore another important issue with regards to the gene expression mechanisms mediated by TDP-43. It is well established that TDP-43 is an ubiquitous protein found in all organs of the body. It follows that mis-regulation/localization/modifications of TDP-43 should cause damage in other body tissues beside neurons. Indeed, the early experimental evidences from transgenic mice lines in which expression of this gene is disrupted agree in the indication that TDP-43 plays a fundamental role in embryonic development, as previosuly mentioned. Therefore, it is obvious to ask why the effects of TDP-43 may be felt particularly at the neuronal level and not in other organs of the body. Certainly, part of the answer could reside in the peculiar metabolism and structure of neurons with respect to many other cells in the body (long life, very extended cytoplasm etc.). However, it is also possible that the cellular transcripts that are regulated by TDP-43 in different cell lines may well present considerable variation. Indeed, the very recent evidence from highthroughput experiments that deal with TDP-43 depletion/overexpression points in this direction.

Cell-Specific Effects of TDP-43 Knockdown on Cellular Transcript Levels

At present, there are only two published analysis that have described the effects of TDP-43 depletion in specific cell lines using highthroughput methodologies.

In the first case, Ayala et al.[106] have used microarray analysis to examine the type of transcripts that are up or downregulated in HeLa cells following its depletion by addition of siRNA against this protein. The results have shown that several hundred factors significantly change their expression levels upon TDP-43 depletion. Among the most significant ones, there are many proteins whose functions have been associated with the retinoblastoma protein (pRb) pathway. The pRb acts as a tumor suppressor gene essential for the control of cell cycle progression, cellular differentiation and maintenance of genome integrity. It is inactivated

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Table 1. Summary of common transcripts altered by TDP-43 depletion in human HeLa and HEK-293E cells

Accession no.	Transcript[a]	HeLa	HEK-293E
NM_000700	annexin A1 (ANXA1)	+2.1	+4.0
AK021882	cDNA FLJ11820 fis, clone HEMBA1006445, highly similar to GTP-binding protein Di-Ras3	-3.1	+2.7
AF133207	protein kinase (H11)/heat shock protein beta8 (HSPB8)	+1.2	+2.6
NM_002041	GA binding protein transcription factor, beta subunit 1 (GABPB1)	+1.2	+2.6
BC005961	parathyroid hormone-like hormone	-1.8	+2.5
NM_014656	KIAA0040 (KIAA0040), transcript variant 2	-1.4	+2.1
BF062139	Polymerase (RNA) III (DNA directed) polypeptide G	+1.0	+2.0
NM_021249	sorting nexin 6 (SNX6)	+1.0	-2.0
NM_003272	G protein-coupled receptor 137B (GPR137B)	+1.5	-2.1
NM_003428	zinc finger protein 84 (ZNF84)	+1.1	-2.1
NM_002056	glutamine-fructose-6-phosphate transaminase 1 (GFPT1)	+1.1	-2.2
NM_005983	S-phase kinase-associated protein 2 (p45) (SKP2)	-2.4	-2.3
NM_003940	ubiquitin specific peptidase 13 (isopeptidase T-3) (USP13)	-1.9	-2.3
NM_022474	palmitoylated 5 (MAGUK p55 subfamily member 5) (MPP5)	+1.3	-2.3
NM_007375	TAR DNA binding protein (TARDBP)	-2.8	-2.4
NM_019018	Homo sapiens family with sequence similarity 105, member A (FAM105A)	+1.1	-2.5
BC005941	Homo sapiens similar to vesicle-associated membrane protein 3 (cellubrevin)-VAMP3	+1.4	-2.5
AW025579	NCI_CGAP_Kid3 Homo sapiens cDNA clone IMAGE:2525839 (probably a library tracer)	-1.4	-2.5
BC003570	Homo sapiens similar to vesicle-associated membrane protein 3 (cellubrevin)-VAMP3	+1.5	-2.7
NM_004781	VAMP3	+1.4	-2.7
AF054589	HIC protein isoform p40 and HIC protein isoform p32 mRNAs	+1.4	-2.8
NM_005328	hyaluronan synthase 2 (HAS2)	-2.3	-2.9
NM_002627	phosphofructokinase, platelet (PFKP)	-2.0	-3.2

[a]shading highlights transcripts that are consistently up or downregulated in both experiments.

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by gradual phosphorylation by Cdks during the G_1 phase of the cell division cycle and this results in the activation of transcription factors that promote cell proliferation. One of the most interesting results of this study was the observation that expression levels of the CDK6 transcript and protein were increased by several fold. In addition to CDK6, a major controller of pRb phosphorylation, the levels of several other transcripts related to the control of cell cycle progression were also observed to change specifically in TDP-43 depleted cells. These include POLD4, cyclin B1, Cdk2, UBE2C and SKP2. In addition, changes were also observed in the levels of other factors that are known to either directly interact with pRb (i.e., HDAC1, RBBP4 and CRI1) or act in response to pRb modulation (i.e., E2F8 and NAP1L1). In keeping with these results, removal of TDP-43 in U2OS cells showed an alteration of the cell cycle pattern with a 60% decrease of cells in G_0/G_1 accompanied by a corresponding increase in S and G_2/M cells.[106] At present, the mechanism through which TDP-43 regulates CDK6 expression levels remains unknown. However, the observation that CDK6 levels do not change in chicken cells whose CDK6 gene lacks internal UG repeats, the preferred binding site of TDP-43,[60] suggests that these may occur through an alteration in the processing of this mRNA.[106] Interestingly, this increase in CDK6 expression could be observed to various degrees in several types of cells: HeLa, U2OS and MRC-5, but not in HEK293 cells.

More recently, a second microarray experiment has been reported following TDP-43 depletion in HEK-293E cells using siRNA technology.[107] In this microarray experiment, these authors have identified the HDAC6 transcript and protein as a major direct target of TDP-43. With regards to TDP-43 proteinopathies, the finding that HDAC6 levels may be downregulated following TDP-43 depletion represents an important finding, as the HDAC6 protein is known to control protein aggregate formation and degradation. Indeed, in a pathological model of aggregate formation based on expression of the Atx3-Q148-eGFP protein, the absence of TDP-43 and concomitant reduction of HDAC6 caused a significant increase in cell death with respect to control cells. Beside HDAC6, other targets that were significantly found to be affected in these HEK293 TDP-43 depleted cells included annexin 1 (ANXA1 gene), chromogranin B (CHGB), major vault protein (MVP), nicotinamide nucleotide adenylyltransferase 2 (NMNAT2)and secretogranin III (SCG3).

One interesting feature of these microarray experiments (keeping in mind their great variability) is represented by the observation that there is very little overlap with each other. In the case of CDK6, the failure of its overexpression following TDP-43 depletion in HEK-293 cells has been confirmed independently by us (Baralle et al., unpublished observations). Likewise, in Hela cells the only HDAC protein whose expression was observed

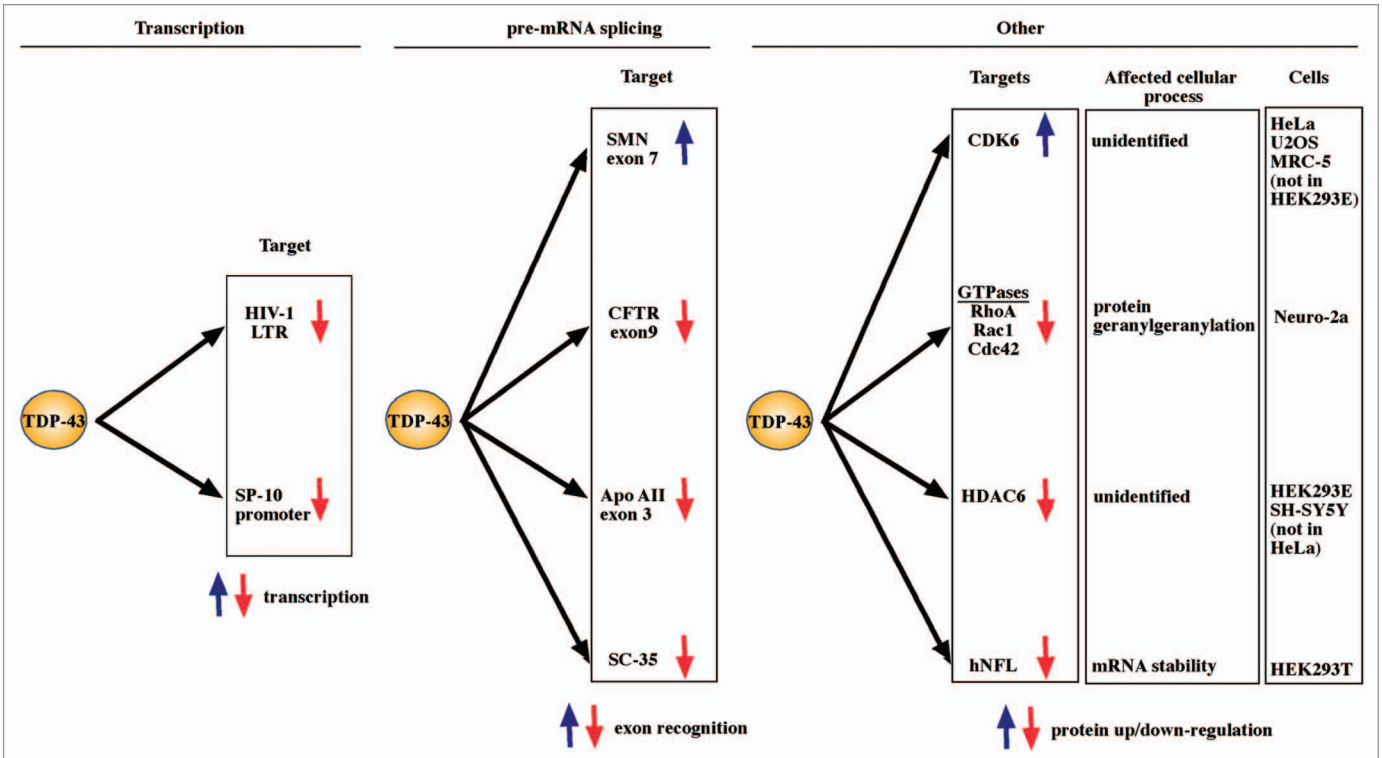

Figure 5. Genes directly controlled by TDP-43. These figures schematically report the genes known to be functionally and directly affected by TDP-43 through the control of transcriptional processes (left), mRNA splicing processes (middle), and other/unknown processes (right). In the case of some genes the cell lines in which gene expression variations have been observed to occur is also reported.

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to change in TDP-43 minus cells was HDAC1.[106] In keeping with this, there is very little overlap between the two microarray profiles. Being publicly available, we have compared the several hundred transcripts (approx. 300–400 in each experiment) that were reported to change following TDP-43 depletion in HeLa[106] and HEX-293E cells.[107] The results are reported in Table 1 and demonstrate that only 23 transcripts vary in common with both experiments (including, as expected, TDP-43 itself). Moreover, of these 23 transcripts only 10 (still including TDP-43) are regulated in the same direction (either up or down). Finally, no other proteins that have also be recently observed to be significantly affected in other studies were observed to change significantly in either study. These include several of the Rho GTPase enzymes,[108] SC-35,[64] and, at least at the mRNA level, other possible targets of TDP-43 action including SMN.[63] It should be pointed out that this is a common feature of many independent microarray experiments and that the conditions of the cells and the many variables in each individual experiment (that usually is self consistent) lights a warning signal about the reliability of not properly validated shifts in transcript levels in depletion experiments. In any case, a selection of the transcripts altered by TDP-43 depletion in the various studies appeared until now is summarized in **Figure 5**.

Of course, as mentioned above, technical differences could be at the heart of many of these differences. At this stage it is still very difficult to separate real functional effects from potential artefactual ones. However, it is also possible that this considerable heterogeneity observed in different cell types may help explaining why the effects of mutated TDP-43 may be evident only in a few of cell types (i.e., motoneurons).

Conclusions

As presented in this chapter, there are still many unknowns with regards to TDP-43 and FUS/TLS role in gene expression mechanisms that will have to be solved before we even begin to have a fair idea regarding the complete picture. Even more so, there is the need to understand which of these mechanisms plays a major role in neurodegeneration in order to target them specifically for therapeutic intervention. It is for this reason, therefore, that basic research in these factors should still play a major role in the coming years.

Acknowledgements

This work was supported by EURASNET and by AriSLA.

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