Mesenchymal cell differentiation and diseases: involvement of translin/TRAX complexes and associated proteins

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Translin and translin-associated factor X (translin/TRAX) proteins have been implicated in a variety of cellular activities central to nucleic acid metabolism. Accumulating evidence indicates that translin/TRAX complexes participate in processes ensuring the replication of DNA, as well as cell division. Significant progress has been made in understanding the roles of translin/TRAX complexes in RNA metabolism, such as through RNA-induced silencing complex activation or the microRNA depletion that occurs in Dicer deficiency. At the cellular level, translin-deficient (Tsn–/–) mice display delayed endochondral ossification or progressive bone marrow failure with ectopic osteogenesis and adipogenesis, suggesting involvement in mesenchymal cell differentiation. In this review, we summarize the molecular and cellular functions of translin homo-octamer and translin/TRAX hetero-octamer. Finally, we discuss the multifaceted roles of translin, TRAX, and associated proteins in the healthy and disease states.

Keywords: translin; TRAX; mesenchymal cell differentiation; miRNA depletion

Introduction

Multiprotein complexes (either homomeric or heteromeric) play an essential role in diverse biological processes and diseases. Some examples of these include the homomeric and heteromeric complexes for the transforming growth factor-β and bone morphogenetic protein receptors or between interferon regulatory factor 3 and coactivator CBP/p300.1,2

In this review, we focus on the roles of translin/translin-associated factor X (TRAX) complexes and their associated proteins in the healthy and disease states. Translin was first identified as a DNA-binding protein exhibiting general binding activity to the breakpoint junctions of chromosomal translocations in many cases of lymphoid neoplasms.3–6 Electron microscopy and crystallographic studies indicated that the native form of translin is a ring-shaped structure consisting of eight subunits. Subsequent analysis showed that translin binds to RNA as well as single-stranded DNA (ssDNA). Further studies to investigate translin-associated proteins revealed a binding partner, TRAX, showing extensive amino acid homology with translin.7 In the last decade, a wide variety of functions for translin/TRAX complexes have been identified at the molecular and cellular levels.8 Notably, at the molecular level, significant progress has been made in understanding the roles of asymmetric translin/TRAX hetero-octamer in RNA metabolism, such as through RNA-induced silencing complex (RISC) activation or the microRNA (miRNA) depletion that occurs in Dicer deficiency. Interestingly, a recent report demonstrated that learning induces translin/TRAX complexes to suppress miRNA-mediated silencing of ACVR1C (activin A receptor type 1C) for persistent memory.9 At the cellular level, translin-deficient (Tsn–/–) mice display delayed endochondral
ossification or progressive bone marrow failure with ectopic osteogenesis and adipogenesis, suggesting involvement in mesenchymal cell differentiation. In the present review, we will discuss the multifaceted roles of translin/TRAX complexes, as well as associated proteins, in mesenchymal cell differentiation and diseases.

Identification and characterization of translin

Previous studies identified leukemia cells derived from a 10-month-old boy (patient DOC) with T cell acute lymphoblastic leukemia (T-ALL) as members of the CD3⁺CD4⁺CD7⁺CD8⁻ T cell receptor (TCR) γδ lineage that appears early in thymic ontogeny. Cytogenetic and molecular analysis revealed a t(8;14)(q24;q11) rearrangement on one chromosome 14. However, functional rearrangement of the TCR δ gene (V₆δ₁-J₆δ-C₆δ) on another chromosome allowed cell surface expression of the TCR γδ complex. Preliminary studies indicated this particular rearrangement to be unusual in that J₆δ 1 was translocated further downstream from the structural locus of the c-myc oncogene on chromosome 8q24. An extensive analysis was then undertaken to identify the precise chromosomal breakpoint of the variant t(8;14)(q24;q11) translocation using a chromosome walking approach coupled with pulsed-field gel electrophoresis. The results clearly showed that the J₆δ 1 locus of the TCR δ gene was translocated 280 kb downstream from the structural locus of c-myc on chromosome 8q, which is reminiscent of Burkitt’s lymphoma variants that translocate to the pvt-1 locus.

The breakpoint sequence on chromosome 8q24 of the DOC leukemic cells was incidentally found to be almost identical to that of chromosome 1p32 involving the tal-1 locus in T-ALL patients carrying the t(1;14)(p32;q11) translocation. Similar sequences have also been found at chromosomal breakpoint junctions in many human lymphoid neoplasms. The consensus sequence motifs are ATGCAG and GCCC(A/T)(G/C)(G/C)(A/T), with gaps or a few inserted nucleotides, and do not bear any similarity to heptamer–nonamer V-D-J recombinase signal-like sequences. In most cases, the sequences were found at the 5′-flanking sites of breakpoint junctions, with genes encoding physiologically important proteins located in their vicinity. These findings raised the possibility that, during early stages of γδ T cell ontogeny, chromosome 8q24 and 1p32 regions are fragile and susceptible to nucleases that produce double-stranded breaks.

Subsequent analysis led to the identification of a novel DNA-binding protein named translin that exhibits general binding activity to the above described consensus sequences. Because of high expression in TCR βδ T cell leukemia DND-41, translin could be purified to near homogeneity from DND-41 nuclear extracts by a combination of chromatographic techniques including DE52, Q Sepharose, hydroxyapatite, phenyl Sepharose, and heparin agarose. The gene for translin was then cloned using PCR amplification with degenerate primers encoding the peptide sequences of the purified protein. Human translin gene encodes a protein of 228 amino acids with a predicted molecular weight of 27 kDa. Amino acid homologies to human translin are 99% for mouse and 86% for chicken proteins. SDS-PAGE analysis under reducing and nonreducing conditions showed that translin polypeptides form dimers. Under native gel electrophoresis conditions, however, the molecular weight of translin was estimated to be approximately 220 kDa, suggesting a ring-shaped octamer formed by four dimers. Confirming this hypothesis, electron microscopy and crystallographic investigations to determine its three-dimensional character indicated a ring-shaped structure consisting of eight subunits. The quaternary organization and the dimerization of subunits in the ring are very similar to those observed for hexameric ring helicases.

Translin has a heptad repeat of hydrophobic amino acids (five leucines and one valine), which could span at least ten α-helical turns. To assess whether this leucine zipper motif at the COOH-terminus (amino acids 177–212) is involved in formation of the native translin structure, a point mutation analysis was performed. Substitution of leucines with proline in this leucine zipper motif disrupted the octameric form of translin and completely abrogated its binding to target sequences situated only at the ends of ssDNA. However, point mutations in the basic region (amino acids 86–90) completely removed the DNA-binding activity without affecting the octameric form. These results clearly indicate that the DNA-binding domain of translin is formed by basic region polypeptides in the octameric barrel structure conserved in evolution.
Subsequent molecular analysis revealed that translin binds to RNA as well as ssDNA, and participates in transcriptional regulation or mRNA processing.\textsuperscript{15–17} The findings also demonstrated involvement of translin in microtubule-dependent mRNA transport.

**Aberrant mesenchymal cell differentiation in Tsn\textsuperscript{–/–} mice**

Generation of Tsn\textsuperscript{–/–} mice has provided insights into the multifaceted roles of the protein in cellular activities. Intriguingly, Tsn\textsuperscript{–/–} mice were significantly smaller in body size than their wild-type littermate controls at birth, and growth retardation was the most pronounced at 4–5 weeks of age. To investigate this phenomenon in more detail, histological studies focusing on bone formation were conducted. Delayed replacement of cartilage by bone, known as endochondral ossification, was noted in the tibias of 10-day-old Tsn\textsuperscript{–/–} mice when compared with wild-type mice (Fig. 1A). Furthermore, epiphyseal plates in the femurs of the same Tsn\textsuperscript{–/–} mice were very thin and capillary formation was also reduced (Fig. 1B), suggesting an important role of translin in bone formation.

In addition, young Tsn\textsuperscript{–/–} mice, especially those around 3 weeks of age, displayed a low lymphocyte count in the peripheral blood, attributable to developmental arrest of B lymphocytes in the earliest progenitor stage.\textsuperscript{10} In the developing mouse embryo, the first hematopoietic stem cells (HSCs) appear in the aorta–gonad–mesonephros region.\textsuperscript{18} Subsequently, HSCs are maintained in the fetal liver and adult bone marrow, although many uncertainties remain as to how they are related in these two sites. Previous studies have, however, demonstrated that the adult pattern of lymphopoiesis occurring in bone marrow is not fully established shortly after birth.\textsuperscript{19} Therefore, peripheral blood cytopenias in young Tsn\textsuperscript{–/–} mice might support the idea that translin plays a crucial role in peripheral lymphopoiesis during this period. As aging proceeded, some of the mutant mice began to exhibit a decrease in the number of bone marrow cells and massive splenomegaly with extramedullary hematopoiesis. Eventually, ectopic osteogenesis and adipogenesis were observed in the bone marrow. Despite progressive bone marrow failure, however, the frequency of HSCs (Lin\textsuperscript{−} CD34\textsuperscript{−} Sca1\textsuperscript{+} c-Kit\textsuperscript{+}) in the bone marrow was increased in Tsn\textsuperscript{–/–} compared with Tsn\textsuperscript{+/+} mice. These results are in good agreement with the previous observation that elimination of c-Myc activity in the bone marrow causes severe cytopenia and accumulation of HSCs, presumably through impaired interactions with specialized microenvironments (also called niches).\textsuperscript{20} Collectively, these findings support the idea that delayed endochondral ossification and bone marrow failure in Tsn\textsuperscript{–/–} mice could be due to defective mesenchymal cell differentiation.

**Identification and characterization of TRAX**

To investigate whether a particular protein is associated with translin, DNA encoding the full-length translin was cloned into the yeast GAL4 DNA-binding domain vector and used as bait to screen a human spleen cDNA library in a two-hybrid interaction analysis. One clone product gave specific activation with the translin bait. Its nucleotide sequence revealed an open reading frame encoding a protein of 290 amino acids with a predicted molecular weight of 33 kDa, and the encoded protein was named TRAX.\textsuperscript{7,21} TRAX exhibits extensive amino acid homology with translin. Although homology was found to exist throughout the two molecules, the C-terminal region of TRAX (amino acids 180–264) proved to be the most conserved (38% identity). Comparative studies confirmed similar transcription patterns of mRNA, together with evidence of in vivo and in vitro interaction of the two proteins, suggesting that TRAX belongs to the translin protein family. TRAX possesses nuclear localization signals in its N-terminal region, suggesting involvement in the nuclear transport of translin, which itself lacks any nuclear targeting motifs. TRAX contains a heptad repeat of hydrophobic amino acids referred to as the leucine zipper. This raises the question of whether TRAX homodimerizes or heterodimerizes with translin to regulate cellular functions. However, homodimerization of TRAX is unlikely because depletion of translin leads to complete loss of TRAX without affecting mRNA levels, indicating that the stability of TRAX depends on interaction with translin.\textsuperscript{22}

**A link between translin/TRAX expression and cell division**

Accumulating evidence indicates that the rate of cell proliferation correlates with the expression level of translin or TRAX.\textsuperscript{23,24} One way to follow up
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Figure 1. Delayed bone formation in translin-deficient (Tsn<sup>–/–</sup>) mice. (A) Delayed endochondral ossification in tibias of young Tsn<sup>–/–</sup> (TSN KO) compared with Tsn<sup>+/+</sup> mice (WT). Longitudinal sections of bone were stained with hematoxylin and eosin (H&E). The lower panels show higher magnification views of the images above. (B) Abnormally thin epiphyseal plates and reduced venous capillaries in femurs of young Tsn<sup>–/–</sup> mice. Histology of a femoral epiphyseal plate in 10 days old Tsn<sup>–/–</sup> (TSN KO) compared with Tsn<sup>+/+</sup> mice (WT). The gray arrows at both ends indicate an epiphyseal plate and the yellow arrowhead indicates venous capillaries.

these observations would be to ask whether translin expression ceases with cell cycle arrest after exposure to ionizing irradiation. Ataxia telangiectasia (AT) is a recessive human genetic disorder resulting from mutations of the gene Atm, characterized by hypersensitivity to ionizing radiation. Therefore, Atm-deficient mice can provide a good model to study the role of target proteins in cell cycle control. Translin levels in spleen cells of wild mice were significantly downregulated after exposure to a 5 Gy dose of ionizing radiation, whereas those in Atm-deficient mice did not change at all. Thus, translin expression appears to be associated with cell cycle checkpoint defects in AT cells. Consistent with this conclusion, the level of translin was found to be periodic during the cell cycle, with a rise starting in S phase becoming maximal during the G2/M phase. This tight link between translin expression and cell division is in line with translin participation in DNA synthesis. Indeed, stable transfectants expressing inducible translin under the control of a tetracycline-responsive promoter incorporated bromodeoxyuridine more efficiently as compared with doxycycline-untreated control cells. All of these
results suggest that translin participates in processes ensuring the replication of DNA as well as rapid cell division.

**Roles of translin and TRAX in DNA damage responses**

Several lines of evidence indicate that translin and TRAX play roles in DNA damage responses. Erdemir et al. reported DNA damage-dependent interaction of TRAX with the nuclear matrix protein C1D, an activator of the DNA-dependent protein kinase, which is essential for repair of DNA double-strand breaks and V(D)J recombination. Interestingly, the interaction of these two proteins only occurred following γ-ray irradiation and prevented the association of TRAX with translin. These observations suggest a possible involvement of translin and TRAX in DNA double-strand break repair.

Another line of evidence for the role of translin or TRAX in DNA damage responses was provided by examining hematopoietic colony formation in Tsn−/− mice after sublethal ionizing irradiation. Histological features of extramedullary hematopoiesis showed delayed colony formation in the spleens of Tsn−/− compared with Tsn+/+ mice. Considering that the stability of TRAX is thought to be maintained by translin, these findings suggest that a lack of translin/TRAX is linked with loss of DNA damage responses. This was further supported by the recent finding that downregulation of TRAX resulted in failure of ATM activation upon DNA damage. A recent report indicated that translin and TRAX differentially regulate the level of long noncoding telomeric repeat-containing RNA, however, this did not correlate to the telomere DNA damage response. Given that DNA damage enhances chromatin dynamics through nucleosome degradation and promotes efficient repair, the functional roles of translin and TRAX deserve further exploration.

**Requirement of translin/TRAX for miRNA depletion in Dicer deficiency**

In the last decade, increasing attention has been focused on the contributions of translin/TRAX complexes to RNA metabolism. Notably, an asymmetric octameric assembly of translin/TRAX subunits, consisting of two homomeric translin dimers and two heteromeric translin/TRAX dimers, was shown to be a key activator of RISC by degrading Argonaute 2–nicked passenger strands. These findings collectively suggest that an asymmetric spatial arrangement of translin/TRAX subunits is critical for the endonuclease activity that cleaves RNA at the interior surface. Conserved translin/TRAX complexes were also found to influence tRNA processing in Neurospora, suggesting their multifaceted biological properties. miRNAs are short, single-stranded noncoding RNAs that play key roles in the regulation of gene expression. Mature miRNAs of approximately 22 nucleotides are processed from pre-miRNAs by the RNase III enzyme Dicer. Accumulating evidence suggests that a global downregulation of miRNAs is a common feature of human and murine cancer cells. Furthermore, impaired miRNA processing enhances cellular transformation and tumorigenesis, suggesting that the global loss of miRNAs is due to loss of function of miRNA processing machinery. A recent study, however, suggested the existence of a negative regulator of miRNA biogenesis. Furthermore, biochemical fractionation identified the translin/TRAX ribonuclease complex as a pre-miRNA degrading enzyme that competes with pre-miRNA processing, indicating that depletion of miRNAs in Dicer deficiency is due to both loss of miRNA processing ability and the pre-miRNA degradation function of the translin/TRAX complex. Although these results leave open the possibility that the latter could be a drug target for restoring miRNA in cancers that are haploinsufficient for Dicer, further elucidation of translin and TRAX functions under normal conditions will be required before any clinical trials can be initiated.

**Association between translin monomers and the transcriptional repressor RP58**

As described above, protein–protein interaction analysis for functional characterization of translin identified an associated 33 kDa protein partner, TRAX (Fig. 2A). To avoid self-association of translin to form an octameric structure, DNA encoding its domain lacking the leucine zipper motif was cloned into a yeast GAL4 DNA binding domain vector and used as bait to screen a human spleen cDNA library in a two-hybrid interaction analysis. Unlike the TRAX case, this analysis identified one clone whose product gave the strongest activation only with the translin bait lacking the leucine zipper motif (Fig. 2B). The protein encoded...
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Figure 2. Schematic representation of human translin and associated proteins. (A) Comparison of human translin and TRAX proteins. The human translin gene encodes a protein of 228 amino acids with a predicted molecular weight of 27 kDa. Native translin demonstrates an octameric barrel structure with an approximate molecular weight of 220 kDa. Translin has a heptad repeat of hydrophobic amino acids referred to as the leucine zipper at the COOH terminal (amino acids 177–212), which is involved in formation of the native form. TRAX was identified in two-hybrid analysis as a protein that interacts with full-length translin. The human TRAX gene encodes a protein of 290 amino acids with a predicted molecular weight of 33 kDa. TRAX possesses nuclear localization signals in its N-terminal region and shows extensive amino acid homology with translin (38% identity of the C-terminal amino acid residues). (B) Translin lacking the leucine zipper motif and transcriptional repressor RP58. RP58 was identified in two-hybrid analysis as a protein that interacts with translin lacking the leucine zipper motif (amino acids 1–189). The human RP58 gene encodes a protein of 522 amino acids with a predicted molecular weight of 58 kDa, featuring a BTB/POZ domain in its amino-terminal region and Kruppel-type zinc finger motifs in the carboxyl-terminal region.

by this clone, named RP58, was shown to repress transcription from a promoter linked to its target sequence, (A/C)ACATCTG(G/T)(A/C) containing the E box motif. Immunogold electron microscopy revealed that RP58 is localized in condensed chromatin regions, suggesting a role for sequence-specific transcriptional repression in heterochromatin.

Gene inactivation by a knockout approach has demonstrated that RP58 plays a crucial role in neuronal proliferation, migration, and differentiation in the developing cerebral cortex, as well as regulation of embryonic myogenesis. Further analyses showed that Id (inhibitor of differentiation) genes are direct targets of RP58. Protein structure analysis revealed that RP58 contains an extensively conserved region at the amino terminus, termed the BTB/POZ domain, and Kruppel-type zinc finger motifs in the carboxyl-terminal region. The BTB/POZ domain from many zinc finger proteins, including BCL-6, PLZF, and ThPOK, has been shown to regulate gene expression through modification of nucleosome structure. Therefore, RP58 may influence the multifaceted activities of translin and TRAX proteins. Although it seems likely that the interaction occurs during processing of the multimeric translin structure, definitive conclusions regarding any role of RP58 can only be drawn when...
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the transient protein–protein interactions of these molecules are proven in vivo.

Conclusions

A wide variety of functions for translin/TRAX proteins have been identified at the molecular and cellular levels. However, it should be emphasized that the same protein in different species may be functionally altered during the long evolutionary process. This review highlights the molecular and cellular functions of translin, translin/TRAX, and associated proteins, focusing on vertebrates (Fig. 3). There is a good deal of support for translin participation in processes ensuring the replication of DNA, as well as cell division. Several lines of evidence also indicate roles of translin/TRAX in DNA damage responses. Of particular interest is the fact that Tsn−/− mice display delayed endochondral ossification for several weeks after birth. Furthermore, as aging proceeds, progressive bone marrow failure together with ectopic osteogenesis and adipogenesis were observed, suggesting that translin is involved in mesenchymal cell differentiation. Although information is accumulating regarding roles of translin/TRAX complexes in RNA metabolism, we are only beginning to understand the biology of translin, TRAX, and associated proteins with reference to chromosome dynamics that influence DNA replication and repair, as well as cell division. For the development of clinical trials, future studies should focus on physiological settings impacting on the multifaceted roles of translin homo-octamer and translin/TRAX hetero-octamer in the healthy and disease states.

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Competing interests

The authors declare no competing interests.

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