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T-cell intracellular antigens in health and disease

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T-cell intracellular antigen 1 (TIA1) and TIA1-related/like protein (TIAR/TIAL1) are 2 proteins discovered in 1991 as components of cytotoxic T lymphocyte granules. They act in the nucleus as regulators of transcription and pre-mRNA splicing. In the cytoplasm, TIA1 and TIAR regulate and/or modulate the location, stability and/or translation of mRNAs. As knowledge of the different genes regulated by these proteins and the cellular/biological programs in which they are involved increases, it is evident that these antigens are key players in human physiology and pathology. This review will discuss the latest developments in the field, with physiopathological relevance, that point to novel roles for these regulators in the molecular and cell biology of higher eukaryotes.

From Gene to Protein

TIA1 and TIAR possess a modular design characteristic of the classical view of RNA-binding protein (RBP) architecture.[1,2] This structure consists of 3 RNA recognition motifs (RRM) of around 100 amino acids each, and a domain that is rich in glutamine and asparagine, of around 90 amino acids located at the C-terminal region (Q-rich domain). Two short peptide domains formed by an amino acid hexamer and octamer, named RNP2 and RNP1, respectively, are conserved in the RRM regions[1,2] (**Fig. 1**).

The human TIA1 gene is located in the chromosomal region 2p13 and contains 13 exons. Exons 1–4, 5–8 and 9–11 encode the RRM1, 2 and 3 domains, respectively. Exons 12 and 13 encode the Q-rich domain (**Fig. 1A**). The human TIAR gene locates in the chromosomal region 10q and consists of 12 exons. Exons 1–4, 5–7 and 8–10 encode the RRM1, 2 and 3 domains, respectively. Exons 11 and 12 encode the carboxyl-terminal 'helper' domain (**Fig. 1B**).[3] Two isoforms of both TIA1 and TIAR exist, generated by the alternative splicing of the pre-mRNAs. The TIA1a isoform (43 kDa) differs from isoform TIA1b (40 kDa) by inclusion of an 11 amino acid residue sequence at the beginning of the RRM2 motif, encoded by exon 5 (**Fig. 1A**).[1,2] Also, isoform TIARa (50 kDa) differs from isoform TIARb (42 kDa) in that it contains a sequence of 17 amino acids between the RNP2 and RNP1 motifs in RRM1, encoded by the last 51 nucleotides of exon 3 (**Fig. 1B**).[3,4] Particular residues contained in isoforms TIA1a and TIARa determine the specificity of their binding to RNA and/or the interaction with other proteins, which expands their regulatory capacity.[6] In mice, the TIA1 and TIAR genes are located in the chromosome regions 6D2 and 7F4, respectively. The exon-intron organization is conserved between the murine and human genes, and there is also a high degree of identity between the primary amino acid sequences.[4,7]

TIA1 and TIAR share 80% identity in their amino acid sequence.[2,4] The presence of structural and functional orthologs in different eukaryotic taxonomic groups highlights the biological importance of these proteins in cells, given that they are highly conserved since the first ancestors.[8] In fact, the RRM2 domain is highly conserved in all of the reported structural and/or functional orthologs and is the major domain responsible for protein-RNA/DNA binding, which implies a high degree of functional conservation in the mechanism of action of these proteins.[9-14] The RRM is a very well characterized domain and a significant amount of structural information exists. Indeed, the structural topology and functional contribution of each of the 3 RRM domains in both TIA1 and TIAR proteins has been the subject of investigations by several laboratories.[9-14] Consequently, a detailed text summarizing all important aspects has been recently published by Wilce and coworkers.[15] However, no high resolution structure of TIA protein RRM domain in complex with oligonucleotide has yet been reported. Until such data is available, the precise structural basis for the RNA binding specificity of TIA proteins will remain elusive.[15]

Regulators and/or Modulators of Gene Expression

Gene expression in eukaryotic cells is a vectorial process that encompasses DNA-dependent transcription and post-transcriptional processes such as pre-mRNA processing/splicing, transport, location, stability and/or translation of mature mRNAs. Transcriptional and post-transcriptional regulatory mechanisms occur to orchestrate cellular programs and decisions *via* modulating the function, half-life and fate of the RNAs and/or proteins inside the cell in a developmental, spatio-temporal and/or environmental-dependent manner. For example, a comprehensive study on the transcriptome of HeLa cells using microarray approaches, where expression of TIA1, TIAR, or both was transiently knocked down, permitted the identification of a large number of mRNAs associated with the processes of inflammation, cellular signaling, immune response, angiogenesis,

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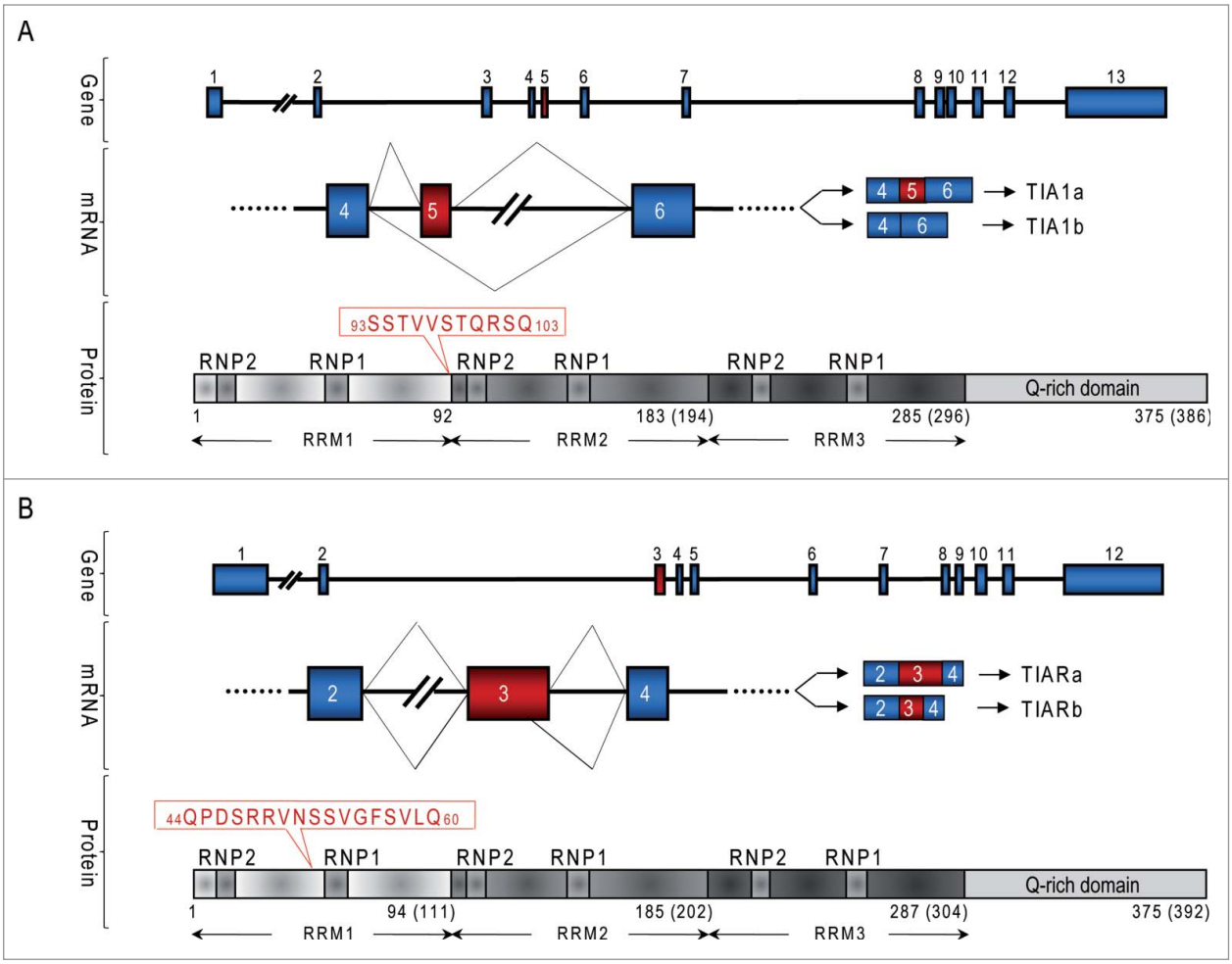

Figure 1. Diagrams of genes and proteins of TIA1 and TIAR in human and mouse. (**A** and **B**) Organization of exons and introns of TIA1 and TIAR genes, the major isoforms a and b generated by alternative pre-mRNA splicing, and functional domains of TIA1 (**A**) and TIAR (**B**) proteins. Both proteins contain 3 RNA-recognition motives (RRM) and an auxiliary domain in rich-asparagine and glutamine residues (Q-rich domain). The different amino acid sequences between the isoforms are shown in red for TIA1 and TIAR proteins, respectively.

apoptosis, metabolism and cell proliferation.[16] Similar results have been obtained recently in the study of the transcriptome of neural tissues –spinal cord and cerebellum- from an adult mouse lacking TIA1.[17] Thus, given their interaction properties with DNA, RNA and other proteins in the cell, TIA proteins, participate in the regulation and/or modulation of many of these processes and networks, *via* impacting prevalently the pleiotropic roles of specific RNAs and proteins in cell physiology, defining their fates into ribonucleoprotein complexes such as speckles, paraspeckles, messenger ribonucleo/cytoplasmic RNA-protein complexes, processing bodies and/or stress granules (**Fig. 2**).[9-15]

Transcription

The first evidence for the involvement of TIA proteins in transcriptional regulation came from the functional capacity of TIA proteins to bind DNA and the carboxyl-terminal domain of RNA polymerase II.[18-21] In the case of TIA1, it has been shown that RRM1 binds to T-rich ssDNA.[19] Further, RRM1 and RRM2 of TIAR are able to interact with DNA with micromolar affinity[21] and T-rich DNA,[11,21] respectively. Thus, this represents an unusual case of an RRM preferentially binding DNA over RNA.[15] These interactions suggest a putative co-regulation of the transcription and splicing of pre-mRNAs in the cellular nucleus during early biogenesis of RNAs.[15] This process might be facilitating a slowdown in the speed of RNA polymerase II and the coupling of the transcription and the final 3′ processing (**Fig. 2**).[18-22] Some genes, such as *Procollagen, type II* (COL2A1),[20] *Insulin-like growth factor binding protein-3* (IGFBP-3)[23] and *Pituitary adenylate cyclase-activating polypeptide* (PACAP)[24] could be preferentially regulated by this TIA-dependent pathway.

Pre-mRNA splicing

The first 2 identified events of TIA protein-dependent splicing involved the pre-mRNAs of *Fibroblast growth factor receptor 2* (FGFR2)[25] and *Fas cell death surface death receptor* (FAS/CD95/APO-1)[26]. In both cases, TIA proteins facilitated the recognition between weak 5′ splice-acceptor sites and degenerate sequences

for the hybridization of the RNA complementary to U1 snRNP.[25-27] In this process, the recognition motif RRM2 in the TIA protein, facilitated by RRM3, attaches to the uridine-rich regions proximal to the intron's 5′ splice site, and the Q-rich domain binds to the N-terminal region of the subunit U1-C in U1 snRNP through a process facilitated by RRM1.[11,15,27-29] There are also some studies that point to the participation of TIA proteins in the recruitment of U6 snRNP.[30,31] The cellular relevance of TIA proteins in the regulation of constitutive and alternative splicing was confirmed by mapping the binding of these regulators to RNA using an experimental approach in HeLa cells consisting of *in vivo* irradiation of the cells with UV light and subsequent immunoprecipitation of the RNA-protein complexes.[32] These approaches demonstrated that TIA1 and TIAR preferentially bind to sequences rich in uridine and adenosine pentamers, UUUUA or AUUUU, proximal to the 5′ splice-acceptor sites in the introns, to facilitate the recruitment of U1 snRNP and the inclusion of the adjacent exon, enabling also the selection of distant 3′ splice-acceptor sites. Thus, they facilitate splicing of pre-mRNAs via improving the selection of constitutive and atypical 5′ splice sites through shortening the time available for definition of an exon by enhancing recognition of the 5′ splice sites.[32] From these studies, it has been estimated that TIA proteins regulate 10% of the constitutive and alternative splicing events in the human genome, whereas ~20% was initially estimated by an *in silico* approach.[33]

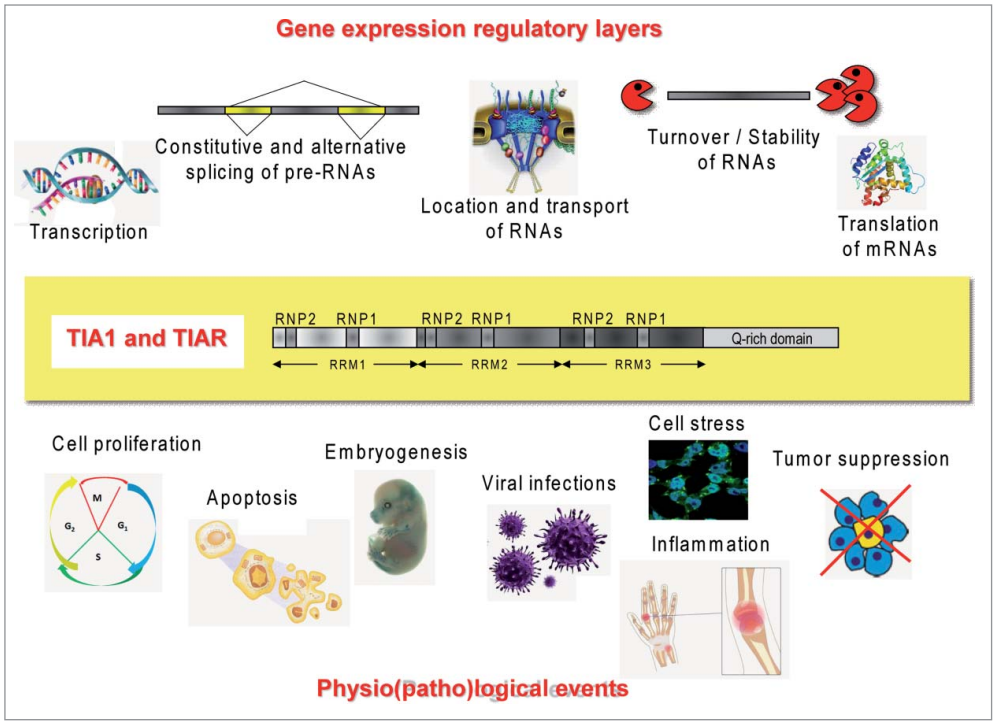

Figure 2. The multifunctional regulatory roles of TIA proteins in the gene expression layers and physio(patho) logical-associated events.

Translation of mRNAs

TIA antigens have the ability to regulate and/or modulate the process of cellular translation by limiting the availability of the ribosomal machinery and also the translational efficiency of specific cellular mRNAs, either in stress conditions, to guarantee cell viability, or in conditions of cellular homeostasis (**Fig. 2**). Under conditions of stress, the α subunit of the translation initiation factor *Eukaryotic translation initiation factor 2* (eIF2) is phosphorylated, principally at serine 51, by a family of kinases that includes *Eukaryotic translation initiation factor 2-α kinase 1* (HRI), *Eukaryotic translation initiation factor 2-α kinase 2* (PKR), *Eukaryotic translation initiation factor 2-α kinase 3* (PERK) and *Eukaryotic translation initiation factor 2-α kinase 4* (GCN2), depending of the types of stresses and cellular lines involved.[34-42] This phosphorylation abolishes the ability of eIF2B to exchange GDP for GTP, which results in a decrease in the levels of eIF2-GTP-tRNAMet ternary complex. In turn, this leads to incorrect formation of the translation pre-initiation complexes. It is at this moment when TIA1 and TIAR play a role, associating with the complex formed by several canonical translational initiation factors such as, eIF4E, eIF4G, eIF4A, eIF4B and eIF3 together with the small ribosomal subunit, in an anomalous 48S complex lacking eIF2 and eIF5.[34,35] These inactive translation pre-initiation complexes associated with mRNAs accumulate in the cytoplasm and, due to the aggregation properties of the Q domain of TIA and *Poly (A+) binding protein* (PABP) proteins, bind among themselves (self-aggregate), creating large foci of mRNA and protein known as stress granules (SG).[36-37] SG formation favors cell survival in stress conditions, such as starvation or limitations in amino acid availability, oxidative or osmotic stress, etc., as well as pathophysiological situations, as for instance viral infection[37] and Alzheimer disease.[38] In these adverse conditions, the cell enters a cellular biology resting state, inhibiting translation in general and allowing energy to be saved for repair of the damage caused by the stressful insult.[39-42] Although the appearance of SG is that of stable and poorly-dynamics inactive structures, their size is variable and the majority of their components are in a constant exchange or a dynamic flux of assembly/disassembly.[35-43] They appear approximately 15 minutes after the onset of the stressing stimulus and their formation is reversible, disappearing a few hours -between 2 to 6- after the stimulus ends depending on cell type, provided that the stimulus is not lethal.[34,35,41-46] It is important to note that controversy exists regarding the process of SG formation mediated by TIA1 and/or TIAR. Indeed, some studies suggest that TIAR cannot form SG

without the aid of TIA1.[45] However, other results show that only one of the 2 proteins is sufficient for SG formation.[47] In addition, recent studies suggest that perhaps the role of these proteins/antigens, including TIA proteins, would not be to facilitate SG formation, but rather the disintegration of these transient structures.[48] Further, it has been described that TIA1 and other proteins containing Q-rich domains can form porous hydrogel-nature structures,[49] which suggest a model of SG organization whereby SG-proteins and RNA are able to diffuse in and become associated with the hydrogel matrix.[15] Given these controversies, we are facing a very interesting challenge with significant implications for cell biology, which requires new experimental approaches to be fully understood. A comprehensive analysis of these possibilities awaits further study.

Immunoprecipitation studies on RNA-protein complexes and identification of immunoprecipitated mRNAs using microarray analysis have permitted the identification of approximately 2 hundred mRNAs associated with TIA1 and/or TIAR.[44,47,50] These studies revealed the binding of TIA proteins to motifs rich in uridine, adenosine and cytidine in the 5′ and/or 3′-UTRs of several cellular mRNAs. Also, the participation of TIA proteins in the translational regulation of different mRNAs, such as *Tumor necrosis factor* α (TNFα),[51] pro-inflammatory cytokines,[52,53] *Cyclooxygenase-2* (COX-2),[54] mitochondrial cytochrome *c*,[55] C-MYC oncogene,[56] *Hypoxia inducible factor 1*, α *subuni*t (HIF-1α),[57] β-actin subunit,[58] some isotype of tubulin,[59] some mRNAs implicated in the cell-cycle G2/M transition and DNA repair[60] as well as tumor suppressors *Breast cancer 1* (BRCA1)[61] and Programmed cell death 4 (PDCD4),[62] have been suggested.

mRNA stability

mRNA turnover is the process by which an mRNA is degraded before or after translation. This can occur at the 5′ or the 3′ end of the mRNA. Degradation from the 5′ end requires the activity of *Dipeptidyl carboxypeptidase* 1 (DCP1) and *Dipeptidyl carboxypeptidase* 2 (DCP2) enzymes, which promote the removal of 7-methyl-guanosine (5′ decapping), and the activity of *5′-3′ exoribonuclease 1* (XRN1) exonuclease.[63] Degradation from the 3′ end is mediated by the exosome and is produced by the shortening or deadenylation of the poly(A+) tail of the mRNA and the subsequent recruitment of exonucleases.[64] The mRNA regions implicated in this process are sequences rich in adenosine and uridine (ARE sequences) situated in the 3′-UTR, which favor the binding of proteins such as TIA, *AU-rich element (ARE) RNA-binding protein 1* (AUF1), *KH-type splicing regulatory protein* (KSRP) and *Tristetrapolin* (TTP) and, consequently, the recruitment of proteins associated with the degradation process. Binding of TIA proteins to these regions facilitates the deadenylation of the mRNA and also stimulates cap removal at the 5′ end. In contrast, proteins such as HuR stabilize mRNA, likely due to its inability to recruit exosomes.[65,66]

microRNAs

A further means to regulate mRNA translation and stability is through binding to micro(mi)RNAs, which leads to their translational repression and/or degradation. miRNAs are small RNA fragments, 19–24 nucleotides in length, that regulate gene expression through base-pairing with complementary sequences, usually in the 3′-UTR regions of mRNAs. The interaction of miRNA with mRNA leads to the recruitment of the *RNA-induced silencing complex* (RISC) and, subsequently, to mRNA degradation. Several studies suggest that around 20–30% of gene expression is regulated by miRNAs.[67] A high-throughput study using microarray analysis revealed an overexpression of 29 miRNAs after transient silencing of TIA1 and TIAR protein expression by RNA interference in HeLa cells. This result was interpreted as a response to counteract the differential expression and phenotypes associated with the short-term reduction of TIA proteins.[68] Another study showed that miRNA-579 and miRNA-125b interact with TIAR in the 3′-UTR of TNFα mRNA, leading to its degradation and a decrease in its translation.[69] Also, in cellular microvesicles that abundantly express TIA1 and TIAR, which constitutes a mechanism for cell communication in stem cells, 365 miRNAs have been identified whose target mRNAs are related to organ development, survival and differentiation, and also with the regulation of immune responses.[70] These observations suggest that TIA proteins are able to regulate/modulate miRNA expression by still unknown mechanisms. Finally, it is important to note that miRNA-15a and miRNA-16–1 have been identified as silencers of TIA1 and TIAR expression,[71,72] and adenovirus VA RNA-derived miRNAI-138 targets TIA1.[73] These findings indicate that the regulator/modulator can be also regulated/modulated and suggest the existence of autoregulatory loops that could serve to amplify/inhibit complex cellular responses.

TIA1 and TIAR: Biological Processes, Embryonic Development and Physiopathology

The multifunctional capacity of TIA proteins to regulate/modulate gene expression points to a relevant role for these regulators/modulators in cellular homeostasis, and also in the regulation of several biological and physiopathological processes (**Fig. 3**).

Cell death: apoptosis and autophagy

The first experimental evidence for the participation of these proteins in the regulation of the cell death program came from the observation that incubation of (permeabilized) cellular targets of cytotoxic T lymphocytes with TIA1 and TIAR proteins triggered nuclear DNA fragmentation (**Fig. 3**).[1,2] Later, it was demonstrated that TIA proteins regulate the gene expression of several components of the cell death pathways.[16,17,24-74-76] However, there are other routes through which TIA proteins could modulate cell death, for example by scavenging of *Ribosomal protein S6 kinase, 90 kDa, polypeptide 3* (RSK2) in the SG, facilitating cell survival,[77] or activating/repressing the synthesis of other proteins involved in the processes of cellular death/survival.[16,17] Recently, we have reported that an increased expression of TIA1 or TIAR in HEK293 cells results in diminished rates of cell

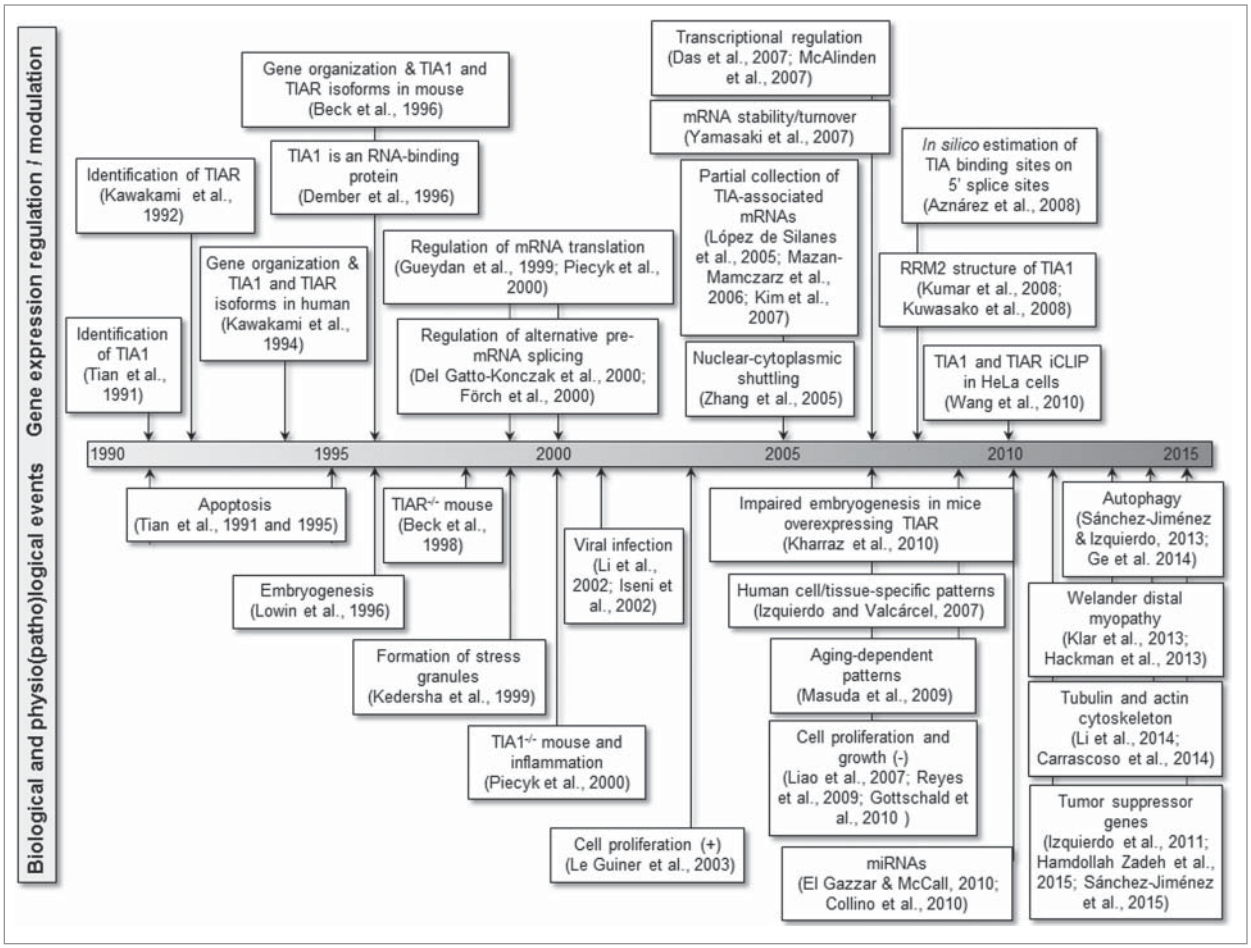

Figure 3. Scientific milestones related to the biological processes regulated/modulated by TIA proteins.

proliferation and growth. This is accompanied by cell-cycle arrest at G1/S and cell death through caspase-dependent apoptosis and autophagy. Genome-wide profiling analysis suggest a specific upregulation of p53 signaling pathway-related genes.[78] In the same vein, a role for TIA1 in autophagy via interaction with annexin A7 has been described in vascular endothelial cells.[79-81]

Cell proliferation

TIA1 and TIAR proteins modulate cell proliferation by favoring or inhibiting cell growth. For example, it has been described that decreasing the expression of TIA proteins in the chicken cell line DT40 -lymphoma- promotes a decline in their growth relative to control cells (**Fig. 3**).[82] However, in human tumor cell lines, such as HeLa cells, short- or long-term reduction in TIA1 or TIAR expression, or both, leads to an increase in cell proliferation associated with a tumorigenic phenotype.[16,17,83-85] This behavior has also been reported in other human cell lines including K562 (myeloma),[56] HCT116 (colorectal carcinoma),[83] HEK293 (adenotransformed embryonic kidney cells),[78] A549 (lung adenocarcinoma)[57] and LS174t colon cancer cells.[86] The roles of TIA proteins associated with the cell proliferation could be prevalently linked to the coordinated control of global and specific translational rates.[47,53-62,78,85] Taken together, these observations are possibly consistent with the relevance of the genetic background for the expression of the TIA proteins, which determines their functionality in an environmental-dependent way.

Embryonic development

The importance of TIA proteins during embryogenesis was addressed in vivo by studying genetically-modified mice deficient in TIA1 and/or TIAR (**Fig. 3**).[51,87,88] Homozygous mice lacking TIA1 and TIAR died before embryonic day 7 (E7). Experiments performed in several mouse strains revealed that, in the absence of TIA1, 46% of the mice died between E16.5 and 3 weeks after birth. The surviving mice did not show any apparent abnormalities until the end of their lifespan (2 years), which was characterized by a phenotype associated with arthritis[51] and a higher sensitivity to dust produced by an exacerbated allergic reaction accompanied by pulmonary inflammation and an increase in Th2/Th17 cytokines in the lymph nodes.[89] However, mice lacking TIAR presented different phenotypes that were dependent on the mouse strain studied.[88] Thus, in BALB/c mice, the absence of TIAR expression was embryonic lethal in 100% of offspring, whereas in C57BL/6 mice, the lack of TIAR led to death in 90% of the embryos. Intercrosses of BALB/c TIAR+/− with

C57BL/6 TIAR+/− resulted in 60% embryonic lethality. Of the remaining mice, half of them survived until adulthood, although they were sterile –mice showed abnormalities in the spermatogenesis and oogenesis processes, and also in the gonad architecture-, obese –despite being born with less body mass- and with neurological disorders –abnormal behavior-. These mice also develop cervical tumors.[88] Further, an essential role for TIAR has been described in self-renewal and/or differentiation of mouse embryonic stem cells.[90] Additionally, in a transgenic mouse model overexpressing TIAR, 77% of the embryos showed abnormalities at day E7.5.[91] This myriad of phenotypes suggests that the equilibrium in the expression of TIA1 and/or TIAR proteins is important, spatially and temporally, for early mouse development.[51,88,90-92]

Physiopathological implications

The ability of TIA proteins to regulate/modulate gene expression confer on them an important functional role in human pathology given their participation in antiviral, inflammatory, immune, and possibly oncogenic and aging-associated responses, among others (**Fig. 3**).

Viral infections

Several studies suggest a relevant functional role of TIA proteins during viral infections. When viral infection occurs, PKR kinase is activated and phosphorylates eIF2α, inhibiting the translation of cellular and viral proteins by directing the mRNAs to SG, and increasing the expression of proteins involved in the innate immune response to guarantee cell viability.[34,35] This is the case in infections caused by *Vesicular stomatitis virus* (VSV)[93] or *Transmissible gastroenteritis coronavirus* (TGEV).[94] Evolution has resulted in many viruses developing mechanisms to evade this response in favor of their own survival.[95-97] Indeed, some viruses benefit from TIA proteins to favor their own biology, for example *West nile virus* (WNV) uses TIA proteins as transcription factors to synthesize its own RNA[98,99]; *Hepatitis C virus* (HCV) uses TIA proteins for the replication of the viral genome, assembly and delivery of viral particles[100]; and *Minute virus of mice* (MVM) and *Human papillomavirus* (HPV) use TIA proteins as splicing factors for the synthesis of their own proteins.[101,102] Nevertheless, TIA proteins can also act as potent antiviral agents independently of SG formation. Thus, TIA1 can directly bind to the PRE regulatory element in *Hepatitis B virus* (HBV) and inhibit its function.[103] It has been described that in the early stages of hepatitis C infection in chimpanzees, several gene expression changes take place including an increase in TIA1, which allows removal of the virus before chronic infection develops. This constitutes a primary response to eliminate infected hepatocytes.[104]

Inflammation and immune processes

Regarding the inflammatory processes, TIA1 and TIAR function as gene suppressors in arthritis.[105] Consequently, TIA-deficient mice develop arthritis.[51] It is important to note that infliximab –a potent anti-inflammatory drug- therapy increases the ratio of TIA1:HuR.[106] In fact, TIA proteins can regulate/modulate the expression of inflammatory proteins such as TNFα, IL-1, IL-6, MMP13 or COX-2.[5,16,51,52,54,107-109] For example, in women with endometriosis, TIA1 expression in eutopic and ectopic endometrium was reduced compared with TIA1 expression in eutopic endometrium of unaffected control women. Lipopolysaccharide and TNF-α increased TIA1 expression in human endometrial stromal cells (HESCs) in vitro, whereas IL-6 or steroid hormones had no effect. In primary cultured HESCs, down-regulation of TIA-1 resulted in elevated IL-6 and TNF-α expression, whereas TIA-1 overexpression resulted in decreased IL-6 and TNF-α expression. Thus, endometrial TIA1 is regulated throughout the menstrual cycle, TIA1 modulates the expression of immune factors in endometrial cells, and downregulation of TIA1 may contribute to the pathogenesis of endometriosis.[109]

Regarding cytotoxicity mediated by TIA proteins and, in particular, TIA1 as a component of cytotoxic T lymphocyte granules, there are several reports describing that apoptosis mediated by cytotoxic T-lymphocytes provokes the onset of a series of reactions that are uncomfortable for the patient such as, for example, organ transplant rejection,[110,111] food allergy,[112] Crohn's disease and ulcerative colitis,[113] aplastic anemia[114] or platelet inhibition.[115] However, an increase in cytotoxic T-lymphocytes is not always negative; it has been demonstrated that a higher percentage of infiltrated CD8+ T cells is associated with better prognosis in cancer patients, suggesting a role for CD8+ T lymphocytes in the anti-tumoral response.[116-120]

Tumor suppressor genes

The IntOGen-mutations platform (www.intogen.org/mutations) summarizes somatic mutations, genes and pathways involved in tumorigenesis.[121] Analysis of this database provides support to link human cancers with somatic mutations in TIA1 and/or TIAR/TIAL1 genes. Accordingly, mutated TIA1 has been found in corpus uteri, kidney, brain, lung, stomach, and breast tumors; while mutated TIAR/TIAL1 has been identified in oropharynx, stomach, liver, lung, breast, corpus uteri, ovary and brain tumors. These cancer mutations associated with TIA1 and TIAR proteins show a heterogeneous distribution across the primary structure of TIA proteins and they are preferentially located on RRMs domains, suggesting a loss-of-function of TIA proteins as DNA/RNA-binding proteins.[121] TIA proteins regulate, modulate and/or interact with a large number of mRNAs involved in cell proliferation control, apoptosis, angiogenesis, inflammation, invasiveness and metastasis capacity of tumor cells, and in immune evasion, which suggests a putative role for TIA proteins in preventing tumorigenic processes[16,17,25,31,42,51,55-58,60-62,85,86,116-123] (**Fig. 3**). Thus, TIA proteins can regulate the translation of the C-MYC oncogene[32,56] and tumor suppressor gene BRCA1,[61] the splicing of FGFR2,[25] FAS[26,27] or the tumor suppressor genes *Neurofibromatosis-1* (NF1)[31] and *Wilms' tumor suppressor* (WT1),[122] mRNA stability of tumor suppressor gene PDCD4[62] or *Growth arrest and DNA-damage-inducible protein 45*α (GADD45α),[124] as well as the expression of inflammatory or angiogenic factors, such as TNFα, COX-2, VEGF, IL-8 or HIF1α [16,51,52,54,57,86] and metastatic factors including MMP13.[5]

Accordingly, TIA1 and/or TIAR reduction in HeLa cells resulted in an increase in cell proliferation and both anchorage-dependent and independent growth, and also in greater cell migration capacity, facilitating the ability to generate xenotumors in immunocompromised mice. Moreover, studies of TIA1 and/or TIAR expression in a cohort of human epithelial tumors showed a significant reduction in these proteins, pointing to a putative role for TIA1 and/or TIAR as tumor suppressors.[57,85,86,123] Remarkably, nude mice injected with doxycycline-inducibe cells expressing TIA1 or TIAR delay, or even abolish, growth of xenotumors. Further, low expressions of TIA1 and TIAR correlate with poor prognosis in patients with lung squamous cell carcinoma.[78,123] Collectively, these findings strongly suggest that TIA proteins can act as tumor suppressor genes and cellular gatekeepers.

Welander distal myopathy

The distal myopathies comprise a group of inherited disorders with shared clinical expression involving mainly the functionality of the hands and feet of patients.[125,126] To date 20 different distal myopathies have been described and at least 14 of them have a genetic cause.[126] Welander Distal Myopathy (WDM; MIM #604454) was one of the first described with such a clinical pathology in the distal myopathies[127] group. It is a distal muscular dystrophy, autosomal, dominant and late. This disease manifests itself around 40–50 years.[126] A homozygous mutations is associated with a more severe phenotype.

The symptoms usually begin with weakness of the extender of the index fingers, leading to problems in precision movements, progressing to other fingers. This is usually accompanied by weakness in distal areas of the lower extremities, involving the *tibialis anterior* and the extensor muscles and feet that involve walking difficulties and leads to an equine gait. The pendulum foot movement is also found in patients with sclerosis amyotrophic lateral, multiple sclerosis and Parkinson disease. The disease is more common in the Middle East of Sweden, with a high incidence of 1/100 in local areas, as well as in areas of Finland.[129,130] The defect has been associated with a single mutation in WDM supported by a common haplotype in chromosome 2p13 in all the patients of Swedish and Finnish origin.[131,132] The haplotype was extended to more than 60 candidate genes, as well as the search for genomic rearrangements, which initially did not result in the identification of the causative mutation. In the first study where a mutation was associated was the genetic analysis of 43 patients of 35 families with clinical and histopathological findings compatible with WDM. In this study the WDM associated 2p13 chromosome haplotype was restricted, and within this region a heterozygote mutation in origin was identified (c.1362G > A; p.E384K) in the gene that encodes TIA1.[133] Independently, another study found in a fragment of <806 kb on chromosome 2p13 a single point mutation, G > A (p.E384K) affecting the same gene.[134] In the first study, the TIA1 mutation in WDM was associated with alterations in the alternative pre-mRNA splicing of SMN2[133] and in the second study with the dynamics of the formation of stress granules.[134]

The Emerging Picture

In this review, we have addressed how TIA proteins, together with their surrounding regulatory environment regulate/modulate gene expression in eukaryotic cells. We have dissected the multitude of molecular and biological events by which these regulators/modulators contribute to cell physio(patho)logy and discussed how this knowledge can be integrated into cellular decisions, which may represent some therapeutic opportunities. Thus, some progress has been made in studies on the regulatory and functional properties of TIA proteins. Recent technical advances will help to provide reference meta-analyses involving transcriptomes, translatomes, proteomes, ribosomal profiling and/or interactomes for cells, tissues, organisms and individuals, including qualitative and quantitative information about regulatory/modulatory events associated with TIA1 and TIAR proteins and other RNA-binding proteins in different biological situations or pathophysiological conditions. The detailed description of these regulatory phenomena and their cellular and molecular basis will provide important insights in our understanding of many biological processes and networks. For example, the mechanistic nature and molecular events by which components of the p53 pathway and DNA damage response induce cell-cycle arrest and/or cell death during TIA1 or TIAR expression await further exploration. Future studies will elucidate the regulatory characteristics that occur in loss- and gain-of-function models of TIA proteins in genotoxic stresses and under conditions of genomic instability. On the other hand, data from murine models and observations from cancer patients suggest that it may be advantageous for tumors to lose or down-regulate TIA expression, since this reduction could play a role in cancer progression by activating genes involved in neoplastic and malignant transformation, evading the immune system and enhancing the growth and survival of cancer cells. These observations suggest that TIA proteins could be good biomarkers of some cancer types. These proteins could be used to: (i) identify individuals at high risk for metastasis, (ii) differentially diagnose early-late cancer and (iii) assess the efficacy of therapy and chemopreventive agents. Thus, TIA biomarkers may have survival value. However, more studies, for example, cell/tissue specific-conditional TIA1 or TIAR expression, are required to draw firm conclusions about the tumor-suppressive functions of TIA proteins that might be context dependent. Future research should elucidate the specific environmental settings under which TIA proteins act as barrier, i.e. as cellular gatekeepers, to cancer development and/or progression. Indeed, a clearer understanding of the mechanisms controlling cell fate determination by TIA proteins may lead to the identification of novel molecular targets, which could selectively sensitize cancer cells to cell death.

Additionally, many exciting questions remain: How do TIA proteins function as epigenetic regulators/modulators, for example, transcription and/or splicing enhancers, translational repressors and/or stabilizer activators? What are TIA-associated epigenetic and/or post-translational modifications? Can TIA proteins be found that control biomedical relevant

regulatory events with sufficient specificity? Will mutated TIA proteins be sufficient to circumvent functional reprogramming linked to cellular transformation, Welander distal myopathy, or aging and other related diseases? What fraction of TIA1 and/or TIAR regulatory events and layers contributes to phenotypic differences relevant for conserved or prevalent changes between cells, tissues and/or species? We are still far from understanding the regulatory message associated with the TIA proteins, but their secrets and potential constantly invites us to try.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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