Gene Section

Review

EEF1A1 (eukaryotic translation elongation factor 1 alpha 1)

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Abstract

Review on EEF1A1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: CCS-3, CCS3, EF1A, EEF1A, EEF-1, GRAF-1EF, LENG7, PTI1
HGNC (Hugo): EEF1A1
Location: 6q13
Local order
Distal to LOC100129409, proximal to SLC17A5.

DNA/RNA

Description

8 exons, 7 introns (1\textsuperscript{st} intron within 5'UTR), plus a rare optional exon within first intron as found in several ESTs (e.g. emb-CR981691.1, dbj-DC388133.1, dbj-DC406334.1).
Presumably a second promoter, about 800 nt upstream of the most common transcription start, provides an alternative first exon about 320 nt long, as deduced from some ESTs at NCBI (e.g. dbj-DC316623.1, gb-BU173251.1, dbj-DC358918.1).
Introns number 2, 3, 4, 6 are phase 0 (between codons), introns number 5, 7 are phase 1 (between 1\textsuperscript{st} and 2\textsuperscript{nd} base of codon).
A validated C-G non-synonymous polymorphism has been reported at 1\textsuperscript{st} position of codon 382 (Arg-Gly), plus a few single-hit non-synonymous and some synonymous within CDS. Several others within 3'UTR and introns (SNP source).

Transcription

The main processed mRNA encompasses exons 1, 2, 3, 4, 5, 6, 7, 8, this last can be in short or long form. In a few cases also exon 1' is retained.
In a few cases exons 1 (and 1') are substituted by the alternative exon from a putative upstream minor promoter, as described above.
Moreover, a quite high number of processed transcripts that, after exons 1 and 2, retain intron 2, which introduces a stop codon 22 residues downstream of exon 2 are found (see for instance some of the many ESTs: dbj-DC389722.1, dbj-DC341899.1, dbj-DC414491.1).

Box = exon (blue = 5'UTR, yellow = CDS, light blue = rare optional exon, red = 3'UTR, light red = extended 3'UTR to a downstream polyA signal); line = intron.
**Pseudogene**
About 20 complete or approximately complete intronless pseudogenes, likely generated by retrotransposition, a few of them exempt from frameshifs and with only a few missenses, are present throughout the genome.
Two of them harbour a few hundreds nt long insert each, not related to introns of the expressed gene. All of them show a higher homology to EEF1A1 than to EEF1A2.
Most of the pseudogenes find an orthologous counterpart within the chimpanzee genome. EEF1AL3 (9q34) (highly homologous); EEF1AL4 (7p15.3) (highly homologous but with 1 frameshift); EEF1AL5-LOC390924 (19q13.12) (contains a 502 nt insert); EEF1AL6 (3q27.1); EEF1AL7 (4q24); EEF1AL8-LOC100132804 (7q35); EEF1AL9 (1p21.3); EEF1AL10-LOC644604 (2q12); EEF1AL11 (5p15.1) (rather highly homologous); EEF1AL12-LOC647167 (1q31.3); EEF1AL13-LOC100130211 (Xq21.2) (lacking about 300 initial codifying nt); LOC124199 (1p12.1) (contains a 307 nt insert); LOC387845 (12p12.3); LOC389223 (4q28.3); LOC401717 (12q12); LOC442709 (7q21.13) (harbours a 21 nt deletion); LOC645693 (15q21.2); LOC645715 (19q13.12); LOC646612 (3q22.3) (lacking about 120 initial codifying nt); LOC728672 (12p12.3); LOC100128082 (5p12).

**Expression**
EEF1A1 is constitutively expressed in all tissues, with the exception of adult brain, heart and skeletal muscle, where EEF1A2 expression is found.

**Localisation**
Mostly cytoplasmic, but also nuclear.

**Function**
Canonical function: aa-tRNA delivery to ribosome in mRNA translation
The eukaryotic elongation factor 1A (eEF1A1, formerly EF-1alpha or eEF1A) protein belongs to the G-protein superfamily, is one of most abundantly expressed protein in mammalian cells and participates to mRNA translation. It carries aminoacyl-tRNA (aa-tRNA) to the A site of the ribosome as a ternary complex eEF1A1-GTP-aa-tRNA. In mammalian, it is ubiquitously expressed with exception of skeletal muscle, heart and brain where during terminal differentiation eEF1A2 is produced (Knudsen et al., 1993).
Moonlighting functions: cytoskeletal remodelling, protein folding and degradation, cell signalling modulation, control of cell growth, apoptosis and cell cycle

1) eEF1A1 and cytoskeletal remodelling.
The most relevant non canonical function of eEF1A1 is the modulation of cytoskeleton organization. eEF1A has activity on microtubule severing and bundling. It has a specific site to bind actin that is different from that for the binding of aa-tRNA (Gross and Kinzy, 2005). eEF1A binding to F-actin is modulated by Rho/Rho-kinase pathway. Phosphorylation by Rho kinase decreases the binding of eEF1A1 to F-actin and F-actin bundling. Myosin phosphatase acts in antagonist fashion on eEF1A1 to modulate actin cytoskeletal organization (Izawa et al., 2000).

2) eEF1A1 and protein degradation and folding.
eEF1A controls translational fidelity by binding to incorrectly folded proteins but not to correctly folded ones. The incorrectly folded proteins are then directed to degradation pathway (Hotokezaka et al., 2002). eEF1A plays a role in recognition and degradation of co-translationally damaged and ubiquitylated proteins promoting their translocation.
to proteasome through interaction with proteasome subunit Rpt1 (Chuang and Madura, 2005). eEF1A exhibits chaperone-like activity by promoting renaturation of enzymes such as aminoacyl-tRNA synthetases, likely contributing to maintain the efficiency of translational machinery (Lukash et al., 2004). eEF1A1 takes part in the aggresome formation upon proteasome failure by activating heat shock response to degrade uncorrected folded proteins, to favor clearance of protein aggregates and to protect cell from proteotoxicity by favoring autophagy (Merin et al., 2012).

3) eEF1A1 and control of cell cycle, growth and death. eEF1A as ribonucleoprotein complex, containing a non-coding RNA, binds to and mediates activation of heat-shock transcription factor 1 (HSF1) to protect the cell from heat-shock (Shamovsky et al., 2006). Induction of the non-constitutive eEF1A1 expression in cardiomyocytes as response to lipotoxic ER-stress promotes cell death likely by activation of eEF1A1-dependent cytoskeletal modifications triggering apoptosis (Borradaile et al., 2006). eEF1A1 interacts with the HDM2 gene product at a binding site for eEF1A1 overlaps with that for p53. In normal cells eEF1A1 could promote cell apoptosis by preventing p53 sequestration by HDM2 (Frum et al., 2007). Likely both eEF1A1 and eEF1A2 interacts with the zinc finger protein ZPR1 in response to mitogenic stimuli, redistributing eEF1A1/2 and ZPR1 in the nucleus. This interaction is essential for normal cell proliferation and growth. Thus the interaction eEF1A1/2-ZPR1 is required for normal cell cycle progression (Mishra et al., 2007). eEF1A1 is an interactor of Bood POZ containing gene type 2 (BPOZ-2) that promotes eEF1A1 ubiquitylation and degradation via 26S proteasome. BPOZ-2 inhibits GTP binding to eEF1A1 thus preventing translation. BPOZ-2 is transcriptionally activated by phosphate and tensin homologue deleted on chromosome 10 (PTEN). It has been suggested that PTEN exerts growth inhibition effects in cells not only by antagonizing PI3K-Akt signalling pathway, but also inducing BPOZ-2 expression to degrade eEF1A1. In this manner, in normal cells, the transition from growing to resting phases is mediated by BPOZ-2/eEF1A1 interaction, thus leading to prevention of translation and induction of eEF1A1 degradation by 26S proteasome pathway (Koiwai et al., 2008). eEF1A1 is implicated in a novel cell cycle check-point to prevent tetraploidy in binucleated cells. In tetraploids, cell death, preventing aneuploidy malignancies, is mainly controlled in a caspase-independent manner by the down-regulation of eEF1A1 levels. eEF1A1 mRNA accumulates in specialized P bodies to reduce the expression of the proteins. The prominent signal in the eEF1A1 mRNA for its translational repression and degradation is in the 5'-UTR. Exogenous expression of eEF1A1 inhibits cell death in tetraploids. Notably, exogenous expression of eEF1A2 whose mRNA 5'-UTR differs from that of eEF1A1 inhibits cell death in tetraploids, thus suggesting another mechanism by which eEF1A2 could promote tumour development (Kobayashi and Yonehara, 2009).

Cell adhesion to the extracellular matrix is an essential biological event for cell survival and proliferation in multicellular organisms. Disruption of integrin-mediated cell adhesion leads to a specific type of apoptosis known as anoikis in most non-transformed cells. Recent evidences show eEF1A to act as a membrane receptor for the cryptic anti-adhesive site of fibronectin, which contributes to cell regulation, including anoikis, through negative modulation of cell anchorage. Possibly, the membrane-resident eEF1A may interact with beta1-integrins inactivating their functions in cell adhesion (Itagaki et al., 2012).

Down-regulation of eEF1A1 seems to be specific to senescence. Changes in eEF1A1 expression levels has been proposed also as promising marker for the detection of cellular cancer senescence induced by a variety of treatments, such as ionizing radiation (Byun et al., 2009).

4) eEF1A1 and cell signalling modulation. Besides eEF1A2, in adult mouse neurons eEF1A1 is expressed too and it is able to regulate the recycle of M4 muscarinic acetylcholine receptors (mACHR). Thus, eEF1A1 plays a role in locomotor activity of neurons (McClatchy et al., 2006). eEF1A1 modulates the activities of sphingosine kinases (SK1 and SK2). Phosphorylated and non-phosphorylated eEF1A1 forms interact with phosphorylated and non phosphorylated SK1 and SK2 and this results in an increased enzymatic activity of both SK1 and SK2. In this respect, overexpression of eEF1A1 in quiescent cells has been suggested to play a role in oncogenesis by increasing SK1 and SK2 activities (Leclercq et al., 2008). eEF1A1 is involved in the regulation of vascular function mediated by TNF-alpha. eEF1A1 binds to 3'-UTR of the endothelial nitric oxide synthase (eNOS) to regulate post-translational eNOS mRNA stability. In the human endothelial cell line HUVEC, TNF-alpha-mediated eNOS mRNA destabilization involves eEF1A1 to reduce eNOS mRNA levels (Yan et al., 2008). The different phosphorylation pattern between eEF1A1 and eEF1A2 especially at tyrosine levels has been suggested to determine structural differences of the two isoforms. In particular, eEF1A1 behaves a more extended structure with respect to the more compact one of eEF1A2 (Negrutskii et al., 2012). Phosphorylation of eEF1A1 on serine (S21) and threonine (T88) residues by Raf kinases regulates
In particular, TGFβ1 signaling regulates cell proliferation by acting on TβR-I that phosphorylates eEF1A1 at the Ser300 located in the domain for aa-tRNA binding. This impairs protein synthesis and leads to a lower proliferation rate of the cells. Worth of note that this effect is exerted directly on mRNA translation without transcriptional activation (Lin and Souchelnytskyi, 2011).

eEF1A1 is also a component of the ribonucleoprotein complex in the transcript-selective translational regulatory pathway mediated by the TGFβ-activated translational element (BAT). BAT is a 33-nt structural RNA element in the 3'-UTR of disabled-2 (Dab2) and interleukin like EMT inducer (ILEI). Dab2 and ILEI are two mRNAs mediating epithelial to mesenchymal transition. TGFβ-induced EMT is essential during embryonic development. In BAT element, eEF1A1 interacts with hnRNP E1 to inhibit translation, blocking the progression of the 80S ribosome by preventing eEF1A1 release from A site following hydrolysis of GTP. In this way the translation is inhibited by the stall at the eEF1A1-dependent elongation stage. Thus eEF1A1 and hnRNP E1 play a fundamental role in EMT by repressing specific gene expression (Hussey et al., 2011).

In U343 glioma cells eEF1A1 was found to be the target of heteroalkylketones, compounds that lower interleukin-6 (IL-6) activity in chronic inflammation. By this finding, eEF1A1 was shown to play a critical role in chronic inflammation sustaining IL-6 activity by forming a complex with STAT3 and PKCδ that promotes phosphorylation of STAT3 at serine 727. This in turn triggers NFκB/STAT3 interaction enhancing IL-6 expression (Schulz et al., 2014).

In neurons, both eEF1A1 and eEF1A2 isoforms have been found to bind to gephyrin protein, a scaffold protein which is thought to anchor GABAA-receptors to the cytoskeleton. Overexpression of both eEF1A proteins in cultured hippocampal neurons has been also associated with a significant increase in number, size and density of postsynaptic gephyrin clusters. Therefore, eEF1A proteins involvement in modulating receptor cluster formation and/or maintenance in neurons and in the morphology of postsynaptic membrane specializations at inhibitory synapses, is strongly emphasize (Becker et al., 2013).

Homology

Highly homologous over the entire length to:
- EEF1A2 (92% identities).

Moderately homologous over all three domains, higher for the first one, to:
- HBS1L, a member of the GTP-binding protein family expressed in erythroid progenitor cells (39% identities),
- GSPT1, a GTP-binding protein involved in G1 to S phase transition (38% identities),
- GSPT2, a GTP-binding protein involved in G1 to S phase transition (37% identities),
- TUFM, Tu translation elongation factor, mitochondrial (31% identities).

Implicated in

Head and neck cancers

Note
eEF1A1 overexpression is observed in cisplatin-resistant human head and neck cancer cell lines (Johnsson et al., 2000).

Breast cancer

Note
EEF1A1 was found to be up-regulated in invasive breast cancer cells derived from snap-frozen adenocarcinoma samples suggesting a role in mediating invasive activity of cancer cells (Zhu et al., 2003).

Treatment of the breast human cancer cell line MCF-7 with the histone deacetylase inhibitor sodium butyrate decreases significantly in a dose-dependent manner the eEF1A1 transcription levels. Thus, overexpression of eEF1A1 contributes to breast cancer survival (Gonçalves et al., 2005).

An analysis of human breast cancer cases revealed a decrease of eEF1A1 phosphorylation at Ser300 in malignant tumor cells as compared to epithelial cells in noncancerous tissues (Lin et al., 2010).

Tongue squamous cell carcinoma

Note
A suggestive down-regulation of EEF1A1 expression has been observed in human tongue squamous cell carcinoma with positive lymphonodes and extracapsular spread. Thus
EEF1A1 down-regulation might be involved in the tumour cell progression toward the metastasis (Zhou et al., 2006).

**Hepatocarcinoma**

**Note**
eEF1A1 overexpression in human hepatocarcinoma cell lines correlates with an increase of proliferation rate and with the ability to escape apoptosis under suboptimal growth conditions. In particular eEF1A1 overexpression is higher in the more aggressive phenotype cell line JHH6 with respect to the more differentiated HepG2 and HuH7 cells (Grassi et al., 2007).
eEF1A1 regulates the half-life of osteopontin (OPN) mRNA, eEF1A1 is a trans-acting factor that binds to 5'-UTR of OPN. This has strong implications in the invasive process as demonstrated in hepatocellular carcinoma cells, OPN being the major secreted phosphoprotein which is overexpressed by tumour cells in advanced metastatic cancer. The higher expression of OPN in invasive cancer cells is due to the different localization of eEF1A1: in non-invasive Hep3B cells it is mainly bound to G actin whereas in invasive HepG2 type eEF1A1 and G actin association is minimal. Thus eEF1A1 is an indirect regulator of OPN by affecting the OPN mRNA stability through the interaction with G actin. Only F actin-bound eEF1A1 cannot interact with 5'-UTR of OPN (Zhang et al., 2009).

Recently, it has been proposed a model in which eEF1A1 is a binder of the ubiquitin-like protein HLA-F adjacent transcript 10 (FAT10), a small ubiquitin-like modifier which functions include modulation of cytokine responses, apoptosis, mitosis, and tumorigenesis, to carry out, in part, functions in regulating tumorigenesis in human Hep3B hepatocellular carcinoma cell line. Thus eEF1A1 can play a role in this type of cancer by its mutual regulation with FAT10 (Yu et al., 2012).

Trichloroethylene (TCE) is a major pollutant found in many occupational and environmental sites. TCE exposure is known to promote cancerogenesis. In particular eEF1A1 overexpression is higher in human testis-specific Y-encoded (TSPY) gene. It has been demonstrated that the binding to TSPY complex in the cell with a nuclear co-localization. A role of the TSPY-eEF1A1/2 complex has been suggested in promoting neoplastic transformation and in sustaining cancer cell growth in human testicular germ tumours, prostate cancer, as well as in other somatic cancers (Kido and Lau, 2008).

**Testicular germ tumours**

**Note**
eEF1A1, as well as eEF1A2, is an interactor of the human testis-specific Y-encoded (TSPY) gene. It has been demonstrated that the binding to TSPY leads to a redistribution of the TSPY-eEF1A1/2 complex in the cell with a nuclear co-localization. A role of the TSPY-eEF1A1/2 complex has been suggested in promoting neoplastic transformation and in sustaining cancer cell growth in human testicular germ tumours, prostate cancer, as well as in other somatic cancers (Kido and Lau, 2008).

**Cervical cancer**

**Note**
A variant form of eEF1A1 named cervical cancer suppressor 3 (CCS-3) lacking the 101 aminoacids at the N-terminal region, has been identified as tumour suppressor that is present in non-transformed human cell lines. Its ectopic expression in a cervical tumour cell line leads to cell growth inhibition and apoptosis. CCS-3 seems to act as a co-transcriptional repressor by interacting with the transcriptional regulator PLZF (Rho et al., 2006). The mRNA of CCS-3 (GenBank Accession AF322220) appears to be a fusion product joining the reverse of the end portion of the 3’ UTR of another product (NM_005763, from gene AASS) with most of the normal sequence of EEF1A1 mRNA.

CCS-3 seems to enhance the transcriptional repression of the p21CIP1 gene (hereafter referred to as p21) by FBI-1, a member of the POK (POZ and Kruppel) family of transcription factors, playing a role in differentiation, oncogenesis, and adipogenesis. The POZ-domain of FBI-1 interacts with the co-repressors, SMRT and BCoR. It has been found that FBI-1 directly interacts with eEF1A and CCS-3 via the zinc finger and POZ-domain and that FBI-1 co-localizes with either eEF1A or CCS-3 at the nuclear periplasm. CCS-3 also interacts with the co-repressors independently. This evidence suggests that CCS-3 may be important in cell differentiation, tumorigenesis, and oncogenesis by interacting with the proto-oncogene FBI-1 and with transcriptional co-repressors (Choi et al., 2009).

**Prostate cancer**

**Note**
Overexpression of eEF1A proteins has been reported to have a role in prostate cancer (PCa) and may affect multiple processes involved in tumor progression. eEF1A1 is up-regulated in human prostate cancer as resulted by iTRAQ-based analysis of serum samples derived from patients.
with prostatic disease and by immunohistochemistry of prostate cancer tissues with localized metastasis. Bone metastases represent the major risk in patients with prostate cancer progression. eEF1A1 up-regulation seems to be linked to the osteoblastic nature of the metastasis and high levels of eEF1A1 in patients' sera could mark metastatic progression. At histological level, the median immunostaining intensity of eEF1A1 was significantly higher in osteoblasts in close proximity to metastatic tumour cells compared with osteoblasts in control bone (Rehman et al., 2012).

In vitro studies shown differential expression level of eEF1A1 in four PCa cell lines (22RV1, LNCaP, DU-145, and PC-3), suggesting a possible role of the protein in the pathogenesis of PCa. In DU-145, a high-grade metastatic PCA cell line, eEF1A1 plays an essential role in cellular properties associated with tumor progression, specifically in cell proliferation, invasion, and migration. In fact, eEF1A1 suppression inhibits DU-145 cell migration and invasion (Zhu et al., 2009).

Dissecting the role of eEF1A1 with respect to eEF1A2 in human cancer cell lines, the quote of eEF1A1 associated to the cytoskeleton is significantly up-regulated in cancer cells referring to the non-tumorigenic ones. However, eEF1A2 seems to better mark the prostate cancer onset and progression either in cell lines that or in human prostate tissue samples (Scaggiante et al., 2012).

**Prostate adenocarcinoma, colon adenocarcinoma, pancreatic cancer and gastric cancer**

**Note**

A variant form of eEF1A1 lacking 67 aminoacids at the N-terminal region has been proposed to promote cell transformation and to sustain tumour cells viability. It has been named prostate inducing gene-1 (PTI-1), also known as elongation factor 1A-like 14. Initially identified by differential RNA display screening of cDNA expression library in the human prostate cancer cell line LNCaP, it has been proposed to act as a dominant oncogene in human prostatic adenocarcinoma. Its mRNA contains a 5' UTR of 630 bp that is highly homologous to part of the 23S rRNA of Mycoplasma sp. fused to most of the CDS of EEF1A1, resulting in the substitution of its first 67 N-terminal residues with Met-Gln-Ser (Sun et al., 1997; Mansilla et al., 2005). Ectopically forced expression of PTI-1 in a mouse cell line induces tumours in nude mice and antisense PTI-1 molecule can reverse malignant phenotype of the transformed cells (Su et al., 1998). Silencing of PTI-1 by specific RNAi not affecting eEF1A1 expression, in a human prostate cancer cell line leads to a reduction of cellular growth, to the block of cell cycle in G1 phase and to the promotion of apoptosis (Yu et al., 2006). It has been hypothesized that PTI-1 could promote cell transformation by causing translational infidelity being in competition with eEF1A1 (Gopalkrishnan et al., 1999). PTI-1 mRNA is detected only in human cancer cells upon Mycoplasma infection. It remains under investigation whether PTI-1 can play a role in the natural history of human prostatic adenocarcinoma upon Mycoplasma infection. The origin of the chimeric transcript of PTI-1 remains to be ascertained (Scaggiante et al., 2008). PTI-1 mRNA has been detected in multidrug-resistance colon cancer cell line LoVoDX (Bertram et al., 1998). By using the detection of a unique PTI-1 region between the 5'UTR and the CDS, PTI-1 mRNA has been found in the human pancreatic cancer cell line AsPC-1, in the human gastric cancer TMK-1 cells, and in the hepatoma Alexander cells, but not in several other pancreatic, gastric and hepatoim human cancer cell lines. Interestingly, in AsPC-1 cells the down-regulation of K-ras mRNA by antisense leads to a reduction of PTI-1 level. PTI-1 mRNA was detected in three of five surgical human specimens of pancreatic cancer (Ohnami et al., 1999).

A study conducted with PTI-1 plasmid constructs either in vitro or in transfected NIH3T3 cells, revealed that the oncogenic potential of PTI-1 is related to a transcript product variant derived from the second AUG in frame codon (ORF 2). This transcript of this construct (PTI-1-FL-∆ATG) leads to a 39 kDa protein and the transfected cells gave multiple foci in growth assay. Interestingly cells expressing PTI-1-FL-∆ATG construct gave tumors when injected in NCr nude mice. The oncogenic potential of the 39 kDa PTI-1 protein resulted dependent on the nuclear localization of the protein in the cells which in turn was strictly related to the UTRs-containing transcripts (more likely the 5'UTR). It is speculated that the nuclear localization of PTI-1 is essential to exert its oncogenic potential, may be by interfering with the nuclear eEF1A1 functions modulating cellular proliferation (Dahl et al., 2014).

**Cutaneous T-cell lymphoma**

**Note**

In human sera derived from cutaneous T-cell lymphoma (CTCL) patients one of the new tumour antigens was a truncated version of eEF1A1 lacking 77 aminoacids at N-terminal.

**Leukemia**

**Note**

In the promyelocytic human leukemia cells the differentiation agent all-trans-retinoic acid (ATRA) induces down-regulation of eEF1A1 thus suggesting a role in contributing to cancer survival...
in haematopoietic malignancies (Harris et al., 2004).

An isoform of eEF1A1 with a more basic isoelectric point was identified in human haematopoietic cancer cell lines but not in normal lymphocytes raising the possibility that post-translation modifications of eEF1A1 could be involved in cancer development and progression of haematopoietic tumours (Dapas et al., 2003). The selective inhibition of eEF1A1 isoform by specific GT aptameric oligonucleotides, carried by the ethoxylated polyethylenimine, a weak basic polycation, has been demonstrated to exert specific cytotoxic effect and dose-dependent cell growth inhibition on lymphoblastic cancer cells (Scaggiante et al., 2005). Moreover the more basic isoform expression can be induced by phorbol ester in normal human lymphocytes and inhibited in T-lymphoblastic CCRF-CEM cancer cell line upon differentiation stimuli. Thus, this suggests a role of the more basic isoform in leukemia onset (Scaggiante et al., 2013). In human acute T lymphocytic leukemia Jurkat cell line, eEF1A1 expression sustained cell proliferation inhibiting apoptosis by up-regulating PI3K/Akt/mTOR signaling pathway (Huang et al., 2013). The ectopic expression of eEF1A1 inhibits p53 and p73-induced apoptosis. Interestingly, overexpression of eEF1A1, but not eEF1A2, inhibits chemotherapy-induced apoptosis in cancer cells. In cancer cells following chemotherapy, eEF1A1 negatively modulates p53 and p73 stability thus sustaining pro-survival activity. The silencing of eEF1A1 sensitizes the cancer cells to chemotherapics (Blanch et al., 2013).

**Skeletal muscle trauma and motor neuron degeneration**

**Note**
Several studies have indicated that muscle catabolism is associated with an increased expression and activity of critical components of proteolytic and apoptotic systems. In human tissues, eEF1A1 is ubiquitously expressed, with the exception of skeletal muscle, heart, and brain, where it progressively declines at the early phases of development. In adult muscle, eEF1A2 takes over the eEF1A1-specific function for protein synthesis. In aging rats, muscle eEF1A1 transcription increases, reverting the eEF1A1/eEF1A2 ratio. In contrast to the rat model, in humans, there is no increase of eEF1A1 messenger RNA (mRNA)/protein in the late phases of life. In hypercatabolic traumatized patients eEF1A1 mRNA level significantly rose in skeletal muscle as the result of injury. eEF1A1 expression correlated with overexpression of p66(ShcA) (Bosutti et al., 2007).

An overexpression of genes associated with the regeneration of axons, including eEF1A1, gamma-actin, PMP22, SPARC/osteonectin, CD9, and CD44 has been identified in nerve biopsies from a patient presenting an axonal form of Charcot-Marie-Tooth disease (CMT), one of the most common inherited peripheral neuropathies which is characterized by repeated rounds of nerve degeneration and regeneration (Cavalcani et al., 2009).

Additionally, a novel eEF1A binding protein, immunoglobulin-like and fibronectin type III domain containing 1 (IGFN1), has been discovered in a yeast two-hybrid screening of a human skeletal muscle cDNA library. IGFN1 is specifically expressed in skeletal muscle and is substantially up-regulated during muscle denervation. It presents immunoglobulin I and fibronectin III sets of domains characteristic of sarcomeric proteins and shows sequence and structural homology to myosin binding protein-C fast and slow-type skeletal muscle isoforms. Increased expression of IGFN1 has been proposed to down-regulate protein synthesis via interaction with eEF1A during denervation (Mansilla et al., 2008). Noteworthy, the reciprocal pattern of expression of eEF1A1 and eEF1A2 in muscle fits with the timing of onset of the phenotype of wasted mice: eEF1A1 declines after birth until and it is undetectable by 3 weeks; on the contrary eEF1A2 expression increases over this time. No other gene is present in the wasted deletion, and transgenic studies have shown that the

**Felty’s syndrome**

**Note**
Characterized by rheumatoid arthritis, splenomegaly and neutropenia. eEF1A1 is found as autoantigen (Ditzel et al., 2000).
phenotype is due to loss of eEF1A2 translation activity in muscle (Doig et al., 2013; Abbott et al., 2009).

In neuronal cells, an eEF1A1 interaction with the yeast two-hybrid protein K (HYPK), highlights the involvement of HYPK in the regulation of cell growth, cell cycle, unfolded protein response and cell death. Cellular responses were significantly enhanced with HYPK-interacting partners and eEF1A1 - protein interaction (Choudhury et al., 2012).

Gb2x gene, encoding a DNA-binding transcription factor, is required to the development of the anterior hindbrain, spinal cord, inner ear, heart, and neural crest cells, during embryogenesis. EEF1A1 has been reviled as one of the top candidate gene vital to Gbx2 action in nervous system development. Gbx2 activates transcriptional activity through the promoter of EEF1A1, suggesting that GBX2 could also regulate gene expression indirectly via EEF1A1 (Roeseler et al., 2012).

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