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Post-transcriptional regulation of cytokine and growth factor signaling in cancer

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Abstract

Cytokines and growth factors regulate cell proliferation, differentiation, migration and apoptosis, and play important roles in coordinating growth signal responses during development. The expression of cytokine genes and the signals transmitted through cytokine receptors are tightly regulated at several levels, including transcriptional and post-transcriptional levels. A majority of cytokine mRNAs, including growth factor transcripts, contain AU-rich elements (AREs) in their 3' untranslated regions that control gene expression by regulating mRNA degradation and changing translational rates. In addition, numerous proteins involved in transmitting signals downstream of cytokine receptors are regulated at the level of mRNA degradation by GU-rich elements (GREs) found in their 3' untranslated regions. Abnormal stabilization and overexpression of ARE or GRE-containing transcripts had been observed in many malignancies, which is a consequence of the malfunction of RNA-binding proteins. In this review, we briefly summarize the role of AREs and GREs in regulating mRNA turnover to coordinate cytokine and growth factor expression, and we describe how dysregulation of mRNA degradation mechanisms contributes to the development and progression of cancer.

Keywords

cytokine and growth factor signaling; post-transcriptional gene regulation; ARE; GRE; mRNA stability; cancer

1. Introduction

In addition to regulating cell proliferation, differentiation, and apoptosis, cytokines and growth factors also play important roles in coordinating growth signal responses during development. The ability of cytokines to affect cellular self-renewal capacity, migration, senescence, or apoptosis is often impaired in cancer. PubMed citations include approximately 7000 publications related to abnormal cytokine and growth factor signaling in

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cancer. Researchers have shown altered levels of expression or function of numerous cytokines, including growth factors and chemokines in malignant tissues relative to healthy tissues (reviewed in [1, 2]).

The expression of cytokines and growth factor signaling proteins are highly regulated at transcriptional and post-transcriptional levels [3, 4]. Cytokine and growth factor receptors and components of downstream signaling pathways are frequently overexpressed in cancer cells through abnormal mRNA stabilization, which promotes uncontrolled protein translation [5, 6]. Thus, it is crucial that the expression of cytokines and downstream signaling pathways are managed through multiple molecular mechanisms, including tightly regulated control of mRNA half-life [7, 8].

2. Levels of Post-transcriptional regulation

Expression of mammalian mRNA is regulated at multiple post-transcriptional levels that include splicing, cap addition, polyadenylation, transport, localization, degradation, and translation. mRNA molecules move from nucleus to the cytoplasm within messenger ribonucleoprotein (mRNP) complexes, dynamically associating with RNA-binding proteins (RNA-BPs) that bind to conserved cis-elements found in subsets of coordinately regulated transcripts (reviewed in [9, 10]). In the cytoplasm, the association of specific RNA-BPs with subsets of mRNAs containing conserved regulatory cis-elements coordinates the fate of these bound transcripts through post-transcriptional processes such as translation [11, 12], storage in stress granules [13], or mRNA decay (reviewed in [14, 15]). In addition to RNA-BPs, mRNA fate is also controlled by microRNAs (miRNAs) and non-coding RNAs that bind to cis-elements in mRNA (reviewed in [16–20]). Expression of cytokines and growth factor signaling molecules are most prominently regulated at post-transcriptional levels by conserved sequences found in the 3' untranslated regions (3'UTRs) of their transcripts.

3. Regulation of cytokine and growth factor signaling by AREs

AREs are conserved sequences found in the 3'UTR of certain transcripts, including numerous cytokine, chemokine, and growth factor transcripts. AREs regulate post-transcriptional processes such as mRNA degradation and translation by binding to ARE-BPs that recruit other proteins to the mRNA that mediate post-transcriptional events. The sequence characteristics and decay patterns of different AREs allowed them to be initially categorized into three classes, based on the degradation kinetics and the number of overlapping AUUUA pentamers within the 3'UTR of a transcript [21]. An intensive genome-wide bioinformatics approach was used to classify ARE-containing transcripts into 5 clusters based on the number of overlapping AUUUA pentamers [22–24]. Cluster I AREs, which contain 5 overlapping AUUUA repeats, are enriched in secreted proteins, such as cytokines, chemokines, and growth factors, and are involved in the growth of hematopoietic and immune cells. The other ARE clusters are found within a diverse set of signaling transcripts. Remarkably, ARE-containing transcripts compose less than 8% of the human transcriptome [25], but they are highly enriched in transcripts involved in cytokine networks, found in up to 80% of transcripts within the cytokine and growth factor groups. AREs function to mediate mRNA degradation through their interaction with ARE-BPs, which

compete with each other for ARE binding. Certain ARE-BPs such as ZFP36 (also called TTP), KSRP, or HNRNPD (AUF1) bind to AREs and mediate transcript degradation [26–28], while other ARE-BPs, such as ELAVL1 (also called HuR) or GAPDH [29], bind to AREs and mediate transcript stabilization, possibly by preventing binding by ARE-BPs that promote decay [30].

AREs play important roles in turning off the expression of immune activation genes during the resolution phase of immune responses (reviewed in [7, 31, 32]). For example, T cell receptor stimulation of human T lymphocytes induces expression of ARE-containing cytokine transcripts, such as IFN γ , IL2, IL4, TNF α , CSF etc., through increased transcription. This transcriptional induction is followed by transcript degradation mediated by the AREs found in the 3'UTRs of these transcripts [33, 34]. Premature post-transcriptional silencing of cytokine expressions through AREs may lead to an anergic, self-reactive T cell phenotype, which was observed in inflammatory types of cancer [35].

Cell activation can induce the expression of RNA-BPs (e.g. ZFP36, ZFP36L2, HNRNPD) that later bind to ARE-containing cytokine transcripts and recruit the cellular mRNA degradation machinery (e.g. deadenylases, exoribonucleases, or decapping enzymes) to the transcripts [36–38]. A subset of ARE-containing cytokine transcripts, such as IL6 and CXCL8, form stem-loop structures with double-stranded regions that activate exonucleases or endonucleases (e.g. RNase L) that degrade the transcripts [39–42]. In malignant cells, a number of ARE-containing cytokine mRNAs are constitutively stable, suggesting that the function of the mRNA decay machinery in cancer is altered [43, 44]. The function of AREs and ARE-BPs can be altered due to atypical expression of ARE-BPs, post-translational alterations, mutations in binding regions, or dysregulated interplay with miRNAs, leading to changes in ARE-BP binding affinities [45–47].

4. ARE-BPs in cancer

The destabilizing functions of AREs and their ability to bind to distinct ARE-BPs differ in diseased versus healthy cells. The ELAVL1 and ZFP36 ARE-BPs have been shown to compete with one another for certain ARE-containing transcripts and exert opposite effects on the stability of ARE-containing mRNAs [48]. According to recent observation, ELAVL1 and ZFP36 share more than fifty percent of 3'UTRs target sites [49]. Binding by ELAVL1 promotes mRNA stabilization and upregulation of ARE-containing genes [50, 51], whereas, binding by ZFP36 promotes mRNA degradation and down-regulates the expression of ARE-containing genes [49, 52]. Remarkably, the expression and function of ELAVL1 is increased, but the function of ZFP36 is almost completely abrogated, in numerous types of tumors (reviewed in [53, 54]). Decreased function of ZFP36, ZFP36L1, and ZFP36L2, combined with elevated function of ELAVL1 result in increased expression of cytokine genes that promote cell growth and angiogenesis [55–58]. In humans, single nucleotide polymorphisms in ZFP36 and ELAVL1 genes are associated with poor outcomes in cancer patients [59, 60]. For the sake of brevity of this review, we shall focus on two ARE-BPs: ELAVL1 and ZFP36, as the malfunction of either, or both, has been reported as a trait of acquisition of tumorigenic and pro-metastatic properties (Fig. 1).

4.1 ELAVL1 promotes tumor growth

Overexpression of the stabilizing protein ELAVL1 is strongly associated with proliferation: in cancer cell models, mice and in humans [61–66]. In fact, the link between ELAVL1 and cancer was initially discovered through observations of increased TNF α , VEGF, TGF β , COX2, and CXCL8 mRNA expression in colon or brain cancer cells [67–69]. ELAVL1 gets rapidly phosphorylated following exposure to different stress stimuli, which may be an important mechanism utilized by cancer cells to keep up with cytotoxic stresses [70, 71]. For example, in colon carcinoma cells, the phosphorylation of ELAVL1 by PKC isozymes promotes COX2 overexpression through increased mRNA stability [72]. In hypoxic conditions, cytoplasmic localization and ARE-binding activity of ELAVL1 increases, leading to expression of pro-angiogenic mRNAs, likely due to activation of ELAVL1 by PKC and other kinases [73–77]. Moreover, ELAVL1 promotes chemo-resistance by binding to and stabilizing HIF1 α and other hypoxia-associated mRNAs [78–80]. Interestingly, the mTOR inhibitor, rapamycin, inhibits ELAVL1 phosphorylation by PKC and decreases VEGF mRNA stability, suggesting that rapamycin might inhibit production of VEGF through its effect on ELAVL1, and thereby prevents neoplastic angiogenesis [81].

ELAVL1 increases not only pro-angiogenic, but also pro-inflammatory cytokine expression [82]. ELAVL1 is known to stabilize a number of pro-inflammatory mRNAs, and the overexpression of ELAVL1 in inflammatory types of glioblastoma, breast or lung cancer, is a risk factor for rapid disease progression [83–86]. Paradoxically, overexpression of ELAVL1 in breast cancer xenografts in athymic mice led to significant retardation of tumor growth, perhaps due to lack of angiogenesis in this xenograft model [87].

Overall, most existing data suggests that increased expression or cytoplasmic localization of ELAVL1 is associated with uncontrolled cell growth and chemoresistance [88–90]. In addition, the progression of cancer requires pro-inflammatory and pro-angiogenic signals from non-cancerous cell types within the tumor microenvironment, and these cancer-promoting signals may also be influenced by ELAVL1 [91]. Furthermore, genetic deletion of ELAVL1 in thymocytes [92] and myelocytes [93] predisposed mice to exaggerated inflammatory responses and inflammation-driven oncogenesis, likely due to malfunction in the cancer immune surveillance mechanism, which allows the formation of pro-tumorigenic milieu.

4.2 ZFP36 is a tumor suppressor

In contrast to ELAVL1, whose expression is upregulated in numerous forms of cancer, down-regulation of ZFP36 and ZFP36 family member's expression or function was documented in many types of cancers [94, 95]. In fact, low ZFP36/ELAVL1 mRNA ratios correlate with high levels of the mitotic ARE-mRNA signature in a number of solid cancers [47]. ZFP36 functions to prevent the pathological overexpression of pro-inflammatory mRNAs that are associated with tumorigenesis, including IFN γ , IL1, IL2, IL6, IL8, IL10, IL16, IL17, IL23, TNF α , TGF β , VEGF, and CSF1 [96–103]. These cytokine mRNAs are normally produced by immune and non-immune cells for a very short period of time in response to inflammatory signals, but are constitutively overexpressed in various types of tumors. The excessive production of cytokines in cancer has been attributed to absence or

malfunction of ZFP36 (through transcriptional or post-translational mechanisms), which renders malignant cells unable to degrade ARE-containing transcripts in timely manner [104–107]. Thus, ZFP36 deficiency in tumors and immune cells may account for overproduction of these cytokines in the tumor microenvironment [108–110], leading to tumor cellular proliferation, vascularization and metastasis (Fig. 1). In support of this statement, knockdown of ZFP36 from tumors resulted in increased secretion of pro-inflammatory cytokines and accelerated tumor growth [104, 111]. In contrast, exogenous overexpression of functional ZFP36 triggered apoptosis of invasive breast cancer cell lines [112] or induced retardation of tumor growth and decreased metastatic potential in different cancer cell models (e.g. breast, cervical or colon carcinoma cell lines) [113]. The cancer therapeutic agent, Sorafenib, causes re-expression of ZFP36 in melanoma cells, which led to decreased expression of pro-angiogenic ARE-containing cytokines [114]. Overall, current literature supports the notion that the function of ZFP36 appears to counteract the cancer promoting properties of ELAVL1. In cancer cells, deficiency of ZFP36 is often seen in combination with increased expression/function of ELAVL1 [115–117]. Unbalanced expression of these two ARE-BPs appears to drive uncontrolled growth and contributes to tumorigenesis. Future research and development toward pharmacological agents that inhibit ELAVL1 and increase expression of ZFP36 may allow favorable control of post-transcriptional ARE networks and could potentially be used to treat devastating types of cancer, including gliomas and invasive types of breast, ovarian, or pancreatic cancers [118–122].

5. Regulation of cytokine and growth factor networks by GREs

Studies regarding AREs and ARE-BPs have led to the identification of other cis-elements and proteins that globally regulate mRNA decay [123]. For example, bioinformatic analyses of short-lived transcripts expressed in different cell types led our research team to identify the GRE sequences as highly enriched in the 3'UTRs of mRNAs that encode growth-promoting proteins [124, 125]. The GRE motif binds to the protein CELF1, leading to the decay of GRE-containing mRNA. These GRE-containing transcripts have variable nucleotide repeats, that can be defined as UGU[G/U]UGU[G/U]UGU [126]. More recent computational studies identified a number of mature miRNAs containing a 5'-UGUGU-3' motif, which is known to stimulate of innate immune responses [127]. These miRNAs could also directly bind to CELF1 and affect mRNA stability and cellular protein expression [128]. Of note, GRE-containing mRNAs encode numerous transcripts involved in cytokine and growth signaling pathways that are binding targets of CELF1 [7, 129]. In primary cells, CELF1 binds and regulates expression of transcripts encoding hundreds of activators of cellular proliferation, presumably maintaining cell transitions through appropriate developmental stages [130–132]. We identified that in response to immune stimuli, CELF1 becomes phosphorylated, which prevents CELF1 binding to mRNA. This leads to transient stabilization and upregulation of GRE-containing transcripts, including components of cytokine and growth factor signaling [7, 130] [133]. Thus, CELF1 functions in normal cells to down-regulate the expression of GRE-containing transcripts that promote cell growth, including multiple components of cytokine and growth factor signaling pathways [134].

6. CELF1 expression and function in cancer

There are inconsistent results about levels of CELF1 protein expression in different types of malignant tissues, varying from overexpression to no changes [135–139]. A bioinformatics search using Oncomine did not reveal significant difference in CELF1 mRNA expression between normal and various human cancer transcriptomes (oncomine.org). CELF1 function, however, may be changed even if the protein levels are not altered in malignant cells, contributing to dysregulation of cytokine signaling. Our data indicate that in HeLa cells and malignant leukemia and lymphoma cell lines, CELF1 is unable to bind to mRNA targets identified in normal T cells, even though the target mRNAs were expressed in each cell type and the CELF1 protein levels did not differ. This failure to bind to target transcripts by CELF1 in malignant cell lines, might be explained by post-translational alterations of this protein (specifically, phosphorylation), and also increased retention to the nucleus, which correlates with stabilization and increased expression of GRE-containing target transcripts in the cytoplasm [126, 137]. These stabilized transcripts included transcription factors, cytokines and growth factor signaling molecules such as STAT5, JUN, CEBPB α/β , IL15, IL1RB, IFN γ , beta-catenin, and CCR5,7 [137, 140, 141]. We found that CELF1 was expressed in a hyper-phosphorylated form in these cancer cell lines, and this phosphorylation prevented it from binding to and degrading GRE-containing transcripts that control cell growth. Unexpectedly, we also identified that hyper-phosphorylation of CELF1 caused it to gain the ability to bind to and facilitate the degradation of another subset of GRE-containing transcripts that encode suppressors of proliferation (e.g. SOCS5, TNFRSF4, PIAS1, NKIRAS1). It is unknown how exactly CELF1 switches preferences for binding to mRNA targets, but this switch seems to be related to the phosphorylation state of CELF1. Thus, additional studies are needed to determine if post-translational modification of CELF1 causes dysregulation of the GRE network in cancer cells.

In addition to its role in mRNA degradation, CELF1 regulates many other aspects of mRNA metabolism. In fact, it was first discovered in patients suffering from myotonic dystrophy type 1 (DM1), a toxic RNA disease [142]. Links between DM1 and aberrant CELF1 function prompted clinical investigations of cancer incidence in individuals suffering from this inherited disorder. These studies revealed an increased overall risk of cancer in DM1 patients, and specifically thyroid cancer and choroidal melanoma [143–145]. In the general population, the association between the abnormal function of CELF1 and myelogenous leukemias [146], as well as hepatic [147], and mammary [148] cancers have been described, with cancer pathogenesis linked to dysregulation of C/EBP β and p21 (CDKN1A) mRNA expression by CELF1. Thus, CELF1 dysregulation is a common feature of neoplastic growth and proliferation.

7. Cross-talk between ARE and GRE networks in cancer

The network of ARE-containing transcripts encodes various cytokines and growth factors that depend on circuits of downstream GRE-containing signaling transcripts to function (Fig. 2A,B). Furthermore, many GRE-containing CELF1 target transcripts are also targets of the ARE-BP ELAVL1, indicating that CELF1 and ELAVL1 may have opposing effects on target RNA stability or translation [149]. RNA recognition motifs for CELF1 require (GU) n or

GUUUU repeats, whereas the recognition sequence for ELAVL1 is more broad, and ELAVL1 binds to a variety of AU/GU-rich sequences, including a poly-U sequence [150, 151]. Thus, CELF1 and ELAVL1 often compete for G/U-rich binding sites on a subset of target transcripts. We compared GRE-containing transcripts that were CELF1 targets in normal T cells [130], but lost binding to CELF1 in malignant cell lines [126, 137, 141], with ELAVL1 targets identified by in similar malignant cell types [152]. We found numerous transcripts that appeared to switch their binding preferences from CELF1 to ELAVL1 (see Fig. 2A,B). Depending on environmental conditions or cell type, these two proteins can change their preferred localization from the nucleus to the cytoplasm or vice versa, which affects their availability to bind to and regulate target mRNAs [153–156]. Thus, depending on which protein is more abundant in the cytoplasm, and on which protein has a higher affinity for the GU-or-U-rich binding site in a given target transcript, transcripts may undergo stabilization and translation versus decay. The increased abundance of phosphorylated cytoplasmic ELAVL1 in cancer cells may promote stabilization of numerous GU-or-U-rich mRNAs, especially in the setting of CELF1 inactivity due to hyper-phosphorylation [137].

We proposed a model as such: In normal cells, many cytokine and growth factor signaling transcripts are bound to CELF1 and targeted for degradation after they are transiently expressed following cellular activation; In cancer cells, CELF1 becomes hyper-phosphorylated and is rendered unable to bind to certain GRE-containing transcripts [157]. The increased levels of cytoplasmic ELAVL1 and enhanced binding affinity of ELAVL1 for mRNA, in cancer cells, leads to increased binding by ELAVL1 to GRE-containing mRNAs, stabilizing them and allowing them to be translated [158, 159]. Although further evidence is needed, this model could explain the overexpression of certain ARE and GRE-containing transcripts in malignancy.

8. Post-transcriptional regulation of growth factor signaling in cancer

Tumor cells have been shown to acquire the ability to produce growth-promoting cytokines and to overexpress growth factor receptors [160]. Growth factor – induced cell proliferation, adhesion and migration often depend on ARE and GRE post-transcriptional regulatory networks. The TGF β signaling cascade, for example, is encoded by ARE- and GRE-containing mRNAs (Fig. 2A). Activated by TGF β , TGF receptors (TGFR) and downstream SMAD proteins regulate the transcription of a number of GRE-containing mRNAs (ex. CITED2, SNAILs, Cadherins, occludin, TWIST, CDKN1A, ETS1/2, TGFBR1, myc, jun, fos, etc.), which in turn become a subject of post-transcriptional regulation by CELF1 or ELAVL1 once they leave the nucleus [161–163]. TGF β treatment causes nuclear ELAVL1 to translocate into the cytoplasm, where it binds to TGF β mRNA and increases its stability, completing a positive feedback loop [164, 165]. In pathological conditions, GFRs also signal through a RAS oncogenic pathway, which leads to upregulation of a large set of ARE-containing transcripts and specifically VEGF mRNA, due to dysfunctional mRNA degradation and translational upregulation [166]. Overproduced VEGF acts on vascular endothelial cells to increase vascular permeability via tyrosine kinase receptors (TKR), which heightens the metastatic potential [167]. In addition to VEGF mRNA, ARE and GRE-containing transcripts encoding components of cell adhesion and motility pathways (e.g.

ICAM1, VCAM1, E-selectin, β -actin or catenin) and proteins with enzymatic activities (e.g. heparanases, matrix metallo-proteinases MMP2,7,8,9 or uPA (PLAU), PIA) are stabilized and upregulated in cancer [118, 168–171] (see fig. 2B). The RAS-mTOR pathway is a well-established signaling axis that modulates the proliferation and survival of many cell types downstream of growth factor receptors. Abnormal growth factor signaling through RAS/RAF/MEK/ERK and PI3/Akt/mTOR pro-survival pathways can fuel cancer growth and metastases, in part through posttranscriptional mechanisms [157, 172, 173]. Since ARE and GRE-containing transcripts encode important regulators of apoptosis and the cell cycle that function downstream of growth factor receptors, transformed cells may usurp these post-transcriptional networks to their advantage as they become malignant [174–177] (Fig. 2A).

Key regulators of epithelial-to-mesenchymal transitions (EMT), such as SNAIL, β -catenin, and TWIST are encoded by ARE and GRE-containing molecules, and are regulated through post-transcriptional effect of ELAVL1, ZFP36, and CELF1 [178–181]. EMTs are driven by many soluble growth factors, including FGFs, HGF, EGF, PDGFC, IGF, and their cognate receptors [135, 182]. For example, activation of the EGFR pathway in triple-negative breast cancer increases the cytoplasmic localization of ELAVL1, leading to stabilization and translation of ARE-containing mRNAs such as CA9, SNAIL2, β -catenin and IL6, contributing to the development of a stem cell-like and aggressive basal-like breast cancer phenotype [183]. Tumor cells often overexpress growth factor mRNAs through ELAVL1-directed stabilization, thereby creating positive auto-feedback loops in which more growth-promoting cytokines are produced and become available in the tumor microenvironment. On the background of poor anti-tumor immune response [184, 185], hypoxia [186], and proliferative signals from extracellular matrix components (e.g. Wnt and JAG/DLL), these feedback loops foster the disruption of adherence junctions and promote tumor angiogenesis and metastases (Fig. 1) [187–190]. Under normal conditions, ZFP36 and ZFP36L1 [191, 192] destabilize and degrade ARE-containing growth factor signaling transcripts, but in malignant cells these transcripts are stable and upregulated [43]. Given that cancer cells are often deficient in ZFP36, mRNA stabilization mechanisms could drive overexpression of growth-promoting networks in malignant tissues [193, 194]. Figure 2B depicts transcripts encoding NOTCH and WNT/ β -catenin signaling components that differentially function in a growth factor- and hypoxia- dependent manner [195]. As can be seen, GRE-containing transcripts (grey transcripts) encode components of these signaling pathways downstream from Frizzles and NOTCH receptors. Overall, these receptors transduce a range of intracellular signals that alter the rate of proliferation and production of other cytokines, growth factors (e.g. IL1,6,8, FGF, VEGF), and markers of EMT, in part through the post-transcriptional mechanisms described above.

In this review we have examined only a small portion of published scientific data in the field of post-transcriptional regulation of cytokine and growth-factor signaling. New research results will undoubtedly contribute to further expansion of our knowledge of post-transcriptional networks and their complexity. For example, other proteins and miRNAs that directly associate with RNA-RBPs may introduce conformational changes, and alter RBP interactions with mRNAs in the malignant milieu [196–198]. Building a comprehensive cancer interactome of RNA-BPs, in malignant and tumor-associated cells, may provide

insight into dysregulated post-transcriptional events. As a result, useful prognostic markers of cancer progression may be realized.

9. Summary

The important roles of AREs and GREs in regulating the dynamic expression of cytokine and growth factors as well as their signaling pathways is increasingly appreciated [199]. Many studies suggest malfunction of ELAVL1 in cancer causes overexpression and stabilization of target mRNAs [47, 200]. In contrast, CELF1 and ZFP36 normally function to limit cellular proliferation, and their inability to function in cancer further promotes uncontrolled cell growth. Thus, the opposing effects of CELF1 and ZFP36 versus ELAVL1 has important implications for the role of post-transcriptional regulation in proliferative diseases such as cancer. Maintaining appropriate balances between RNA-BPs that degrade or stabilize ARE- or GRE-containing mRNAs is a mechanism to ensure appropriate expression of these transcripts and to sustain healthy homeostasis. Understanding the crosstalk between CELF1, ZFP36, ELAVL1 and other RNA-BPs may uncover novel therapeutic strategies to fine-tune the balance in cell growth and cell death pathways involved in human cancer [201, 202]. In the future, more work needs to be done to develop interventions targeting post-transcriptional mechanisms involved in cancer pathogenesis.

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Abbreviations

3'UTR	untranslated region
ARE	AU-rich element
GRE	GU-rich element
RNA-BP	RNA-binding protein
ARE-PB	ARE-binding protein
GRE-BP	GRE-binding protein
ELAVL1	embryonic lethal, abnormal vision-like 1 (Hu antigen R)
ZFP36	zinc finger protein 36
TTP	tristetraprolin
CELF1	CUGBP-ELAV-like family member 1
HNRNPD	heterogeneous nuclear ribonucleoprotein D
KSRP	KH-type splicing regulatory protein

GAPDH	glyceraldehyde 3-phosphate dehydrogenase
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
GF	growth factor
GFRs	growth factor receptors
uPA	urokinase plasminogen activator
CXCL8	C-X-C motif ligand 8, IL, Interleukin
PKC	protein kinase C
MAPK	mitogen-activated protein kinase
mTOR	mammalian target of rapamycin
MMP9	matrix metalloproteinase 9
NFkB	nuclear factor kappa B
STAT	signal transducer and activator of transcription
FGFs	fibroblast growth factors
EGF	epidermal growth factor
TNFα	tumor necrosis factor-alpha
ICAM	intercellular adhesion molecule
VCAM	vascular cell adhesion molecule
CSF1	colony-stimulating factor one
DM1	myotonic dystrophy type 1
EMT	epithelial-to-mesenchymal transitions

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Biographies

Irina St. Louis earned her M.D. and Ph.D. degrees from Ural State Medical Academy, Yekaterinburg, Russia. She completed her residency in lab pathology at Russian Medical Academy for Postgraduate Education, Moscow. Dr. St. Louis joined the Department of Microbiology, at University of Minnesota, as a postdoctoral trainee, followed by fellowships at the University of Minnesota Supercomputing Institute and Lymphoma Research Foundation. In 2013, Dr. St. Louis was appointed as an Assistant Professor at the Department of Medicine. The research in her Lab is centered on the area of post-transcriptional gene expression regulation, specifically through messenger RNA degradation. Dr. St. Louis conducts discovery research in several key areas including infectious diseases, immunology, and oncology.

Paul R. Bohjanen, MD, PhD, Professor of Medicine, Division Director of Infectious Diseases & International Medicine, Director of the Center for Infectious Diseases and Microbiology Translational Research (CIDMTR). He graduated from the University of Michigan with an M.D./Ph.D. degrees, and then completed an internal medicine residency and an infectious diseases fellowship in 2000, both at Duke University. Research in his laboratory focuses on the role of mRNA decay in regulating T lymphocyte activation and function. Many genes that are important for cell growth and immune function are turned on at precise times and turned off at precise times. Dysregulated expression of many of these

genes, including proto-oncogenes and cytokine genes, occurs in disease states such as cancer, autoimmunity, or immunodeficiency.

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Highlights

Examination of published scientific data in the field of post-transcriptional regulation of cytokine and growth-factor signaling.

AREs and GREs regulate mRNA turnover to coordinate cytokine and growth factor expression.

Three RNA-binding proteins that competitively regulate mRNA stability through ARE and GRE are discussed.

Dysregulation of mRNA degradation contributes to the development and progression of cancer.

Fig. 1.

Alterations in post-transcriptional regulatory networks during tumorigenesis. Signals transmitted through prominent receptors that promote tumorigenesis, such as TGF β growth factor receptors (which are also protein tyrosine kinases), WNT/ β -catenin, and NOTCH, result in alterations in RNA-binding protein expression and function. These lead to dysregulation of mRNA stability/translation of major ARE- and GRE-containing transcripts that encode markers of EMT (described in text). Changes in expressions of these ARE- and GRE-containing transcripts cooperatively contribute to the overall phenotypic outcomes of cellular networks, such as feed-back loop activation of growth factor signaling pathways, cell proliferation, disruption of adherence junction, migration, invasion, and metastases.

Fig. 2.

AREs and GREs in growth factor signaling.

A. Schematic representation of tumor growth factor receptors (TGFR), vascular endothelial, epidermal, platelet-derived, or insulin growth factor receptors (VEGFR, EGFR, IGFR, PTDGFR) signaling. Signals transmitted through the tyrosine kinase family (RTK) receptors are directed through several major kinase signaling cascades, such as RAS/RAF/MEK/ERK and PI3/Akt/mTOR/GSK3 pro-survival pathways.

B. Schematic representation of NOTCH and WNT/β-catenin signal-transduction components that differentially function in a growth factor- and hypoxia- dependent manner. Frizzled and NOTCH receptors transduce a range of intracellular signals that alter the rate of proliferation and production of growth factors and markers of EMT through the post-transcriptional mechanisms. GRE-containing transcripts (shown in grey) represent direct binding targets of CELF1 in normal cells, as determined by RNA-immunoprecipitation assays [130, 131]. These transcripts exhibit a switch in their binding preferences from CELF1 in normal cells [130, 131] to ELAVL1 in malignant cells [152]. Transcripts in yellow contain AREs. Nodes labeled as ZFP36, ELAVL1, CELF1, are experimentally validated functional mRNA targets of ZFP36, ELAVL1, or CELF1. Pentagon-shaped nodes represent

transcripts encoding kinases. Arrows indicate direct interactions and/or activations. This network diagram was built using Ingenuity Pathway Assistant Software.

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