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Survey

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.

Contents

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; TFNα, 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; PIA/RICTOR, RPTOR independent companion of MTOR complex 2.

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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 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 IFNγ, IL2, IL4, TNFα, 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 the 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 are 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: