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Editor-in-Chief of *World Journal of Gastrointestinal Oncology*, Monjur Ahmed, MD, Associate Professor, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Thomas Jefferson University, Philadelphia, PA 19107, United States

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REVIEW

AU-rich element-binding proteins in colorectal cancer

Noémie Legrand, Dan A Dixon, Cyril Sobolewski

ORCID number: Noémie Legrand (0000-0003-0516-0786); Dan A Dixon (0000-0001-5631-4365); Cyril Sobolewski (0000-0002-9404-6290).

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Noémie Legrand, Department of Microbiology, Faculty of Medicine, University of Geneva, Geneva CH-1211, Switzerland

Dan A Dixon, Department of Molecular Biosciences, University of Kansas, Lawrence, Kansas, and University of Kansas Cancer Center, Kansas City, KS 66045, United States

Cyril Sobolewski, Department of Cell Physiology and Metabolism, Faculty of Medicine, University of Geneva, Geneva CH-1211, Switzerland

Corresponding author: Cyril Sobolewski, PhD, Research Associate, Department of Cellular Physiology and Metabolism, Faculty of Medicine, University of Geneva, CMU, 1 rue Michel-Servet, Geneva CH-1211, Switzerland. cyril.sobolewski@unige.ch
Telephone: +41-22-3795421

Abstract

Trans-acting factors controlling mRNA fate are critical for the post-transcriptional regulation of inflammation-related genes, as well as for oncogene and tumor suppressor expression in human cancers. Among them, a group of RNA-binding proteins called "Adenylate-Uridylate-rich elements binding proteins" (AUBPs) control mRNA stability or translation through their binding to AU-rich elements enriched in the 3'UTRs of inflammation- and cancer-associated mRNA transcripts. AUBPs play a central role in the recruitment of target mRNAs into small cytoplasmic foci called Processing-bodies and stress granules (also known as P-body/SG). Alterations in the expression and activities of AUBPs and P-body/SG assembly have been observed to occur with colorectal cancer (CRC) progression, indicating the significant role AUBP-dependent post-transcriptional regulation plays in controlling gene expression during CRC tumorigenesis. Accordingly, these alterations contribute to the pathological expression of many early-response genes involved in prostaglandin biosynthesis and inflammation, along with key oncogenic pathways. In this review, we summarize the current role of these proteins in CRC development. CRC remains a major cause of cancer mortality worldwide and, therefore, targeting these AUBPs to restore efficient post-transcriptional regulation of gene expression may represent an appealing therapeutic strategy.

Key words: Colorectal cancer; Adenylate-Uridylate-rich element-binding proteins; Oncogenes; Tumor suppressors; Post-transcriptional regulation

Core tip: Colorectal cancer (CRC) is a deadly cancer associated with the deregulation of

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multiple genetic and epigenetic mechanisms, leading to the silencing of tumor suppressors and the induction of both oncogenes and inflammation-related genes. Among them, a novel class of RNA-binding proteins called Adenylate-Uridylate-rich element-binding proteins have been involved in the post-transcriptional regulation of genes linked to CRC tumorigenesis. Current findings indicate the major regulatory roles these RNA-binding proteins have on deregulated pathways associated with CRC. Therefore, targeting these proteins may represent a novel and efficient therapeutic approach.

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INTRODUCTION

Colorectal cancers (CRCs) represent the third most frequent cancer and a leading cause of cancer mortality worldwide[1,2]. The progression model of CRC tumorigenesis results from a long deregulated process that initiates with the development of small adenomas, large adenomas and finally CRC[3]. In the majority of cases, CRCs develop sporadically (70% of cases) and rarely are due to inherited mutations underlying familial adenomatous polyposis (FAP) and the Lynch syndromes[4]. The causes of sporadic CRC development are still unclear, but several risk factors have been identified, including older age, obesity, diabetes, sedentary lifestyle, alcohol consumption or chronic inflammatory diseases (*i.e.*, inflammatory bowel diseases, Crohn's disease and ulcerative colitis)[2,5,6]. Considering the pandemic of obesity and type-2 diabetes in developed countries[7], the incidence of CRC is expected to increase in the future, making it a major public health concern and economic burden. CRC is primarily treated by surgery, but also by chemotherapy (*e.g.*, FOLFOX: Folinic acid, 5-fluorouracil, oxaliplatin) and targeted therapy[4]. However, despite this myriad of therapeutic approaches, CRC remains one of the most deadly cancers[2]. Several causes contribute to the development of aggressive metastatic tumors, which include the development of chemoresistance and late diagnosis due to the lack of symptoms at early stages. Therefore, deciphering the molecular features of CRC is still a major research effort to identify novel/early biomarkers and therapeutic approaches.

At the molecular level, CRC has been associated with chromosomal instability and microsatellite instability that can affect tumor suppressor (TS) and oncogene (ONC) expression[4]. These mutations trigger various signaling pathways *(i.e.*, Wnt/β-catenin, TP53, KRAS) involved in most cancer hallmarks (*i.e.*, proliferation, migration, survival)[4]. Unfortunately, many of these mutated genes have proven to be difficult to target therapeutically, considerably limiting the amount of therapeutic options. Nevertheless, ONC/TS and inflammation-associated gene expression are also deregulated through mutational-independent mechanisms or aberrant signaling within the tumor microenvironment. These alterations can be mediated by the metabolic status of the intestinal epithelium, the gut microbiota, epigenetic changes (*i.e.*, DNA methylation, histones acetylation)[8] or the pro-inflammatory environment. Among them, increasing evidence indicates that post-transcriptional mechanisms controlling mRNA stability and translation contribute to CRC tumor progression. Over the last decade, extensive efforts have been devoted to deciphering the impact of non-coding RNAs (*i.e.*, long-non-coding RNAs, microRNAs) during CRC development. More recently, the role of a family of RNA-binding proteins (RBP) called "Adenylate and Uridylate-rich elements-binding proteins" (AUBPs) regulating mRNA stability and translation have been highlighted. Alterations in AUBPs expression/activity have been associated with the development of several inflammatory, metabolic disorders (*i.e.*, osteoarthritis, diabetes) and cancers[9]. During carcinogenesis, these proteins contribute to the activation of various ONC and the silencing of TS, thereby triggering critical pathways involved in CRC development. In this review, we discuss the specific role of these proteins in the onset and progression of CRC, with particular emphasis on their ability to regulate the expression of key ONC, TS and inflammation-related genes. Finally, we discuss the potential of targeting these proteins for therapeutic purposes.

ARE-DEPENDENT POST-TRANSCRIPTIONAL REGULATION

Post-transcriptional regulation of gene expression encompasses various mechanisms that control mRNA processing, splicing, stability and translation. In this regard, the 3'UTR is a determinant region of mRNA transcripts that can be targeted by various *trans*-acting factors, such as microRNAs, long-non-coding RNA or RBP. In particular, the AU-rich element present in the 3'UTR of various mRNAs plays a critical role in the control of mRNA stability and translation. The ARE is usually defined as a core AUUUA sequence, and is most often composed of multiple copies of the AUUUA motif. Several ARE classes and clusters have been defined based on the number and context of the AUUUA pentamers[10,11]. The presence of one or more ARE in the 3'UTR of mRNAs is frequently observed in immediate-early response genes (*e.g.*, pro-inflammatory cytokines, ONC), which make ARE-dependent regulation critical for several processes like inflammation[12]. Currently, it is estimated that 5-8% of human genes contain an ARE in their 3'UTR[11], thus highlighting the importance of ARE-dependent regulation. The development of several ARE databases, such as AREsite (http://rna.tbi.univie.ac.at/cgi-bin/AREsite.cgi) or ARED (http://brp.kfshrc.edu.sa/ARED/), has provided researchers with potent bioinformatic tools to identify the presence of AREs in eukaryotic mRNAs[13,14]. Moreover, high-throughput gene expression analyses have allowed the identification of several ARE-containing genes deregulated in as early as stage I CRC[15].

Aberrant ARE-dependent post-transcriptional regulation has been observed in all cancer types, and contributes to the overexpression of pro-inflammatory mediators [*e.g.*, Cyclooxygenase-2 (COX-2)], ONC (*e.g.*, c-myc) and to the silencing of TS [*e.g.*, Insulin-like growth factor-binding protein 3 (IGFBP3), Programmed cell death protein 4 (PDCD4)], thereby triggering key oncogenic pathways involved in the establishment of neoplastic phenotypes[10]. Over the last decade, efforts have been devoted to fully characterize the underlying mechanisms associated with this aberrant ARE-dependent regulation in CRC. Among them, several non-coding RNAs and RBPs have been identified, which may represent novel biomarkers and/or therapeutic targets.

COMPLEXITY OF AUBPS-DEPENDENT POST-TRANSCRIPTIONAL REGULATION

The ARE can be targeted by RBPs called "AU-rich Element-Binding Proteins", which display high affinity for binding to adenine and uridine-rich elements present in the 3'UTR of several immediate-early response genes, such as pro-inflammatory cytokines, growth factors and ONC. To date, more than 20 different AUBPs involved in mRNA stability and translation regulation have been described[11]. Importantly, the expression and role of these proteins may differ depending on the tissue type or the cellular context (*e.g.*, inflammation, hypoxia)[16,17]. AUBPs can promote mRNA decay or regulate mRNA translation by directing ARE-containing mRNAs to P-bodies and stress granules, respectively[18,19]. Therefore, the identification of target mRNAs through transcriptomic approaches is not always suitable, particularly for those involved in translation regulation [*i.e.*, T-Cell-Restricted Intracellular Antigen-1 (TIA1)]. A primary method to identify direct mRNA targets consists of crosslinking ribonucleoprotein (RNP) complexes, followed by the immunoprecipitation of AUBP and RNA sequencing (CLIP-seq, RNP-IP)[6]. Many published studies investigating AUBPs have used *in vitro* cell models. More recently, however, the development of several *in vivo* transgenic models have allowed researchers to better characterize the physiological and pathological functions of several AUBPs in the context of tissue-specific expression.

Most AUBPs are regulated by post-translational modifications (*e.g.*, phosphorylation) that can impact their subcellular localization and activity[20,21]. Therefore, not only the expression but also the activity/localization of AUBPs should be considered in research projects. Moreover, AUBPs can regulate the fate of their own mRNA transcript, as demonstrated for tristetraprolin (TTP)[22]. This may result in the transient modulation of their expression, as previously demonstrated for TTP with insulin stimulation[23]. This aspect should also be considered in the design of experimental settings aimed at measuring the level of AUBPs in physiological or pathological conditions.

The complexity of ARE-dependent regulation is further enhanced by the fact that one particular AUBP can regulate several mRNAs and, conversely, one mRNA can also be targeted by distinct AUBPs (*e.g.*, COX-2)[24]. This derives from the fact that AUBPs can bind to different classes of AREs or share the same binding sites (*e.g.*, HuR and TTP for COX-2 regulation). Therefore, it is likely that the phenotype observed

with the manipulation of one given AUBP's expression may contribute to the concerted deregulation of several mRNA transcripts.

Another layer of complexity is provided by the competition of AUBPs and miRNAs for the same binding site on a given target (*e.g.*, HuR and miR-16)[25]. Moreover, AUBPs can also directly sequester miRNAs and prevent their binding to their mRNA targets (*e.g.*, HuR and miR-21)[26]. Such competitions have also been reported between long-non-coding RNAs, miRNAs or AUBPs[27], however it is still unclear whether this interplay exists in CRC. Most studies focus on the role of one given miRNA, AUBP or lncRNA, so this dynamic equilibrium between AUBPs and non-coding RNAs is thus poorly considered.

ROLE OF AUBPS IN CRC

ARE-dependent post-transcriptional regulation plays an important role in the development and progression of CRC. This importance derives from an ability of these proteins to directly regulate the mRNA decay and/or translation of several ONC, TS and/or inflammatory mediators.

HuR (ELAVL1)

HuR (ELAVL1) belongs to the Embryonic-Lethal Abnormal Vision in *Drosophila* (ELAV) family of RBPs[28]. This protein is ubiquitously expressed and primarily localized in the nucleus, where it contributes to nucleo-cytoplasmic export[20,29]. The protein displays two tandem RNA-recognition motifs (RRM), followed by a hinge region and a third RRM. The hinge region contains a HuR nucleocytoplasmic shuttling (HNS) domain that can be phosphorylated by various kinases, and is involved in nucleo-cytoplasmic shuttling of the protein. In the cytosol, HuR stabilizes ARE-containing mRNA transcripts (Class I and II mostly) by competing or displacing destabilizing factors, such as microRNAs or other AUBPs (*i.e.*, TTP), that share the same ARE binding sites. Moreover, HuR can directly bind to miRNAs (*e.g.*, miR-21) and thus prevent the downregulation of their targets[26]. HuR is frequently upregulated in most human cancers and exerts oncogenic functions.

Role of HuR in CRC development

HuR is one of the most studied AUBPs in CRC. HuR is overexpressed in CRC when compared to normal colon epithelium[30]. It contributes to the stabilization of inflammation-related transcripts, as well as various oncogenic transcripts involved in cancer cell proliferation, migration, invasion and angiogenesis. Interestingly, HuR was also found overexpressed in colonic epithelial cells from patients with inflammatory bowel disease[31], thus suggesting that HuR induction may represent an early event that promotes CRC development.

The role of HuR in CRC has been extensively studied in various *in vitro* and i*n vivo* models. HuR silencing in CRC cells (*i.e.*, HCT116) is associated with decreased tumor growth in xenograft models[32]. Conversely, HuR-overexpressing RKO cells display larger tumors in nude mice[33]. Finally, intestinal-specific HuR KO mice ($HuRi^{KO}$) display reduced tumor burden in a model of FAP ($APC^{min/+}$ mice), and increased acute intestinal injury following doxorubicin treatment[34].

Efforts have been devoted to identify all HuR targets involved in colorectal carcinogenesis. In this regard, transcriptomic analyses have been performed in various *in vitro* and *in vivo* models with varying levels of HuR. Furthermore, immunoprecipitation of HuR/mRNA complexes has allowed the identification of several HuR targets with significantly more specificity[35]. However, depending on the colon cancer cell lines used for analysis, different targets can be identified. Considering the heterogeneity that exists between CRC tumors, different cellular models should be considered.

Prostaglandin (PG) biosynthesis and inflammation: PGs are bioactive lipid mediators derived from arachidonic acid metabolism. PGs play important functions in the regulation of physiological processes[36]. Thus, the alteration of PG homeostasis is often associated with the development of inflammatory diseases and cancer[37,38]. Following their synthesis, PGs are secreted and act in a paracrine or autocrine manner by binding to nuclear receptors or G-coupled receptors localized at the cellular surface (*e.g.*, EP receptors)[39]. Prostanoid biosynthesis requires several enzymes, including phospholipases, COXs and PGs synthases. In particular, the inducible isoform of COXs, COX-2, is frequently overexpressed in CRC[30,40], thus leading to aberrant PG synthesis while promoting inflammation, immune escape of cancer cells[41], tumor growth and metastasis. In CRC, several PGs were found to be aberrantly expressed (*e.g.*, PGE2), and their secretion in the tumor microenvironment contributes to both

the development and progression of CRC[42]. HuR is a positive regulator of COX-2 expression through its ability to bind the COX-2 3′UTR and mediate its stabilization[24,25,30,43]. Therefore, both HuR and COX-2 are not only frequently overexpressed in colorectal tumors, but also in early adenomas and FAP[44,45]. Moreover, the binding of HuR to the 3′UTR of COX-2 prevents miR-16-dependent COX-2 downregulation[25]. Importantly, HuR indirectly induces COX-2 expression by stabilizing the mRNA transcripts of pro-inflammatory cytokines involved in the transcriptional induction of COX-2 expression (*e.g.*, TNFα)[46,47]. Finally, HuR stabilizes Inducible Nitric Oxide Synthase (iNOS) mRNA transcripts, thereby fostering nitric oxide synthesis, which is a major inflammatory mediator[48].

Cancer cell proliferation: The ability of HuR to regulate cancer cell proliferation is tightly linked to its ability to stabilize COX-2 mRNA. Indeed, PG-related signaling[40,49] can trigger various pathways that promote cancer cell proliferation, such as JAK/STAT, PI3K, MAPKs, Wnt/β-cat signaling and mTORC1 (see[50-52] for more detailed reviews). These all control the transcription of cell cycle-related genes (*e.g.*, cyclin D1, c-myc). In particular, PGE2 levels are increased in CRC, and has been associated with strong oncogenic properties[53].

HuR promotes the overexpression of several proliferation-associated genes. In particular, gene expression analysis of RKO cells (colon carcinoma cell line) displaying different levels of HuR expression revealed 26 upregulated genes when HuR is induced, including cell cycle-related genes (*e.g.*, cyclin D1, cyclin A)[54]. However, only a few of them, including TNFα, c-fos and β-catenin, were identified to be direct HuR targets. It is therefore likely that HuR controls gene expression indirectly by affecting the mRNA stability of key transcription factors. This idea is supported by the fact that HuR can stabilize PLAGL2 (Pleomorphic Adenoma Gene Like-2)[55], a transcription factor frequently overexpressed in CRC and involved in the regulation of several genes, including cyclin-D1[56]. Paradoxically, despite the numerous studies attributing a tumor-promoting function to HuR, another study has reported that HuR can bind to the 3′UTR of p53 and enhance its translation in RKO cells under stress conditions (ultraviolet light irradiation)[57].

Cell death: HuR is an important regulator of apoptosis, which stabilizes the mRNA of anti-apoptotic genes such as Bcl-2[58]. However, the role of HuR in cell death-related processes in CRC remains poorly understood. Only a few studies have shown that HuR is involved in the intrinsic apoptotic pathway by directly regulating Bcl-2 mRNA stability[56]. This effect has been associated with chemoresistance (epirubicin). Similarly, several previously reported HuR targets (in other models) involved in apoptosis (BCL2L2, XIAP, HIF1α) were found downregulated in normal/tumor tissues from intestinal-specific HuRi^{KO} mice as compared to their respective controls[34]. These *in vivo* studies suggest that these apoptosis-associated transcripts are direct HuR targets, consistent with previously reported HuR targets in other models. Moreover, HuRi^{KO} mice display decreased β-catenin expression, leading to the downregulation of target genes, including survivin[34]. This thus indicates that HuR can also inhibit apoptosis indirectly. Furthermore, HuR can also indirectly prevent apoptosis through COX-2/PG pathways (*e.g.*, PGE2), which can trigger the transcription of anti-apoptotic genes (*e.g.*, Bcl-2)[59].

In addition to its regulation of anti-apoptotic genes, HuR can also impair the expression of pro-apoptotic factors like caspases. In particular, HuR blocks IRES-dependent translation of caspase-2 by binding to its 5′UTR[60,61]. This effect confers resistance to radiotherapy in colon cancer cells (*i.e.*, DLD-1 and HCT-15 cells)[62]. Finally, HuR can also mediate chemoresistance by favoring Multidrug Resistance genes, such as ABCG2, in CRC cells[63].

Cancer cell migration/invasion: The development of CRC-derived metastasis is one of the leading causes of CRC mortality[64,65]. HuR overexpression contributes to the stabilization of various mRNAs involved in this process. For instance, HuR contributes to the regulation of lysophosphatidic acid (LPA) by controlling the regulation of a key enzyme involved in its biosynthesis, Autotaxin (ATX). LPA exerts pleiotropic functions by activating G-coupled receptors (LPA_{1-6})[66] and triggering intracellular signaling cascades that inhibit cell death and promote cell proliferation, angiogenesis[66] and cancer cell migration[67,68].

In another study, HuR was found to control HCT116 colon cancer cell migration/invasion by downregulating fibulin 3 expression[69]. The loss of fibulin 3 expression was previously reported in CRC patients, which involved the methylation of its promoter[70]. Moreover, fibulin 3 downregulation correlates with higher tumor stages and lymph node metastasis. HuR plays a critical function in fibulin 3 silencing by promoting the methylation of its promoter. This effect is mediated *via* DNMT3A

mRNA stabilization by HuR, following HuR phosphorylation by p38MAPK. Interestingly, HuR was previously reported to also stabilize DNMT3B in RKO cells[71]. Together, these findings indicate that HuR can function on an epigenetic level by regulating key genes that methylate target genes commonly repressed in CRC[72,73].

The intestinal-specific HuR KO mice (HuRi^{KO}) were also useful to identify potential HuR targets. In this regard, the expression of olfactomedin4 (Olfm4) was found highly upregulated in the small intestine and colon of HuRi^{KO}[34]. Olfm4 is frequently upregulated in human CRC tumors, and is mostly considered to be a stem cell marker involved in cancer cell proliferation and migration[74].

Other specific mechanisms have been associated with the migration-promoting effect of HuR. Claudin-1 overexpression has been tightly associated with CRC progression, invasion and metastasis[75], and HuR stabilizes the claudin-1 transcript[76]. Finally, increased PGE2 synthesis associated with COX-2 mRNA stabilization by HuR can also increase cancer cell migration/invasion through the activation of membrane receptors that promote the expansion of cancer stem cells. Furthermore, PGE2 synthesis can also inducing key regulators of migration/invasion, such as urokinase-type plasminogen activator receptor (uPAR)[42], MMP-2/9[77,78], VEGFR1[79] and VEGF[52].

Regulation of HuR expression/activity in CRC

The mechanisms involved in HuR overexpression in CRC are still unclear, but increasing evidence indicates that non-coding RNAs are involved in HuR induction. For instance, the long non-coding RNA Overexpressed in Colon Carcinoma-1 (OCC1)[80] has been involved in the regulation of HuR overexpression. OCC1 expression is decreased in CRC patients and in colon cancer cell lines, indicating it to be a negative regulator of HuR expression. In work by Lan *et al*[80], OCC1 was shown to promote HuR protein degradation by enhancing the binding of ubiquitin E3 ligase β-TrCP1 to HuR. In agreement with the role of HuR in the regulation of cell cycle-related genes, OCC1-dependent HuR downregulation leads to an arrest of cancer cells in the G0/G1 phase of the cell cycle, as well as to decreased expression of direct HuR target genes (*i.e*., eIF4E, NEK2, MAD2L1, HNRNPA1, HNRNPK).

Deregulation in microRNA expression is also associated with HuR upregulation in human cancers. Interestingly, based on the miRwalk database, more than 3000 miRs (predicted by at least three different algorithms) are predicted to target HuR mRNA in human, but only a few of them have been experimentally validated[58]. In CRC, miR-519c has been reported to downregulate HuR expression[81], leading to an overexpression of HuR targets, including the multidrug resistance gene ABCG2, and thus chemoresistance[63].

Interestingly, although microRNAs have been mostly associated with mRNA decay or translation inhibition, miR-155-5p seems to be a positive regulator of HuR expression[82]. The underlying mechanism is still unclear, but involves the binding of miR-155-5P to ARE (AUUA and AUUU) within the HuR 3′UTR. This study suggests that some miRNAs can inhibit gene expression, while others may stabilize some transcripts similar to AUBPs. This effect may depend on the binding site and/or may also result from interplay between miRNAs and stabilizing RBPs, as previously demonstrated[83].

Several post-translational modifications (*e.g*., phosphorylation) have been involved in the subcellular localization and activity of HuR (see[20] for more detailed reviews). For instance, the cytoplasmic localization of HuR is affected by kinases such as p38, cdK1, PKC and AMPK, which phosphorylate HuR at different residues[29]. In CRC, an increase in cytosolic HuR has been observed in inflamed tissue from patients with inflammatory bowel disease, early adenomas and CRC, indicating that the nuclear-cytosolic shuttling mechanisms are potentially deregulated in both CRC and preneoplastic conditions[31]. While these and other mechanisms have been well-characterized in various cancers, connecting these CRC-related post-translational alterations to HuR is under current investigation. One study has shown that the neddylation of HuR by Mdm2 contributes to its protein stabilization in hepatocellular carcinoma and CRC[84,85]. The phosphorylation of HuR at Ser318 by PKC (delta), and its cytoplasmic localization in DLD-1 colon cancer cells[86], is also involved in HuR-dependent stabilization of COX-2 mRNA. Furthermore, phosphorylation of nuclear HuR by Chk2 and p38MAPK at Ser88 and Thr118, respectively, in oxidative stress conditions is critical for the regulation of the splicing of TRA2β4, particularly by favoring exon 2 incorporation[87]. Interestingly, the silencing of p38α MAPK was also associated with decreased expression of HuR in HCT116 cells[69]. In addition, several studies have associated p38α MAPK with oncogenic properties, including the promotion of cell proliferation, migration, invasion and angiogenesis[88].

Altogether, these data indicate that increased expression/activity of HuR in CRC is most likely not the consequence of a single mechanism, but rather the concerted

deregulation of several factors during transcription, post-transcription and post-translation.

Therapeutic targeting of HuR in CRC

HuR overexpression can modulate a whole network of ONC and TS involved in the various hallmarks of cancer[89]. Therefore, targeting HuR in CRC may represent an appealing therapeutic strategy alone or in combination with existing therapeutic approaches (*i.e.*, chemotherapy, radiotherapy). Several small molecules compounds that have the capacity to block HuR/ARE interactions have been identified by high-throughput screenings[90-93], with a few of them further characterized for HuR specificity. In particular, polyketides purified from plants or microbial extracts (*i.e.*, MS-444, okicenone, dehydromutactin) have shown HuR inhibitory properties[91]. Among them, MS-444 has been further studied and displays several anti-tumor properties[94]. MS-444 is a potent inhibitor of HuR homodimerization, preventing its cytoplasmic export and the stabilization of several mRNA transcripts[94]. The anti-tumor effect of MS-444 was further observed *in vivo* in a model of inflammatory bowel disease and also in a genetic model of FAP (*i.e.*, APC^{Min} mice), but not in inflammatory colon cancer (AOM/DSS mice)[31].

Other compounds have demonstrated an ability to impede HuR expression or activity. For instance, ar-turmerone from *Curcuma longa* prevents LPS-induced translocation of HuR[95]. However, the effects observed with these molecules are not restricted to HuR and, thus, it is likely that the beneficial effects observed may also result from several HuR-independent mechanisms.

Tristetraprolin (TIS11, NUP475, GOS24)

TTP belongs to a small family of Cys-Cys-Cys-His zinc finger proteins comprised of TTP, BRF1 and BRF-2[96,97]. *Zfp36* is an immediate-early response gene[98] whose expression can be induced by diverse stimuli like insulin[98,99], TGF-β[100,101], LPS[102] and TNFα[103]. TTP is one of the best-characterized AUBPs that promote ARE-dependent mRNA decay[96,97,104]. This process is mediated by the nucleation of small cytoplasmic foci called Processing-bodies (P-bodies)[100,105,106], where targeted mRNA transcripts are bound by mRNA deadenylases, translational repressors and decapping enzymes[107-109]. Alternatively, TTP can recruit the exosome complex to degrade ARE-containing transcripts[110,111]. Finally, TTP is also involved in miRNA-dependent post-transcriptional regulation (*e.g.*, miR-16) through its binding to argonaute proteins (Ago/eiF2C). This interaction promotes complex formation with miRNAs, which allow their binding to ARE sequences[112,113].

The physiological significance of TTP is highlighted by *Zfp36* knockout mice, which develop severe inflammatory syndromes and growth retardation[114]. Moreover, TTP expression is frequently lost in human cancers, and this loss is often associated with poor clinical outcomes[115,116].

Role of TTP in CRC development

Several studies have demonstrated that TTP expression is downregulated in early adenomas and adenocarcinomas[24,117,118]. TTP is considered as a TS, whose downregulation in CRC contributes to the enhanced expression of pro-inflammatory cytokines. However, TTP is also critical to ONC and TS gene regulation. Interestingly, no significant difference was observed in the survival rate of patients with colon adenocarcinoma in TTP low-expressing versus TTP high-expressing individuals[119]. Moreover, there were no differences noted in the stage or aggressiveness of the tumors in TTP low and TTP high patients compared to other cancer types (*i.e.*, breast cancer, lung adenocarcinoma)[119]. However, it should be noted that the loss of TTP is frequently associated with an overexpression of HuR during CRC development[24], thus favoring the overexpression of their common targets. Accordingly, not only the loss of TTP, but also the concomitant induction of HuR expression should be considered in these analyses.

PG biosynthesis and inflammation: TTP plays a critical role in inflammation, since most of these targets are inflammatory mediators like TNFα[103,120,121], GM-CSF[122] and COX-2[24,123]. All of them contain AREs in their 3'UTR mRNA. Furthermore, TTP knockout mice develop a severe inflammatory syndrome characterized by cachexia, arthritis, dermatitis, inflammation and autoimmunity[114,124].

In colon epithelium, TTP is a potent inducer of COX-2 mRNA decay through its direct binding to ARE within the 3'UTR[125]. Several studies have reported the downregulation of COX-2 mRNA by TTP in various *in vitro* and *in vivo* models, as well as in human tissues[24,123]. TTP expression is silenced in CRC, and together with HuR overexpression, stabilization of the COX-2 mRNA occurs. These combined AUBP effects allow for pathological protein and PGE2 production, with the

subsequent activation of downstream signaling pathways involved in CRC development[24].

TTP is well-known for its ability to mediate the mRNA decay of pro-inflammatory cytokines, including IL-6 and TNFα[12]. However, the regulation of these cytokines by TTP in CRC is not known. Nevertheless, other pro-inflammatory cytokines seem to be regulated by TTP, such as IL-23, which plays a key role in colon cancer promotion[126]. A study performed in CT26 cells (murine colon cancer cell line) has shown that TTP can induce IL-23 mRNA decay by directly binding to the ARE present within its 3'UTR[127].

Cancer cell proliferation and cell death: The ability of TTP to promote the mRNA decay of several cell cycle-related genes, including cyclin-D1, c-myc or c-fos, is well established in various cancers[128,129]. However, the regulation of all these targets by TTP in CRC remains to be established[117]. Nonetheless, TTP can negatively control cell proliferation by promoting COX-2 mRNA decay, thus leading to decreased PG signaling (*e.g.*, PGE2)[130].

TTP also exerts negative control on tumor growth by mediating mRNA decay of the RBP Lin28[131]. Importantly, Lin28 overexpression fosters adenocarcinoma development[132] through several mechanisms, including the downregulation of let-7 miRNA[132,133]. Let-7 is a critical regulator of cell cycle-related genes (*e.g.*, c-myc)[134], and it is thus likely that the loss of TTP in CRC may indirectly contribute to the overexpression of Let-7 targets involved in cell proliferation. The role of TTP in cell proliferation and cell death was further highlighted by its induction by resveratrol in HCT116 and SNU81 cells. In this study, the induction of TTP expression was associated with a direct binding to several genes involved in apoptosis and cell cycle progression, including cIAP2, LATS2, MDM2 and E2F1[135].

Cancer cell migration, invasion: The loss of TTP in cancer is often associated with an increase in cancer cell migration and invasion. This effect has been attributed to an ability of TTP to destabilize the mRNAs of several migration-related genes such as MMP9 and uPAR[9,136]. In CRC, the relationship between these genes and TTP is not known. However, several genes promoting epithelial-to-mesenchymal transition (EMT) were reported as direct TTP targets, including ZEB1, SOX-9 and MACC1 as evidenced in colon cancer cell lines[118].

Furthermore, the loss of TTP in CRC (*e.g.*, HCT116 and SW480 cells) correlates with an increase in stemness markers (*i.e.*, Bmi-1, ALDH-1 and ABCG2)[137], thus indicating that TTP is a critical regulator of colon cancer cell differentiation. Some cell adhesion molecules (CAMs) are negatively regulated by TTP[138], and thus their overexpression following TTP loss will contribute to the establishment of a metastatic phenotype. TTP promotes the decay of Claudin-1 mRNA in human colon cancer cells through direct binding to its 3'UTR[76]. Claudin-1 overexpression has been associated with TNFα-induced EMT and cancer cell migration[139].

Paradoxically, TTP induction in colon cancer cell lines (*e.g.*, HT-29) has been involved in the inhibition of anti-tumor immunity, thereby fostering tumor growth and metastasis formation. In this study, TTP is induced by Heme Oxygenase-1 (HO-1) and mediates Intercellular Adhesion Molecule-1 (ICAM-1) mRNA decay, thus impairing leucocyte recruitment/adhesion[138,140,141]. However, these effects were observed *in vitro* and, therefore, it is still unclear whether TTP plays the same function *in vivo*. Moreover, it is not clear whether TTP binds directly to ICAM-1 mRNA.

Finally, TTP is a negative regulator of angiogenesis, as evidenced by the increased VEGF mRNA decay in TTP-overexpressing CRC cells (*i.e.*, KM12C, HT-29, SW620 and Colo320 cell lines)[117]. This effect involves the dephosphorylation of p38 MAPK by MAPK phosphatase-1, which is activated by casein kinase 2 (CK2). The dephosphorylation of p38 MAPK prevents the inhibition of TTP activity and thus promotes VEGF mRNA decay[142]. Moreover, TGFβ increases CK2 (Casein Kinase 2) activity and, consequently, increased TTP mRNA decay activity in Colo320 cells[142].

Another important role of TTP in angiogenesis has been associated with an ability to prevent K-homology splicing regulator protein (KSRP)-induced iNOS mRNA decay[48]. iNOS is a critical enzyme involved in NO synthesis, which promotes tumor angiogenesis in CRC[143]. KSRP is another AUBP that promotes iNOS mRNA decay. However, TTP interacts directly with the KSRP protein and prevents its binding to the iNOS 3'UTR in colorectal adenocarcinoma cells[48].

Regulation of TTP expression/activity in CRC and potential therapeutic strategies

Several mechanisms contribute to the silencing of TTP expression in CRC. Among them, an epigenetic mechanism involving the silencing of the transcription factor EGR1 by histone deacetylases (HDAC) has been described[144]. Accordingly, EGR1 and TTP expression could be restored in various colon cancer cell lines by HDAC

inhibitors (*i.e.*, SAHA, Trichostatin-A, sodium butyrate)[144]. In line with these findings, a study by Krishnan *et al*[145] has reported that HDAC inhibitors increase the binding of TTP to claudin-1 3'UTR in SW480 and SW620 cells. Therefore, it appeared from these studies that HDAC inhibitors represent an efficient approach to restore TTP expression. Several HDACs inhibitors have been shown to decrease cell proliferation and promote cell apoptosis in CRC[146], and are currently being used in clinical trials.

Some pathways deregulated in colon cancer, such as Wnt/β-catenin, may also contribute to TTP loss. Indeed, an inverse relationship between TTP and the TCF/β-catenin pathway has been reported in colon cancer cell lines (*i.e.*, SW480, HCT116 and SW620). Furthermore, the treatment of these cell lines with an inhibitor of this pathway (*i.e.*, FH535) was associated with an increase in TTP expression, suggesting a role for this pathway in regulating TTP expression[118].

Other mechanisms leading to the silencing of TTP expression in CRC have been described. Of note, one study demonstrated that p53 can directly activate TTP transcription in CRC cell lines following doxorubicin (DOX) treatment. Accordingly, the decreased TTP expression observed in human colonic adenocarcinoma tissues is partially linked to the loss of p53[131]

Finally, EGFR/ERK signaling has been implicated in TTP loss, since Gambogic acid from the Indian Gambodge tree induces TTP expression through the downregulation of EGFR/ERK pathway signaling[137]. Other compounds of natural origin have also been reported to induce TTP expression in colon cancer cells. In this regard, resveratrol from red grapes promotes apoptosis and inhibits both cell proliferation and metastasis by increasing TTP expression in HCT116 and SNU81 cells[135]

T Cell-Restricted Intracellular Antigen-1

TIA1 was originally identified in activated T lymphocytes, where it plays a nucleolytic role against T cell targets. TIA1 is comprised of three RRMs involved in binding to ARE in the 3'UTR of target mRNA transcripts[147,148]. TIA1 acts as a translational repressor and, during stress conditions (*i.e.*, hypoxia, oxidative stress), interacts with various co-factors (*e.g.*, TIAR) to promote the sequestration of target mRNAs into non-membranous cytoplasmic SG[149]. Therefore, target mRNAs are held translationally silenced and can re-enter translation or proceed to mRNA decay in P-bodies. This mechanism allows cancer cells to survive in stressful conditions (*e.g.*, hypoxia, oxidative stress, chemotherapy). Therefore, SG formation represents a post-cellular stress response that allows cancer cells to re-launch mRNA translation without the high-energy demand of *de novo* transcription[150]. Stress granule formation has been proposed to be a survival mechanism for cancer cells, thus suggesting that targeting SG components may represent an appealing therapeutic approach in combination with chemotherapy/targeted therapy[151,152].

Role of TIA1 in CRC development

The role of TIA1 in cancer is currently unclear. Depending on the cancer type, TIA1 behaves either as a TS or an ONC[153,154]. TIA1 possesses pleiotropic functions and, in addition to its ability to regulate mRNA translation, also contributes to the alternative mRNA splicing of various cancer factors (*e.g.*, SIRT1, CD95)[155,156]. While limited studies have been conducted to decipher the role of TIA1, TIAR and SGs in CRC, COX-2 overexpression in CRC has been associated with a deficiency of TIA1 binding to the COX-2 3'UTR[16]. This study suggests a tumor suppressive function of TIA1 in CRC, and provides further evidence that COX-2 overexpression in CRC is mediated through the deregulation of several AUBPs (*i.e.*, TTP loss, HuR overexpression). The idea of a tumor suppressive role of TIA1 is further supported by survival analysis of CRC patients, showing that high-expressing TIA1 patients display a better prognosis (TCGA/human protein atlas database). Paradoxically, TIA1 has been associated with SG assembly[157], while SG formation has been associated with chemoresistance to 5-FU in CRC cells (HT-29 and HCT-116 cells)[158]. Together, the data currently available are more in favor of a tumor suppressive role of TIA1, yet are still insufficient to fully understand the role of TIA1/TIAR/SGs function in CRC development. Thus, further studies are required to identify TIA1-regulated mRNA targets in CRC.

Regulation of TIA1 expression/activity in CRC

The mechanisms involved in TIA1 silencing are still poorly known. To date, only one study has involved the overexpression of miR-19a, which directly targets the TIA1 3'UTR in CRC tissues and cell lines[159]. Nevertheless, other miRNAs have been involved in TIA1 silencing in other cancers, such as miR-487a in gastric cancer[160]. The role of these miRNAs in TIA1 silencing remains to be investigated in the context of CRC. Moreover, many other miRNAs are potential regulators of TIA1 expression (TargetsScan analysis: http://www.targetscan.org/vert_72/), such as miR-199-3p, which is upregulated in CRC[161].

Butyrate response factor 1 (TIS11b, ERF-1, cMGI, Berg36, ZFP36L1)

The butyrate response factor 1 (BRF1) encoded by the *ZFP36L1* gene, also known as TIS11B, belongs to the ZFP36 zinc finger protein family[96,97]. The *BRF1* gene is localized on chromosome 14q22-q24[162]. Similarly to TTP, BRF1 contains a tandem zinc finger domain bearing a double zinc finger motif (Cys-Cys-Cys-His) and can target mRNAs bearing AREs to P-bodies[106]. BRF1 has mostly been associated with tumor suppressive functions[96] due to its ability to target and promote the mRNA decay of key mediators of angiogenesis (*i.e*., VEGF)[163] or apoptosis (*i.e*., cIAP2)[164]. However, information addressing its expression and role in CRC remains limited. To date, only one study has suggested that 17beta-oestradiol induces an ensemble of genes involved in apoptosis, including BRF1 in COLO205 colon cancer cells[165].

ARE/poly(U)-binding/degradation factor-1 (HNRNPD)

ARE/poly(U)-binding/degradation factor-1 (AUF1) is an RBP implicated in promoting mRNA decay[66]. Moreover, AUF1 can antagonize HuR function[166], and may thus also indirectly regulate the expression of HuR targets. Cancer studies have revealed differential expression and functions of AUF1 that is dependent on the cancer type[167-169]. In CRC, one study has reported the interplay between HuR and AUF1 in the regulation of ATX expression[66]. ATX is a key enzyme involved in the regulation of lysophosphatitic acid (LPA) synthesis, which converts lysophosphatidylcholine (LPC) into LPA. Importantly ATX is involved in cancer cell migration[170]. AUF1 promotes the decay of ATX mRNA in Colo320 cells[66], while HuR mediates its stabilization by preventing AUF1 binding.

KSRP

KSRP is a RNA-binding protein involved in mRNA stability regulation and miRNA-mediated regulation. KSRP displays pleiotropic functions, such as regulation of pre-mRNA splicing, transcription, and miRNA biogenesis/maturation[171-173]. Current studies in cancer suggest that this protein may exert a tumor suppressive function, such as in lung cancer[174]. In colon cancer, one study has shown that KSRP impairs Wnt/β-catenin signaling by directly binding to the CTNNB1 3'UTR and mediating its degradation[175]. KSRP is also a negative regulator of NO synthesis by promoting the decay of iNOS[48]. Increased NO synthesis has been associated with several oncogenic properties (*e.g*., inflammation, proliferation, migration, angiogenesis) in CRC, and the inhibitory effect of KSRP on iNOS reinforces the idea of a tumor suppressive function of KSRP. Importantly, KSRP can compete with HuR for binding to the iNOS 3'UTR in colorectal adenocarcinoma cells[176]. Moreover, the binding of KSRP to iNOS mRNA can be impaired by a direct protein-protein interaction with TTP[48]. Therefore, considering the importance of HuR and TTP in the pathophysiology of CRC, the deregulation of many ARE-containing genes may result from a complex interplay between KSRP, TTP and HuR.

CUG triplet repeat-binding protein 2 (CUGBP2)

CUGBP2 is a member of the CUGBP-ETR-3-like factors family, which is ubiquitously expressed. This protein is comprised of two N-terminal RRMs and one C-terminal RRM[177]. CUGBP2 is involved in mRNA alternative splicing, RNA editing and translation inhibition[178]. CUGBP2 is mostly considered as a TS and its expression is lost in various cancers (*e.g*., breast cancer)[179,180]. In CRC, the loss of CUGBP2 expression is mediated by PGE2 and contributes to the radiation-induced mitotic catastrophe in CRC cells[181]. Moreover, HCT-116 cells stably overexpressing CUGBP2[178] display a cell cycle arrest in G2/M and an induction of apoptosis. This effect was notably associated with the downregulation of the anti-apoptotic protein Mcl-1 through the direct binding of CUGBP2 to the 3'UTR of Mcl-1 mRNA and a blockade of its translation[178].

RNA-binding motif-containing protein 3 (RBM3)

RBM3 belongs to a family of glycine-rich RBP and is comprised of a single RRM[182]. RBM3 is a cold shock protein induced by both hypothermia as well as other cellular stresses like hypoxia[183]. RBM3 plays an important role in various cellular processes, including neural differentiation[184], cell cycle progression[185] and DNA-induced innate immune response, as evidenced in RBM3 KO mice[186]. In cancer, RBM3 is primarily considered as a proto-oncogene[187], but studies have documented the role of RBM3 in CRC. RBM3 is overexpressed in CRC and displays potent oncogenic activities, specifically by stabilizing several mRNA transcripts such as COX-2[187], IL-8 or VEGFα[185]. Accordingly, silencing of RBM3 in colon cancer cells triggers caspase-dependent apoptosis and mitotic catastrophe[185], indicating that RBM3 is essential for cancer cell growth. Moreover, overexpression of RBM3 in CRC cells is associated with stem cell characteristics through increased β-catenin signaling[188]. Paradoxically,

RBM3 expression in patients with colon cancer is associated with a better prognosis[189,190], thus suggesting a potential tumor suppressive function. These discrepancies might be explained by the fact that oncogenic functions of RBM3 were mostly demonstrated *in vitro* in colon cancer cells and thus outside of their physiological context. Moreover, the localization of the protein might be associated with its different functions, as demonstrated for HuR or TTP. However, the molecular mechanisms involved in RBM3 activity/localization are currently unknown in CRC. Taken together, these data indicate that although RBM3 has been associated with oncogenic functions in CRC, some clarifications are still required to fully establish the role of this protein *in vivo*, as well as its clinical relevance.

RNPC1

RNPC1 (encoded by the *RBM38* gene) belongs to the RRM-containing RBP family, which includes HuR and Musashi proteins[191]. RBM38 is located on chromosome 20q13[192] and is expressed in several tissues (including breast, colorectal, lung, skin and ovarian tissue)[193]. RNPC1 plays an important role in the regulation of various biological processes, including cell proliferation, cell cycle and myogenic differentiation[193]. Deregulation of RNPC1 expression/activity was reported in a variety of malignancies, such as prostate[193], ovarian[194], esophageal adenocarcinoma[195] and breast cancer[196]. Mice deficient for RNPC1 display accelerated aging and spontaneous tumor development[197]. However, depending on the cancer type, this protein may perform oncogenic or tumor suppressive functions[192,198-200]. In CRC, this protein is a potent inhibitor of p53 translation through its binding to TP53 3'UTR[201], thus suggesting an oncogenic function. This effect can be inhibited by phosphorylation of RNPC1 by GSK3 at serine 195. Moreover, RNPC1 promotes the translation of the p53-inactivating phosphatase Protein Phosphatase, Mg2+/Mn2+ Dependent 1D (PPM1D), which in turn dephosphorylates RNPC1 at serine 195, thus creating a positive feedback loop that impairs p53 translation.

CONCLUSION

In this review, we summarized the current knowledge related to AUBPs in CRC development and progression. Current studies indicate that these proteins are critical not only for the post-transcriptional control of key inflammatory genes, but also for *ONC* and *TS* genes (Figure 1). Importantly, these findings highlight the role post-transcriptional regulation of these genes plays in influencing major oncogenic pathways associated with CRC (Figure 2). Therefore, early alterations of AUBP expression/activity observed in preneoplastic conditions may provide some clues to better understand the development of neoplastic phenotypes and ultimately serve as biomarkers of early-stage CRC. While most studies have focused on the roles of HuR and TTP in CRC, further research will expand our knowledge of the roles of other AUBPs in CRC etiology and in many other cancers. The development of suitable *in vivo* models will be an indispensable tool to understand the role of these factors in tumor progression. Finally, these proteins may represent appealing therapeutic targets for the treatment of CRC due to their pleiotropic functions influencing the various hallmarks of cancer, as evidenced by small molecule targeting of HuR (Figure 2).

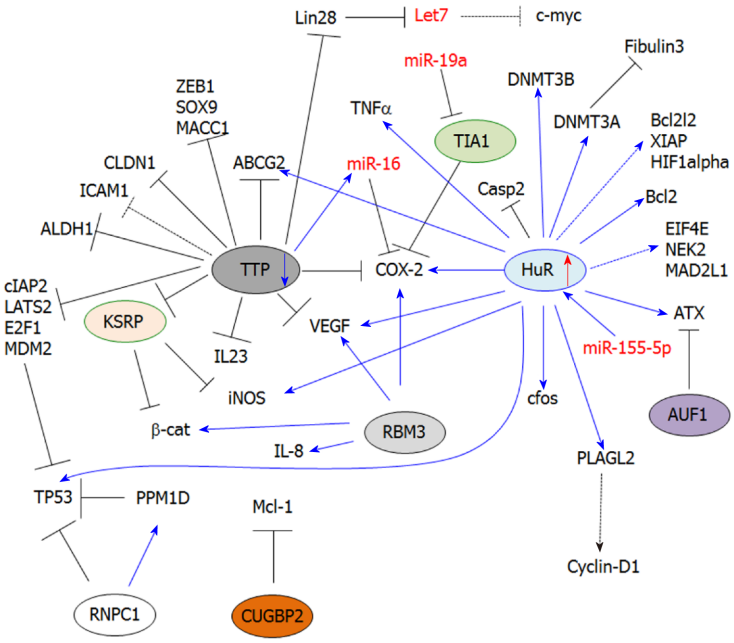

Figure 1 Network of deregulated adenylate-uridylate-rich elements binding proteins and their targets in colorectal cancer. Adenylate-uridylate-rich elements binding proteins (AUBPs) regulate a large variety of mRNA transcripts involved in cell proliferation, cell death, cancer cell migration, angiogenesis and inflammation at the post-transcriptional level. Some AUBPs interact with each other or compete for the same targets, thus forming a complex network involved in colorectal cancer development. Blue lines indicate positive regulation. Black lines indicate negative regulation. Dashed lines indicate a potential link. microRNAs are represented in red. ABCG2: ATP Binding cassette subfamily G member 2; ALDH1: Aldehyde dehydrogenase 1; ATX: Autotaxin; β-cat: Beta-catenin; BCL2: B-cell lymphoma 2; Bcl2l2: BCL2 like 2; Casp2: Caspase-2; CLDN1: Claudin-1; cIAP2: Cellular inhibitor of apoptosis 2; COX-2: Cyclooxygenase-2; DNMT3a: DNA methyl-transferase 3a; DNMT3b: DNA methyl-transferase 3b; E2F1: E2F transcription factor 1; HIF1a: Hypoxia inducible factor alpha; ICAM1: Intercellular adhesion molecule 1; IL (1β, 6, 23): Interleukins 1β, 6, 23; iNOS: Inducible nitric oxide synthase; LATS: Large tumor suppressor kinase; MACC1: Metastasis associated in colon cancer 1; Mad2L: Mitotic arrest deficient 2 like 1; MDM2: Mouse double minute 2; miR: MicroRNA; NEK2: Nima related kinase 2; PLAGL2: Pleomorphorphic adenoma gene-like 2; PPM1D: Protein phosphatase 1D; SOX9: SRY Box 9; TNFα: Tumor necrosis factor alpha; TP53: Tumor protein 53; VEGF: Vascular endothelium growth factor. XIAP: X-linked inhibitor of apoptosis; Zeb1: Zinc finger E-box binding homeobox 1.

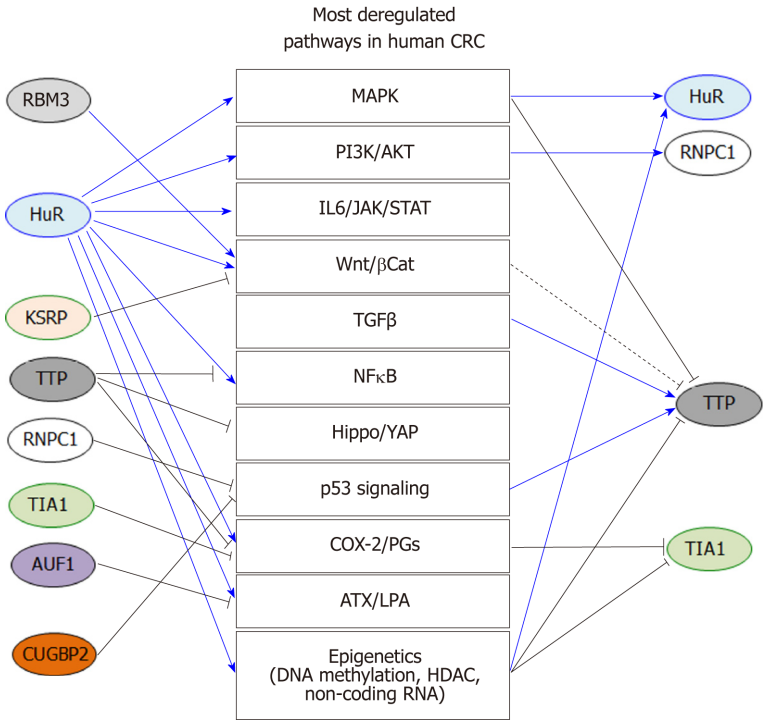

Figure 2 Adenylate-uridylate-rich elements binding proteins are critical regulators of colorectal cancer-associated pathways. Deregulated pathways associated with colorectal cancer development can be regulated by adenylate-uridylate-rich elements binding proteins. Conversely, these pathways can also influence the expression and activity of these proteins. Blue lines indicate positive regulation. Black lines indicate negative regulation. Dashed lines indicate a potential link. AKT: Protein kinase B; ATX: Autotaxin; β-cat: Beta-catenin; COX-2: Cyclooxygenase-2; HDAC: Histone deacetylase; IL6: Interleukin-6; JAK: Janus kinase; LPA: Lysophosphatidic acid; MAPK: Mitogen-activated protein kinase; NFκB: Nuclear factor kappa B; PGs: Prostaglandins; PI3K: Phosphoinositide 3-Kinase; STAT: Signal

transducer and activator of transcription; TGFβ: Transforming growth factor beta; YAP: Yes-associated protein.

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