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Review

RNA-binding proteins, multifaceted translational regulators in cancer ☆

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ABSTRACT

RNA-binding proteins (RBPs) orchestrate transcript fate and function. Even though alterations in post-transcriptional events contribute to key steps of tumor initiation and progression, RBP-mediated control has remained relatively unexplored in cancer. Here, we discuss examples of this promising field focusing on translation regulation, and highlight the variety of molecular mechanisms by which RBPs impinge on translation with consequences for tumorigenesis. This article is part of a Special Issue entitled: Translation and Cancer.

1. Introduction

RNA-binding proteins (RBPs) coordinate the life of mRNAs, from birth in the nucleus to death in the cytoplasm. As soon as the message is transcribed, RBPs associate with the nascent transcript to form highly dynamic ribonucleoprotein (RNP) complexes whose changing composition determines how the transcript is processed, whether and where it is localized, and when or with which efficiency it is translated or degraded [1].

Until recently, the number of classical RBPs in the human genome ranged in the 400's. Recent studies, however, have revealed hundreds of new RBPs in human and non-human cells [2–5]. Many RBPs in the cell repertoire contain multiple RNA-binding domains (RBDs), but surprisingly many lack canonical RBDs. A large proportion contains low complexity, intrinsically disordered regions that may serve to bind RNA in an adaptable manner [3]. Together with evidence that proteins containing general RBDs may cooperate to generate new RNA-binding specificities [6], these observations highlight the potential of RBPs for versatile and combinatorial RNA recognition. RBPs can modulate the accessibility of the mRNA to core machineries that perform essential tasks in RNA metabolism (spliceosome, ribosome, etc.) or to non-coding RNAs (e.g. miRNAs). RBPs and miRNAs are thought to form complex post-transcriptional regulatory networks that coordinate cellular homeostasis. For example, transcripts encoding factors that belong to the same pathway have been found co-regulated by similar RBPs, constituting "RNA regulons" [7]. Several of the newly identified RBPs are enzymes of the intermediary metabolism, raising the possibility of an intimate connection between metabolism and RNA regulation which has been referred to as the "REM" (RNA–enzyme–metabolite) hypothesis of gene expression [8]. A prime example of the "REM" principle is IRP1, which in iron-replete conditions functions as the cytoplasmic aconitase, while in iron-starved cells it binds and regulates mRNAs involved in iron homeostasis [9,10]. Although a role in RNA regulation remains to be proven for most of the newly identified "REM" enzymes, direct connections between metabolism, mRNA translation and cancer are emerging. Translational control of a rate-limiting enzyme of the nucleotide biosynthesis pathway, PRPS2 (phosphoribosyl pyrophosphate synthetase 2), links protein and nucleotide synthesis in Myc-driven cancers and is essential for tumorigenesis [11]. RNA-binding kinases and ubiquitin ligases are also found in the new RBP atlas, suggesting that in addition to code for proteins, mRNAs may serve to modulate protein activity or may guide the function of these factors in *cis*.

Given the central role of RBPs in the regulation of gene expression, it comes as no surprise that RBP malfunction, or mutations in the RNA elements they recognize, can lead to disease, including cancer [12–15]. Alterations in RBP expression have been reported in numerous cancer types [16]. Although RBPs can bind along the message, most regulatory elements described to date are located in the 5′ or 3′ untranslated regions (UTRs). Alternative UTRs generated by differential RNA processing modify the capacity of transcript isoforms to be recognized by RBPs and generate regulatory diversity [17,18]. Shortening of the 3′ UTR through alternative polyadenylation leads to the appearance of mRNA isoforms that have lost regulatory sites for RBPs and miRNAs, and is potentially associated with increased proliferation and enhanced tumorigenesis [19–22]. Whether alternative polyadenylation of a few selected transcripts contributes to certain types of tumors or whether

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global alternative polyadenylation plays a role is a matter of debate [23]. Thus, a fine balance between RBPs, miRNAs and target mRNAs must be kept in healthy cells.

In this review we focus on RBPs that contribute to cancer progression through regulation of translation. Highly proliferating cancerous cells require increased protein synthesis, and hyper-activation of components of the translational apparatus is linked, sometimes in a causal manner, to cancer (reviewed in [24–26]). The cancerous properties of translation factors and miRNAs are extensively addressed in other chapters of this volume. Here, we concentrate on RBPs that are not integral constituents of the translational machinery but play key roles in translational control. We focus on three representative examples that contribute to tumor progression via different molecular mechanisms: the RBPs HuR, CPEB and La. None of these proteins are frequently mutated in cancer, holding a maximum mutation rate of 5–8% according to the cBioPortal database ([27]; http://www.cbioportal.org/public-portal). However, their altered expression or aberrant activation facilitates tumor-specific reprogramming of gene expression. Work featuring regulation by RBPs at other steps of gene expression and their contribution to cancer has been reviewed elsewhere [28–30].

2. HuR: a versatile modulator of translation

Cancer is characterized by a series of hallmarks acquired during the complex multistep process of tumoral development. These include sustained proliferation, evasion from growth suppression, acquisition of replicative immortality, resistance to cell death, metabolic reprogramming, escape from immune destruction, induction of angiogenesis, invasion and metastasis [31]. HuR, through post-transcriptional regulation, has been implicated in many of these traits [32,50] (Fig. 1).

HuR is a member of the human embryonic lethal abnormal vision (ELAV) family of proteins, originally identified in *Drosophila* to be essential for neural development. While other members of this family (HuB, HuC and HuD) are restricted to neuronal tissues, HuR is ubiquitously expressed, and regulates a myriad of transcripts at the levels of mRNA stability and translation. Many of these transcripts encode important effectors of tumorigenesis such as tumor suppressors (TP53, p21, p27), oncogenes (c-fos, c-Myc), cyclins (A, B1, D1), growth factors (VEGF, TGFβ, TNFα) and apoptosis-related factors (Bcl-2, Mcl-1), among others. In fact, HuR has been regarded as a "regulator of regulators", as it binds and regulates multiple other transcripts encoding RBPs [33–36].

In resting cells, HuR is predominantly nuclear. However, upon stimuli HuR translocates to the cytoplasm where it regulates transcripts containing U- or AU-rich elements (ARE) in the 3′ UTR. HuR can also bind to the 5′ UTR of some mRNAs, or to introns with a preference upstream of 3′ splice sites suggesting roles in pre-mRNA processing [34,35]. Consistent with its predominant cytoplasmic functions, cytoplasmic localization or over-expression of HuR is associated with a wide array of cancer types [32]. In addition to its localization, HuR modifications can regulate its capacity to bind RNA in cancer cells [37,38].

Originally, HuR was described to be an mRNA stabilizing factor, and this seems to remain its primary function. The mechanisms of mRNA stabilization are thought to rely on the ability of HuR to interfere with the function/binding of destabilizing ARE-binding proteins or miRNAs [39]. More recent data indicate that HuR is also a *bonafide* translation regulator. Modulation of miRNA binding lies at the basis of some of the translation regulatory activities of this protein. For example, hepatocarcinoma Huh7 cells under amino acid deprivation experience an increase in the translation of cationic amino acid transporter (CAT)-1 mRNA without concomitant changes in CAT-1 mRNA levels. Here, HuR relieves CAT-1 mRNA from miR-122 mediated repression

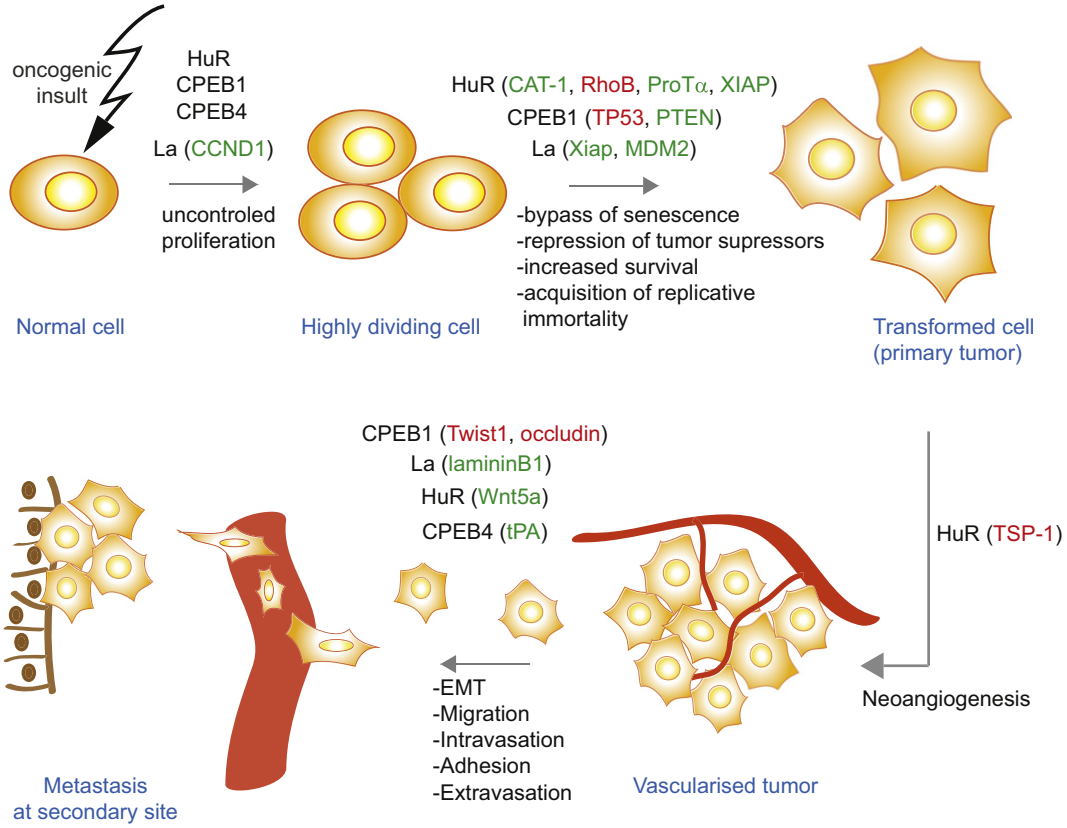

Fig. 1. Translational control of tumor formation. A schematic representation of the tumoral process is shown, where the acquisition of cancer traits is indicated. The RNA-binding proteins and targets discussed in this review are highlighted. Translation regulatory events that impede or promote the step are indicated in red or green, respectively (see text for details). HuR has been shown to regulate proliferation at the level of mRNA stability; see Abdelmohsen and Gorospe [50] for a more comprehensive list of HuR targets. CPEB1 and CPEB4 also promote cell proliferation; a more complete list of CPEB targets can be found at Fernández-Miranda and Méndez 2012 [56]. EMT, epithelial-to-mesenchymal transition.