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The many facets of RNA binding protein HuR

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RNA binding proteins (RBPs) are the best regulator in determining the fate of mRNA that plays an important role in numerous cellular functions. RBPs are present in either the cytoplasm or nucleus or in both places of the cell. Due to its importance in the biological functions, numerous new findings have been recently revealed about RBPs. The interaction of the RBPs begins with mRNA transcription and remains bound permanently or transiently to the mRNA, and it regulates the splicing, processing, transport and localization of RNA. The regulation of gene expression occurs at multiple levels, including transcription, mRNA stability and translation. HuR is one of the well-characterized RBPs; it primarily stabilizes mRNAs and is also known as RNA stabilizing protein (RSP). HuR was first described in Drosophila as being in the embryonic lethal abnormal vision (ELAV) family of Hu proteins, which comprise the human antigen R (HuR or HuA), HuB, HuC and HuD [1]. Among these, HuB, HuC and HuD are predominantly expressed in the nervous system and are also called as neuronal Hu proteins [2].

The modulation of the biosynthetic regulation of HuR protein is the key step in developing new strategies in order to treat various diseases, including cardiac diseases. The mRNA itself contains sequence specific information that determines the stability. It is now well established that the key elements that influence the mRNA stability and translational regulations are the turnover and translation regulatory RNA binding proteins (TTR-RBPs) and noncoding RNAs such as micro RNAs (miRNAs), long noncoding RNAs (lncRNAs), small nucleolar RNAs (snoRNAs), small cajal body specific RNAs (scaRNAs) and circular RNAs (circRNAs) of labile genes [3]. This regulation is mediated by the three categories (class 1, 2, and 3) of AU-rich elements (AREs) located in the 3′ untranslated region (UTR), but HuR is also found to interact with U- and AU-rich sequences in the 5′UTR of the target genes [2]. Most RSPs have multiple RNA targets, and it is extremely challenging to discover the mechanism behind their functions [4]. Characteristically, RSPs bind to ARE sequence

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elements on the 3′ and/or 5′ UTR region of the mRNA, which in turn leads to the stabilization or destabilization of the target transcripts.

In this issue of Trends in Cardiovascular Medicine, the review by Babu et al [5

HuR regulates the mRNA expression that encodes proteins that are involved in cellular proliferation, differentiation, inflammation, angiogenesis, signaling oxidative damage and hypoxia [10, 11]. HuR proteins were the best-known RSP; it has been shown to modulate the protein expression of target genes. Moreover, the HuR protein acts as an enhancer or sometimes repressor of the translation of genes [1, 6]. Srikantan and Gorospe [2] recently reviewed the diverse function of HuR in stabilizing a large subset of target mRNAs, which encode proteins at different pathological conditions.

In cancer cells, HuR promotes the expression of several cyclins and other factors that lead to uncontrolled cell growth [12]. HuR also promotes the expression of numerous pro-survival mRNAs in various tumors [6]. Thus, HuR interacts with many mRNA encoding cancer and regulates its protein expression. All the cancers examined so far suggest that HuR could be a useful marker for cancer diagnosis.

Ischemic heart disease resulting in loss or dysfunction of cardiomyocytes (CMCs) is the leading cause of death worldwide with over 5 million cases in the United States alone [13]. The survivors of acute myocardial infarction (MI) eventually develop chronic heart failure [14]. Recent studies and the review by Babu et al. showed that RSPs play an important regulatory role in various pathophysiological processes, including myocardial ischemia, fibrosis, angiogenesis, cell-death, proliferation and cellular metabolism [5]. Therefore, RSPs are the key deciding molecules that drive cells into a normal or diseased state. In a mouse model of myocardial infarction, the expression of HuR was up regulated with increased inflammatory response and cardiomyocytes cell death, leading to cardiac dysfunction and remodeling [15]. Compelling evidence for the direct role of noncoding RNAs is associated with several genes that are important for normal cardiac development. The HuR knockdown attenuated post-MI inflammatory response and left ventricular dysfunction, and it also identified the critical role of HuR and miRNAs in cardiac pathology [11]. Moreover, HuR knockdown attenuated fibrosis and improved cardiac function and remodeling after heart failure. HuR is important for the pathogenesis of fibrosis development.

The results from deletion and overexpression of RSP studies suggest that these RSP, including HuR, are pathological markers, which could be used as diagnostic clues to detect disease processes. A recent study has shown the synergistic induction of cyclooxygenase-2 (COX-2) by Angiotensin II (AngII) and interleukin 1β (IL-1β) in VSMC involves HuR through an ERK1/2-dependent mechanism. The HuR/COX-2 axis participates in cell migration and vascular damage. This study also suggests that HuR might be a novel target to modulate vascular remodeling in cardiovascular diseases [16]. Ischemia induced cardiomyocytes loss plays a prominent role in the pathophysiology of cardiac remodeling after MI. Ischemia stimulates p53 (a well-known proapoptotic factor), which in turn leads to the apoptosis of cardiomyocytes, including myocytes both in vivo (MI) and in vitro. Interestingly, HuR regulates a group of angiogenic factors and promotes angiogenesis [17].

All these HuR regulated angiogenic factors are required in a functional vasculature formation and for a recovery from ischemia in regenerative medicine. It is also noted that these processes are reversed in tumor angiogenesis where the implication depends on the blocking of the HuR.

The regulatory role of miRNAs, lncRNs, snoRNAs, scaRNAs and circRNAs and the understanding of their biosynthesis and the interaction with RBP during mRNA degradation or stability, might impact disease pathogenesis. Due to their involvement in these cellular processes, their expression and function are tightly regulated through several mechanisms. Intriguingly, these mechanisms could serve as molecular targets in limiting diseases or for therapeutic purposes. Several studies have been performed to establish the prognostic effects of HuR in cancer patients but the prognostic values of HuR in the cardiovascular pathologies are poorly explored. Therefore, further studies will be needed for a better understanding of the role of RSPs in cardiovascular diseases.

Recently, the transcriptional networks governing and maintaining the ground-state pluripotent stem cells have been intensively characterized. The understanding of the combined regulatory networks at the DNA and RNA levels during reprogramming of somatic cells into induced pluripotent stem cells (iPSCs) at the translational level is just the beginning of what is to be revealed. A study from mouse embryonic stem cells (mESCs), out of 555 proteins constituting the mRNA interactome, 283 proteins were not previously annotated as RBPs. Of those, 68 new RBP candidates are highly expressed in mESCs compared to differentiated cells, implicating a role in stem-cell physiology [18]. To know the clinical importance of this study, further studies are needed to examine the role of RBPs in human ESCs as well as induced pluripotent stem cells (iPSCs). Recently, we identified that the success of generating human iPSCs from somatic cells depends on the levels of HuR proteins present in the parent cell that is to be reprogrammed. The parent cells that have greater amounts of HuR protein are likely to be more susceptible for reprogramming than the other cells by using mRNA reprogramming (unpublished data). These findings suggest the importance of HuR during the reprogramming of somatic cells and the establishment of iPSCs. The HuR protein has a dual role, and their functions depend up on the cell types. When the cells undergo stress or insult by antigens, these cells produce high levels of HuR, which may produce inflammatory and proapoptotic stimuli, which lead to cell apoptosis. In cancer cells, HuR induces proliferation and angiogenesis, which leads to tumor formation, whereas high level of HuR is beneficial for an efficient reprogramming of somatic cells and maintaining of pluripotency of iPSCs.

Growing evidence suggests that HuR, in association with other RBPs, might play an important role in vertebrate cardiovascular development. However, RBPs in the field of cardiovascular disease development and stem cells, which is currently in its infancy, has several, unanswered questions and challenges that still to be addressed. Some of the issues remaining are (i) How systematically to analyze HuR and their targets at different stages of diseases? (ii) What are the signaling pathways targeted by HuR during development? (iii) How can the therapeutic potential of HuR be improved? (iv) Does the HuR present in the residential stem cells have any beneficial effects? In the past few years, there have been many studies that aim to understand the mechanism and signaling pathways of HuR in

cardiovascular diseases. However, the currently available data suggest that HuR might be a novel and promising therapeutic target and a marker for treatment response and prognostic evaluation.

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