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Review

RNA binding proteins in the regulation of heart development

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ABSTRACT

In vivo, RNA molecules are constantly accompanied by RNA binding proteins (RBPs), which are intimately involved in every step of RNA biology, including transcription, editing, splicing, transport and localization, stability, and translation. RBPs therefore have opportunities to shape gene expression at multiple levels. This capacity is particularly important during development, when dynamic chemical and physical changes give rise to complex organs and tissues. This review discusses RBPs in the context of heart development. Since the targets and functions of most RBPs — in the heart and at large — are not fully understood, this review focuses on the expression and roles of RBPs that have been implicated in specific stages of heart development or developmental pathology. RBPs are involved in nearly every stage of cardiogenesis, including the formation, morphogenesis, and maturation of the heart. A fuller understanding of the roles and substrates of these proteins could ultimately provide attractive targets for the design of therapies for congenital heart defects, cardiovascular disease, or cardiac tissue repair.

Contents

Abbreviations: 3′ UTR, 3′ untranslated region; AVC, atrioventricular canal; CELF, CUG-BP* Elav-like family; CHAMP, cardiac helicase activated by MEF2 protein; Csm, cardiac-specific isoform of Mov10l1; DGCR8, DiGeorge Syndrome critical region gene 8; DM, dystrophia myotonica (myotonic dystrophy); DGS, DiGeorge Syndrome; EMT, epithelial-to-mesenchymal transition; ESRP, epithelial splicing regulatory protein; FXR1, fragile X mental retardation autosomal homolog 1; HERMES, heart and RRM expressed sequence; hnRNP, heterogeneous nuclear ribonucleoprotein; how, held out wings; KH domain, hnRNP K homology domain; MBNL, muscleblind-like; MET, mesenchymal-to-epithelial transition; miRNA, microRNA; OFT, outflow tract; PTB, polypyrimidine tract binding protein; RBFOX, RNA binding Fox-1 homolog; RBM, RNA binding motif; RBP, RNA binding protein; RISC, RNA-induced silencing complex; RRM, RNA recognition motif; RS domain, arginine/serine-rich domain; SRSF, serine/arginine-rich splicing factor; STAR, signal transduction and activation of RNA.

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1. Introduction

Growing interest in the functional repertoire of RNA binding proteins (RBPs) has emerged as their potential to regulate gene expression has become more broadly appreciated. While the old paradigm of gene expression focused on the activation of transcriptional programs by DNA binding proteins, the roles of RBPs in post-transcriptional regulation have recently been given greater scrutiny. Post-transcriptional regulatory mechanisms have been identified at all levels of the life cycle of a transcript: regulation of pre-mRNA alternative splicing (Kelemen et al., 2013), mRNA editing (Chateigner-Boutin and Small, 2011), transcript stability (Schoenberg and Maquat, 2012), transcript localization (transport and sequestration) (Medioni et al., 2012), and regulation of translation (Kong and Lasko, 2012). RBPs are involved in the regulation of each of these processes [for an overview see (Glisovic et al., 2008)]; some specific examples are illustrated in Fig. 1. Some of these functions are nuclear, while others are cytoplasmic, or take place within other organelles such as mitochondria. There are several different types of RNA binding domains, which divide RBPs into structurally distinct families. While many employ beta sheets as interaction surfaces to interface with client transcripts and utilize aromatic residues and base stacking interactions to achieve recognition of targets, a detailed understanding of the binding properties of many RBPs remain to be elucidated (Lunde et al., 2007). While their RNA binding domains can help catalog these proteins, RBP families are not characterized by unified functions. Individual RBPs may perform several functions within the same cell, and may have different functions in different cell types. The ability of RBPs to circumvent the transcription machinery allows them to quickly and selectively fine-tune expression, and this capacity has been recognized as especially important in developmental and pathological systems (Masuda et al., 2009; Misquitta et al., 2001; Siomi and Dreyfuss, 1997). For example, during early zygotic development, when maternal transcripts are translated but the transcription machinery is silent, RBPs provide robust mechanisms for regulating gene expression to direct processes such as pattern formation and cell-type specification (Lee and Schedl, 2006).

The post-transcriptional regulation of gene expression by RBPs during development also has evolutionary consequences. Because of their generally small size and ability to rely on diffusion for tissue oxygenation, many invertebrate species lack a defined circulatory system. The invertebrate heart is typically a simple, beating tube or sac that moves fluid through the body via peristaltic contractions. Vertebrates, on the other hand, have closed circulatory systems with multi-chambered hearts. It has been proposed that vertebrates exhibit a greater degree of cellular and organismal complexity than invertebrates due in large part to expansion of the transcriptome (without proportional expansion of the genome) via an increase in alternative RNA processing, particularly pre-mRNA alternative splicing (Ast, 2004; Maniatis and Tasic, 2002). Consistent with this, several RBP families involved in alternative splicing regulation are differentially expanded in vertebrates compared to invertebrates, whereas basal splicing machinery proteins are generally invariant among all eukaryotes (Barbosa-Morais et al., 2006; Pascual et al., 2006).

The development of the heart is a complex and finely orchestrated process. RBPs have been shown to be involved in nearly every step of heart development, from the establishment of cardiac lineages to the maturation of the heart after birth (Fig. 2). In addition,

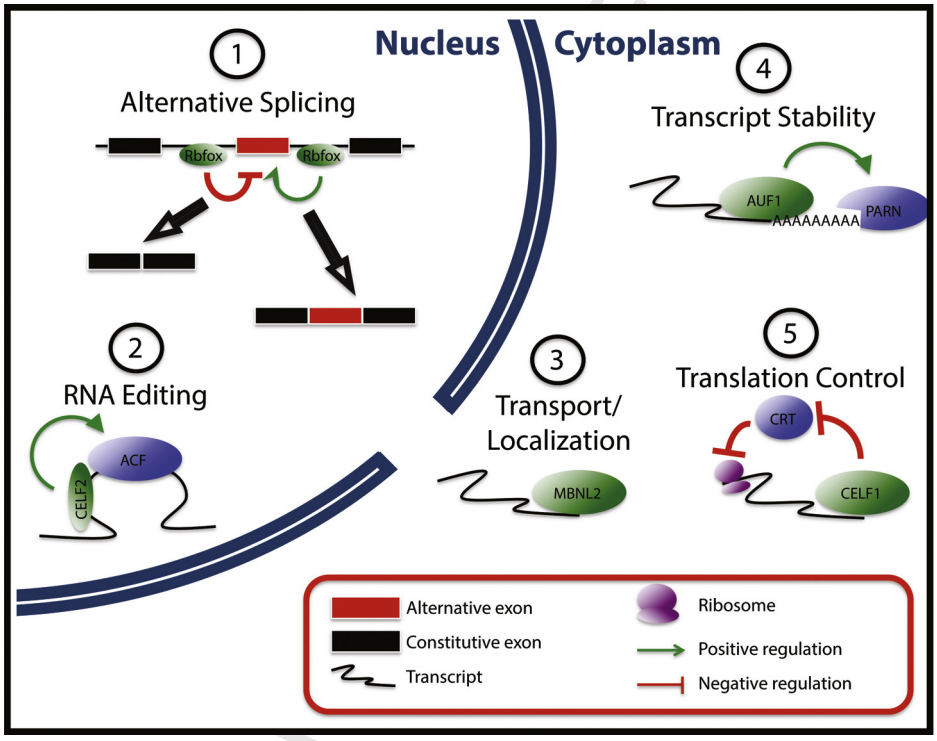

Fig. 1. Mechanisms of RBP-mediated post-transcriptional regulation. Schematic representations of mechanisms by which a number of proteins described in this review have been shown to regulate gene expression. Note that these are provided as examples; an exhaustive survey of RBP-mediated regulatory mechanisms is beyond the scope of this review. (1) RBFOX proteins regulate a variety of alternative splicing events by binding within introns flanking alternative exons. Binding upstream of an exon leads to skipping of that exon, while binding downstream of an exon leads to its inclusion (De Craene and Berx, 2013). (2) CELF2 directs the editing of a cytidine in the *Apob* transcript by binding to an AU-rich sequence element upstream of the editing site and recruiting ACF, a component of the editing machinery (Anant et al., 2001). (3) MBNL2 regulates the transport and localization of the *Itga2* transcript to the plasma membrane by binding to a zipcode sequence in the 3′ UTR of the transcript (Adereth et al., 2005). (4) Multiple mechanisms have been proposed for how AUF1 regulates the stability of target transcripts, including the recruitment of the PARN deadenylase, leading to loss of the poly-A tail and rapid degradation of the RNA (White et al., 2013). (5) CELF1 enhances translation of the *p21* transcript by antagonizing a regulatory protein, CRT, which normally blocks ribosome loading (Iakova et al., 2004).

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