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RBMX family proteins connect the fields of nuclear RNA processing, disease and sex chromosome biology

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ABSTRACT

RBMX is a ubiquitously expressed nuclear RNA binding protein that is encoded by a gene on the X chromosome. RBMX belongs to a small protein family with additional members encoded by paralogs on the mammalian Y chromosome and other chromosomes. These RNA binding proteins are important for normal development, and also implicated in cancer and viral infection. At the molecular level RBMX family proteins contribute to splicing control, transcription and genome integrity. Establishing what endogenous genes and pathways are controlled by RBMX and its paralogs will have important implications for understanding chromosome biology, DNA repair and mammalian development. Here we review what is known about this family of RNA binding proteins, and identify important current questions about their functions.

1. Introduction

RBMX (an acronym of RNA Binding Motif protein, X-linked) was originally identified as one of a functionally diverse group of nuclear proteins that bind to polyadenylated RNA. This group of proteins are collectively called the heterogeneous nuclear ribonucleoproteins (hnRNPs) (Geuens et al., 2016). RBMX is a 43KDa nuclear protein with an N-terminal RNA recognition motif (RRM) (Fig. 1). RBMX is subject to modification by O-linked glycosylation, and was identified as a target for autoantibody production in a dog with a lupus-like syndrome (Soulard et al., 1993).

2. RBMX is encoded by an X chromosome gene

RBMX was initially (and sometimes still is) called hnRNP G (heterogeneous nuclear ribonucleoprotein G). Fluorescence in situ hybridisation experiments originally mapped the gene encoding hnRNP G to human chromosome 6 (Le Coniat et al., 1992). This chromosome 6 gene was subsequently shown to be a non-functional pseudogene (since it does not contain a full open reading frame). A gene containing the full predicted open reading frame for hnRNP G protein was then mapped to the X chromosome of humans and mice (Delbridge et al., 1999; Mazeyrat et al., 1999). Because of its X chromosome location, this latter gene was called *RBMX*, and its encoded protein RBMX.

An *RBMX* gene is found on all mammalian X chromosomes. There is a similar gene on the mammalian Y chromosome called *RBMY* (Ma et al., 1993). While *RBMX* is expressed ubiquitously through the body, *RBMY* genes are specifically expressed in germ cells (cells that eventually develop into sperm). Multiple *RBMY* genes are present on the long arm of the human Y chromosome, each encoding 496 amino acid RBMY proteins that are 99% identical to each other. These individual human *RBMY* genes have been annotated as *RBMY1A1*, *RBMY1B*, *RBMY1D*, *RBMY1E*, *RBMY1F* and *RBMY1J*. Large deletions of the Y chromosome remove *RBMY* genes from some infertile men (Ma et al., 1993; Elliott et al., 1997). This has implicated RBMY with a role in spermatogenesis.

Studies of the evolution of the X and Y chromosomes suggest that *RBMX* and *RBMY* were amongst the earliest recruits to the sex chromosomes over 130 million years ago (Fig. 2) (Lahn and Page, 1999). This means that an *RBMX* progenitor gene is likely to have even been present on the original autosome that evolved into the mammalian sex chromosomes. Vertebrates like zebrafish still have autosomal *RBMX* genes. There is evidence of recombination between *RBMX/Y* before the evolutionary split between humans and cattle (Peneder et al., 2017). The fact that *RBMY* has survived the decay of the Y chromosome, where only 3% of ancestral genes have survived, suggests that *RBMY* has an important role in male viability (Bellott et al., 2014). Human *RBMX* and *RBMY* now show 28% divergence at the nucleotide level and 38% divergence at the protein level (Lahn and Page, 1999).

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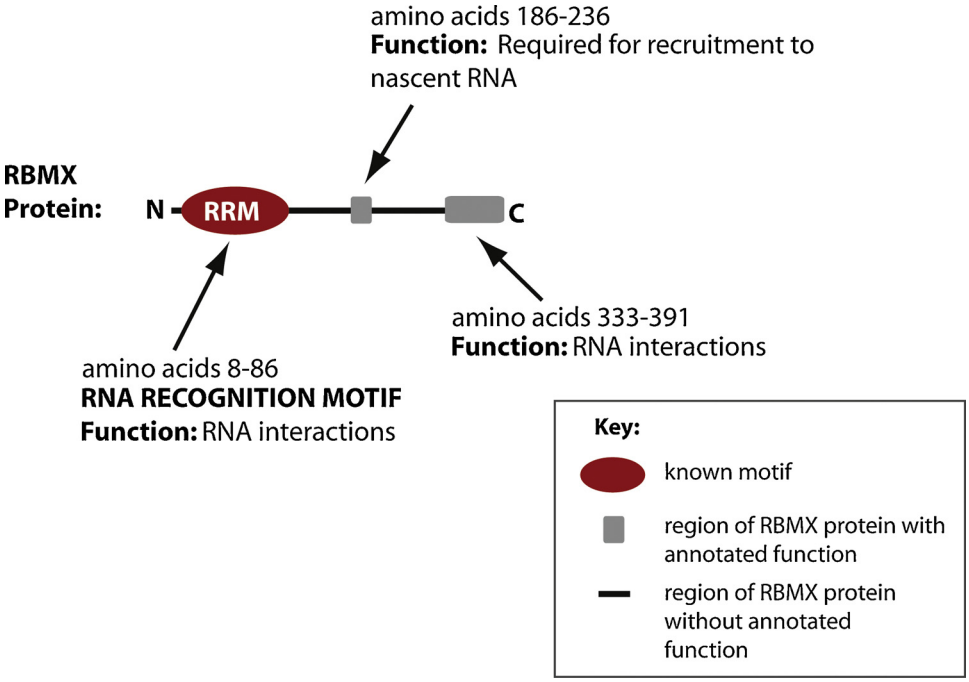

Fig. 1. Structure of RBMX protein. The RRM (an acronym of RNA Recognition Motif) is an ancient domain that binds to RNA, and is predicted by sequence. The protein interaction domain and C-terminal RNA binding domain were functionally identified using ectopic expression experiments in the newt *Pleurodeles waltl* (see text for details).

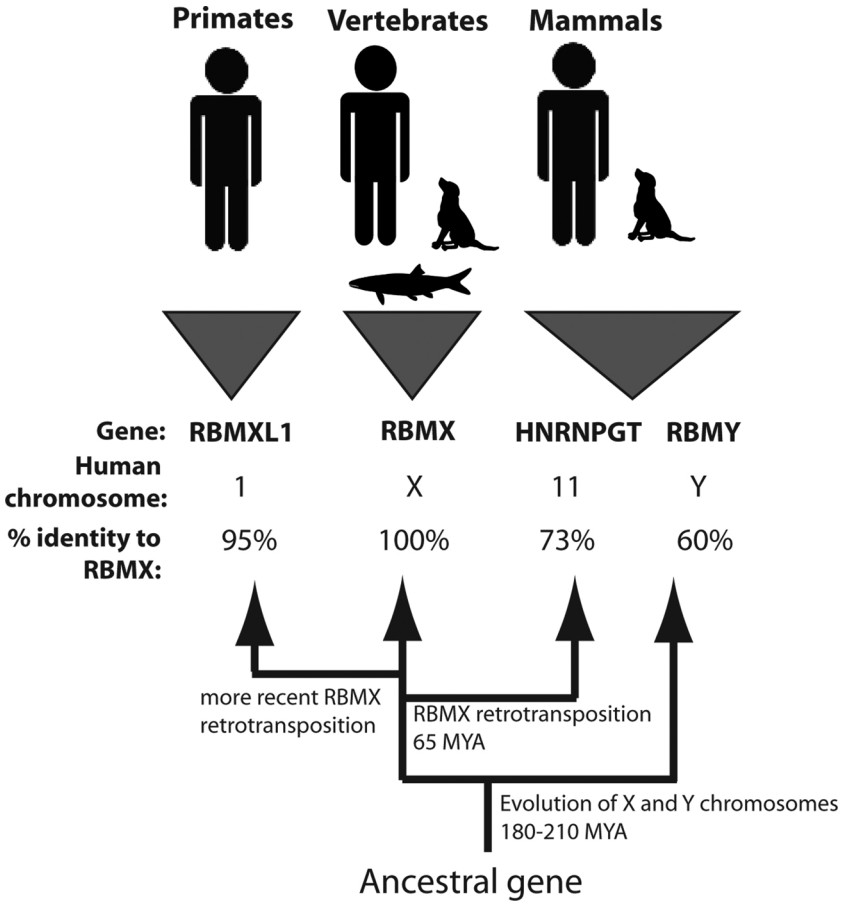

Fig. 2. Cladogram of the *RBMX* family. The *RBMX* gene is X linked in mammals, and autosomal in other vertebrates. *RBMX* and *RBMY* genes evolved with the X and Y chromosomes. Retrogene copies from *RBMX* originated via retrotransposition at early stages of mammalian evolution (in the case of *HNRNPGT* which encodes a meiotically-expressed RNA binding protein), and in the primate lineage (in the case of *RBMXL1*, which encodes a more ubiquitously expressed RNA binding protein).

3. RBMX proteins are implicated in splicing control particularly during nervous system development

The genes and pathways controlled by *RBMX* in the brain may be medically important in the context of intellectual disability. X linked mental retardation syndromes are caused by defects in genes on the X chromosome that are important for brain development. Since males have only a single copy of the *RBMX* gene, this makes them more susceptible to the effects of recessive mutations in this gene, compared to females who have *RBMX* genes on both X chromosomes. A 23bp deletion in exon 9 of the *RBMX* gene has been identified in some males with an X linked mental retardation syndrome called Shashi syndrome

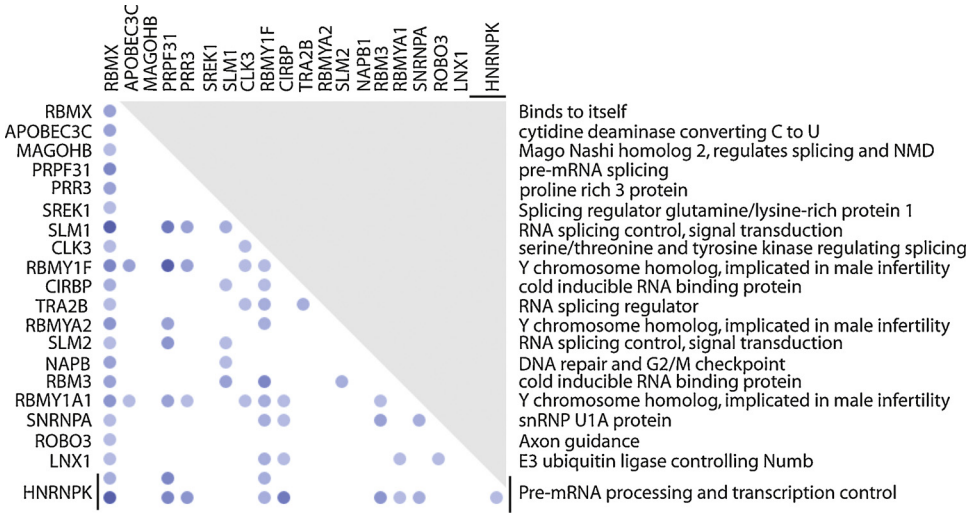

Fig. 3. The RBMX protein interacts with proteins with roles including splicing, brain development and the DNA damage response. Binary protein interactions of RBMX protein detected by yeast 2 hybrid analyses, and downloaded as a screenshot from the Uniprot browser (https://www.uniprot.org/uniprot/P38159). The blue dots indicate identified protein-protein interactions between proteins on the vertical and horizontal axes. For example, RBMX protein binds to itself in the yeast 2 hybrid system. Protein acronyms are RBMX (RNA binding motif protein X-linked); APOBEC3C (alipoprotein B mRNA editing enzyme catalytic subunit 3C); MAGOHB (mago homolog B, exon junction complex subunit); PRPF31 (pre-mrna processing factor 31); PRR3 (proline rich protein 3); SREK1 (splicing regulatory glutamic acid and lysine rich protein 1); SLM1 (saM68-like mammalian protein 1); CLK3 (cdc-like kinase 3); RBMY1F (RNA binding motif protein, Y-linked, family 1, member F); CIRBP (cold inducible RNA binding protein); TRA2B (transformer 2 beta homolog); RBMYA2 (RNA binding motif, Y linked, family 1, member A2); SLM2 (Sam68-like mammalian protein 2); NAPB (nsf attachment protein betA); RBM3 (RNA binding motif protein 3); RBMY1A1 (RNA binding motif protein, Y-linked, family 1, member A1); SNRNPA (small nuclear ribonucleoprotein polypeptide A); ROBO 3 (roundabout guidance receptor 3); LNX1 (ligand of numb-protein X 1); HNRNPK (heterogeneous ribonucleoprotein K) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

(Shashi et al., 2015).

Experiments using animal models support the notion that *RBMX* controls genes and pathways important for brain development. *RBMX* is highly expressed in the Zebrafish brain, where its depletion changes gene expression patterns and impairs head, jaw and brain development (Tsend-Ayush et al., 2005). Defects in neural plate differentiation in the African clawed frog *Xenopus laevis* can be induced by either experimental over-expression or depletion of *RBMX* (Dichmann et al., 2008). In mice, RBMX protein is more highly expressed in peripheral nerves, and its expression in neurons from the central nervous system promotes axon and dendrite development (Buchser et al., 2012). RBMX protein expression increases after spinal and retinal injury in rats (Zhang et al., 2013).

How might RBMX control brain development and intellectual ability? Binary protein-protein interactions have been detected between RBMX and a protein important in neurite growth cone guidance called ROBO3 (roundabout guidance receptor 3). This interaction suggests that RBMX protein may play a direct role in establishing neural networks (Fig. 3). However another likely possibility is that RBMX controls expression of genes that are important during brain development. Supporting a role for RBMX in splicing control, endogenous RBMX protein migrates on glycerol gradients within large molecular complexes called supraspliceosomes (Heinrich et al., 2009). Yeast 2 hybrid experiments have detected binary protein interactions between RBMX/RBMY proteins and splicing regulators including SRSF3 and SRSF7 (serine and arginine rich splicing factor 3 and 7 respectively),Tra2β (Transformer 2β, an splicing regulator protein), SLM1 (sam68-like mammalian protein 1, a KH domain containing splicing regulator), Magoh (a component of the exon junction complex, and involved in splicing regulation), and SAFB1 (scaffold attachment factor B1, involved in transcription, and part of the nuclear matrix) (Venables et al., 1999, 2000; Sergeant et al., 2007; Heinrich et al., 2009; Dreumont et al., 2010). Some of the known binary protein interacting partners for RBMX are shown in Fig. 3. RBMX protein also represses splicing of *Tau* (also known as microtubule associated protein tau), a gene known to be important during brain development (Heinrich et al., 2009).

Splicing control by RBMX has implications for a disease affecting motor neurones called Spinal Muscular Atrophy (SMA). SMA causes muscle weakness and loss of movement, and is caused by deletion of *SMN1 (*survival of motor neuron 1*)* gene. Depending on the size of the deletion some SMA patients still have an adjacent *SMN2* gene. The similar sequences of the *SMN1* and *SMN2* genes mean that in principle *SMN2* could act as a genetic replacement to mitigate the loss of *SMN1*. However, poor splicing inclusion of *SMN2* exon 7 means that only low levels of SMN2 protein are normally made. RBMX protein contributes to *SMN2* exon 7 splicing inclusion and thus helps SMN2 protein production (Hofmann and Wirth, 2002). RBMX protein activates splicing inclusion of *SMN2* exon 7 as part of a synergistic complex with the splicing activator protein Tra2β (Clery et al., 2011; Moursy et al., 2014). Binding of RBMX protein to a 5′-NAA-3′ dinucleotide sequence within *SMN2* gene exon 7 has been visualised at atomic resolution using nuclear magnetic resonance spectroscopy (Moursy et al., 2014). Recent experiments show that an adenosine (A) within this RBMX binding site can be N6-methylated (Liu et al., 2017).

While RBMX and Tra2β cooperatively activate *SMN2* exon 7 splicing, they often seem to function antagonistically in splicing control. RBMX and Tra2β antagonistically control splicing of a dystrophin pseudo-exon and a skeletal muscle-specific exon of *TPM3* (tropomyosin *3*) gene (Nasim et al., 2003). RBMY and Tra2β have antagonistic effects on splicing of testis-specific exons in the *Acinus* and *CREB (*cAMP responsive element binding protein) genes (Dreumont et al., 2010).

4. RBMX protein may control transcription

RBMX has been implicated with a role in transcription repression. Induced pluripotent stem cells (iPSCs) can be differentiated *in vitro* into liver cells. Within these in vitro differentiated liver cells RBMX protein becomes enriched within heterochromatin, and is associated with transcriptionally repressed chromatin marks including H3K9me3 and H3K27me3 (respectively, tri-methylated lysine 9 or tri-methylated lysine 27 of histone H3). siRNA-mediated depletion of RBMX activated expression of 168 genes, and increased responsiveness to liver-specific transcription factors (Becker et al., 2017).

Other data show RBMX protein has a role in activating transcription of the sterol regulatory element *SREBP-1c* ((SRE)-binding protein-1c) gene in response to a high fructose diet. RBMX binding to the promoter of *SREBP-1c* was identified by mass spectrometry, and RBMX activated expression from this promoter (Takemoto et al., 2007).

5. RBMX is implicated in chromosome biology

Further data suggest that RBMX protein functions in chromosome

biology. RBMX protein is associated with human metaphase chromosomes (Uchiyama et al., 2005). RBMX depletion causes accumulation of HeLa cells at pro-metaphase of mitosis, with a failure of chromosomes to align on the metaphase plate (Matsunaga et al., 2012; Cho et al., 2018). RBMX depletion causes premature loss of sister chromatid cohesion, with loss of the outer kinetochore proteins CENP-E and CENP-F (centromere proteins E and F). RBMX function in chromatid cohesion might be independent of RNA binding, since loss of chromatid cohesion after RBMX depletion could be rescued by GFP-tagged RBMX proteins without RRMs. RBMX proteins may function in chromatid cohesion through direct protein interactions with components of the cohesion complex, including the SCC1 (also known as RAD21 cohesin complex), SMC1 (structural maintenance of chromosomes 1) and WAPL (WAPL cohesion release factor) proteins. RBMX protein also associates with satellite I RNA (a noncoding RNA transcribed from human centromeres) in M phase arrested HeLa cells. Interestingly centromeres are heterochromatic structures, so RBMX may impact centromere function via effects on chromatin modification such as those discussed in the previous section.

RBMX also associates with lampbrush chromosomes from the newt *Pleurodeles waltl* (Kanhoush et al., 2010). RBMX is likely to be bound to nascent transcripts on these lampbrush chromosomes (Soulard et al., 1993). Experiments in which human RBMX protein was ectopically expressed within newts identified a central domain of RBMX protein that is important for recruitment to nascent transcripts, and a C-terminal domain that can mediate RNA-protein interactions (Kanhoush et al., 2010).

6. Involvement of RBMX in disease

Several lines of evidence implicate RBMX in cancer. Network analysis of gene expression data taken from thousands of tumours identified RBMX as a key switch that is closely linked to important cancer drivers (Climente-Gonzalez et al., 2017). Genome sequencing identified mutations truncating the *RBMX* gene in lung cancer patients, suggesting RBMX as a potential tumour suppressor (Renieri et al., 2014). Tobacco-induced mutations occurring in RBMX may even predispose smokers to developing lung cancer in the future (Zhang et al., 2018). Some thyroid cancers (papillary thyroid carcinoma) that have developed vemurafenib resistance lose the *RBMX* gene, predisposing them to chromosome abnormalities (Antonello et al., 2017). Increased *RBMX* expression levels correlate with a favourable outcome in endometrial cancer (Ouyang et al., 2011). Within endometrial cancer cells RBMX regulates the splicing of estrogen alpha (Hirschfeld et al., 2015). In breast cancer *RBMX* expression correlates with expression of the pro-apoptotic *Bax* gene (Martinez-Arribas et al., 2006). *RBMX* may prevent development of oral tumours through transcriptional control of an important tumour suppressor called *TXNIP* (thioredoxin interacting protein) (Shin et al., 2006). Consistent with this, RBMX protein expression activates expression of luciferase fused to the *TXNIP* promoter (Shin et al., 2008).

RBMX expression may help protect the genome from damage. A genome-wide siRNA screen in human U2OS cells showed that RBMX depletion sensitises cells to DNA damage (Adamson et al., 2012). In this study an ectopically expressed RBMX-GFP fusion protein transiently localised to sites of induced DNA damage, but rapid RBMX-GFP recruitment was not needed for efficient DNA repair. This suggests that the effect of RBMX on DNA damage control may be indirect, and possibly takes place through the splicing regulation of genes encoding proteins involved in DNA repair. One such RBMX-regulated gene might be *BRCA2* (breast cancer *2*), because expression levels of BRCA2 decreased after RBMX depletion (Adamson et al., 2012). Interestingly, Tra2β (which interacts with RBMX) is needed for productive splicing of the *CHK1* (checkpoint kinase 1) gene that is important for DNA damage control (Best et al., 2014). RBMX protein may also control DNA repair more directly. Most recently RBMX has been shown to be part of a complex important for DNA repair pathways that also includes the long noncoding RNA *NORAD* (noncoding RNA activated by DNA damage) (Munschauer et al., 2018).

While much of the above data is consistent with RBMX being a tumour suppressor, ectopic expression of *RBMY* may have an oncogenic role in men in driving liver cancer (Tsuei et al., 2004, 2011; Chua et al., 2015). Although primarily nuclear, RBMX protein physically interacts with a protein called ARTS-1 (aminopeptidase regulator of TNFR1 shedding) to regulate release of tumor necrosis factor receptor (TNFR1) into the extracellular space (Adamik et al., 2008). TNFR1 release is via small extracellular vesicles called exosomes into the circulation. Exosomes carry cargo including ncRNAs around the body and are important for intercellular communication, including from cancer cells.

RBMX has also been implicated with a role in infectious disease. RBMX protein interacts with the negative strand RNA Borna Disease Virus (abbreviated BDV) (Hirai et al., 2015). BDV causes neurological disease in animals, and forms nuclear inclusions within infected cells called vSPOTs (viral speckles of transcripts). A combination of immunoprecipitation, mass spectroscopy and immunofluorescence experiments showed that RBMX protein promotes vSPOT formation, and the expression and replication of BDV. These vSPOTs themselves were not spatially enriched in RBMX protein. Instead, RBMX tended to localise around the vSPOT periphery.

7. *RBMX* has generated a family of genes encoding nuclear RNA binding proteins

RBMX gene duplications have created a small family of RBMX-like retrogenes. During this duplication process *RBMX* mRNAs were converted into cDNAs by endogenous reverse transcriptase activity, followed by insertions of these cDNAs into the genome at several new locations. This process is called retrotransposition. As a result of being made from spliced mRNAs, *RBMX* retrogenes lack introns. As a general rule, retrogenes are usually either “dead on arrival”, in the case of insertion of truncated cDNAs, or rapidly degenerate in the absence of functional selection (because the parent gene that provided the cDNA is still intact and so can provide function). However, retrogenes can be maintained if they are useful, and conservation of retrogenes between species is indicative of function.

RBMX-derived retrogenes may provide an important function during meiosis, during which time the X and Y chromosomes (and so the *RBMX* and *RBMY* genes) are transcriptionally inactivated within a heterochromatin structure called the XY body (Wang, 2004). *HNRNPGT* (also known as *RBMXL2*) is an RBMX-derived retrogene that is only expressed in the testis, and most highly during meiosis and immediately afterwards. Indicating an important function during meiosis, *HNRNPGT* is likely to have evolved before the radiation of placental mammals ~65 million years ago (Elliott et al., 2000; Ehrmann et al., 2008). During meiosis hnRNP GT protein may provide a like for like replacement for RBMX, or alternatively may control the expression of meiotic-specific RNA processing pathways. Suggesting that their functions might have slightly diverged, the percentage identity between *RBMX* and *HNRNPGT* is around 69% at the nucleotide level and 73% at the amino acid level.

Other RBMX-like genes (RBMXLs) have also evolved by retrotransposition of *RBMX* onto human chromosomes 1, 4, 6, 9 (9p13 and 9p24), 11, 20 and X (Lingenfelter et al., 2001). Some of these *RBMXL* genes could express proteins. On human chromosome 1, *RBMXL1* encodes a predicted protein that is the same size and more than 95% identical to RBMX protein (Lingenfelter et al., 2001). The *RBMXL1* gene is within intron 2 of *CCBL2* gene (which encodes an enzyme called kynurenine aminotransferase 3 that metabolises tryptophan) and is transcribed in the same direction from the same promoter, although there is no overlap in reading frame. *RBMXL9* is on human chromosome 9, and specifically expressed in the testis and to a lesser extent in the brain (Lingenfelter et al., 2001). The open reading frame of *RBMXL9* mRNA predicts a truncated protein that still retains an RRM. *RBMXL3* is

located on the X chromosome within the first intron of the *LRCH2* gene, but transcribed in the opposite direction to its host gene. *RBMXL3* has a reading frame for a much longer protein (of 1067 amino acids, compared to the 391 amino acids of the full length RBMX protein) but with only 53% identity to RBMX. Whether *RBMXL3* is expressed at the protein level is unknown. The other RBMXL genes are predicted to be non-functional copies since they have truncated reading frames.

8. Remaining questions about RBMX and RBMX-family proteins

Many questions about RBMX family proteins still remain to be answered. These questions include what is/are the major molecular function(s) of RBMX? Does RBMX primarily function to control RNA processing? Or does RBMX predominantly function at the level of transcriptional control, and if so of what genes? Do RBMX target genes have functions in processes connected to brain and nervous system, or tumour suppression? To what extent is the primary function of RBMX within DNA repair complexes, or in the transcription/splicing control of genes involved in DNA repair? Such questions could be addressed by RNAseq analysis of cells after RBMX protein depletion. As well as identifying target genes, this type of analysis should reveal if RBMX functions primarily to activate or repress splice sites. Furthermore, direct RNA target sites for RBMX could be mapped by transcriptome-wide approaches such as iCLIP (Konig et al., 2011). The mechanisms of RBMX splicing regulation are largely unknown. Such iCLIP experiments would help indicate how patterns of protein-RNA interaction determine splicing outcomes.

Splicing control by RBMX has largely been investigated using minigenes. Such experiments have raised the important question of whether direct RNA binding by RBMX and paralog proteins is important for splicing control? Alternatively, do RBMX proteins modify splicing through protein-protein interactions with other splicing regulator proteins? There is some conflicting data here. For some minigene targets, splicing regulation by RBMX is RRM-independent –in these cases, RBMX family proteins from which the RRM is deleted can still control splicing. Examples include splicing activation of an exon in the *TLE4* gene (transducin like enhancer of split *4*) by a version of hnRNP GT lacking an RRM (Liu et al., 2009). On the other hand, splicing regulation of *SMN2* exon 7 by RBMX does depend on its RRM, suggesting specific RNA-protein interactions are important (Moursy et al., 2014). Results from minigene-based experiments rely on transfection into cell lines, and may be affected by protein concentrations, with the effects of RRM deletion for splicing control of RBMX being more noticeable at lower concentrations of co-transfected proteins (Heinrich et al., 2009). Another potentially complicating issue that the C-terminus of RBMX can also mediate RNA-protein interactions as well as the RRM (Fig. 1). Fully answering the question of whether direct RNA-protein interactions are important for splicing control by RBMX will require global mapping of RBMX-RNA protein interactions using techniques like iCLIP (Konig et al., 2011).

Another key question is to what extent RBMX splicing targets overlap with those of other interacting proteins such as Tra2β? Globally answering this question will require the targets of both RBMX and Tra2β to be identified transcriptome wide, and ideally in parallel within the same cell type. Another interesting question is whether each of the individual RBMX paralog proteins might have specialised roles in splicing control of distinct targets, or whether they are functionally overlapping? Answering this question will require paralog-specific knockouts or depletions for the *RBMX* family. At the moment the function of RBMX paralogs is only partially understood from transfection experiments using model exons where RBMX, RBMY or hnRNP GT often mediate similar affects (Heinrich et al., 2009; Liu et al., 2009). However, there is a precedent to suggest that X-derived autosomal retrogenes can evolve distinct functions. *CSTF64* (cleavage stimulation factor-64) is another example of an essential X chromosome gene. In this case, CSTF-64 T (cleavage stimulation factor-64 T) protein is encoded by an autosomal retrogene, and replaces activity of the X-chromosome-encoded CSTF64 protein during meiotic prophase. *CST64T* is known to have both overlapping and distinct activity to CSTF64, thus contributing to the selection of meiosis-specific 3′ ends (Dass et al., 2007; Liu et al., 2007; Yao et al., 2013). Thus it is possible that meiosis-specific *RBMX* retrogenes like *HNRNPGT* might also help orchestrate specific patterns of gene expression control during meiosis.

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