Brr2p RNA helicase with a split personality: insights into structure and function

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Abstract

RNA helicases are involved in many cellular processes. Pre-mRNA splicing requires eight different DExD/H-box RNA helicases, which facilitate spliceosome assembly and remodelling of the intricate network of RNA rearrangements that are central to the splicing process. Brr2p, one of the spliceosomal RNA helicases, stands out through its unusual domain architecture. In the present review we highlight the advances made by recent structural and biochemical studies that have important implications for the mechanism and regulation of Brr2p activity. We also discuss the involvement of human Brr2 in retinitis pigmentosa, a degenerative eye disease, and how its functions in splicing might connect to the molecular pathology of the disease.

Introduction

Splicing is the process by which introns are removed from the pre-mRNA to give rise to protein-coding mRNA. This task is catalysed by the spliceosome, a large protein–RNA complex consisting of U1, U2, U4/U6 and U5 snRNPs (small nuclear ribonucleoprotein) particles, as well as numerous non-snRNP protein factors. First the U1 and U2 snRNPs assemble on the pre-mRNA, then they are joined by the pre-formed U4/U6–U5 tri-snRNP. Within the tri-snRNP U4 and U6 snRNAs (small nuclear RNAs) are tightly base-paired to keep parts of the U6 snRNA catalytically inert. To achieve catalytic activation of the spliceosome, U4 is displaced and U6 engages in base-pairing with U2 and the intron. Excision of the intron results from two transesterification reactions, and thereafter the spliceosome is actively disassembled (reviewed in [1]). Although the two transesterification reactions themselves are isoenergetic [2], splicing involves eight RNA helicases that use the energy from ATP hydrolysis to facilitate conformational rearrangements within the spliceosome [3]. Brr2p is one of these, having been identified as an essential splicing factor by four different approaches [4–7]. Alternative names include: Slt22p, Rss1p, Prp44p, Snu246p and, in humans, U5-200K; in the present review we use the common name Brr2p for the yeast protein and hBrr2 for its human orthologue. In the following sections we recapitulate the recent biochemical and structural analyses that have provided further insight into Brr2p function and the regulation of its activity.

Key words: Brr2 protein, pre-mRNA processing factor 8 (PRP8), retinitis pigmentosa (RP), splicing, tri-small nuclear ribonucleoprotein (tri-snRNP), U4/U6 small nuclear ribonucleoprotein.

Abbreviations used: adRP, autosomal dominant retinitis pigmentosa; CTF, C-terminal fragment; hBrr2, human Brr2p; HLH, helix-loop-helix; PRPF, pre-mRNA processing factor; RP, retinitis pigmentosa; snRNA, small nuclear RNA; snRNP, small nuclear ribonucleoprotein; WH, winged helix.

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Brr2p activity is regulated by the U5 snRNP components Prp8p and Snu114p

Brr2p is a stable component of the U5 snRNP. Together with Prp8p and Snu114p it forms a salt-stable complex at the core of the U5 snRNP [8]. Not surprisingly these three proteins interact extensively and directly with each other (Figure 1) [9–12]. Like Prp8p and Snu114p, Brr2p is associated with the spliceosome throughout the splicing cycle [13], thus its activity needs to be tightly controlled and timed. Brr2p activity is required twice. During catalytic activation of the spliceosome, it is believed to disrupt the U4/U6 snRNA duplex [14,15]. Brr2p activity is required again during spliceosome disassembly, where base-pairing between U2 and U6 was suggested as its substrate [16].

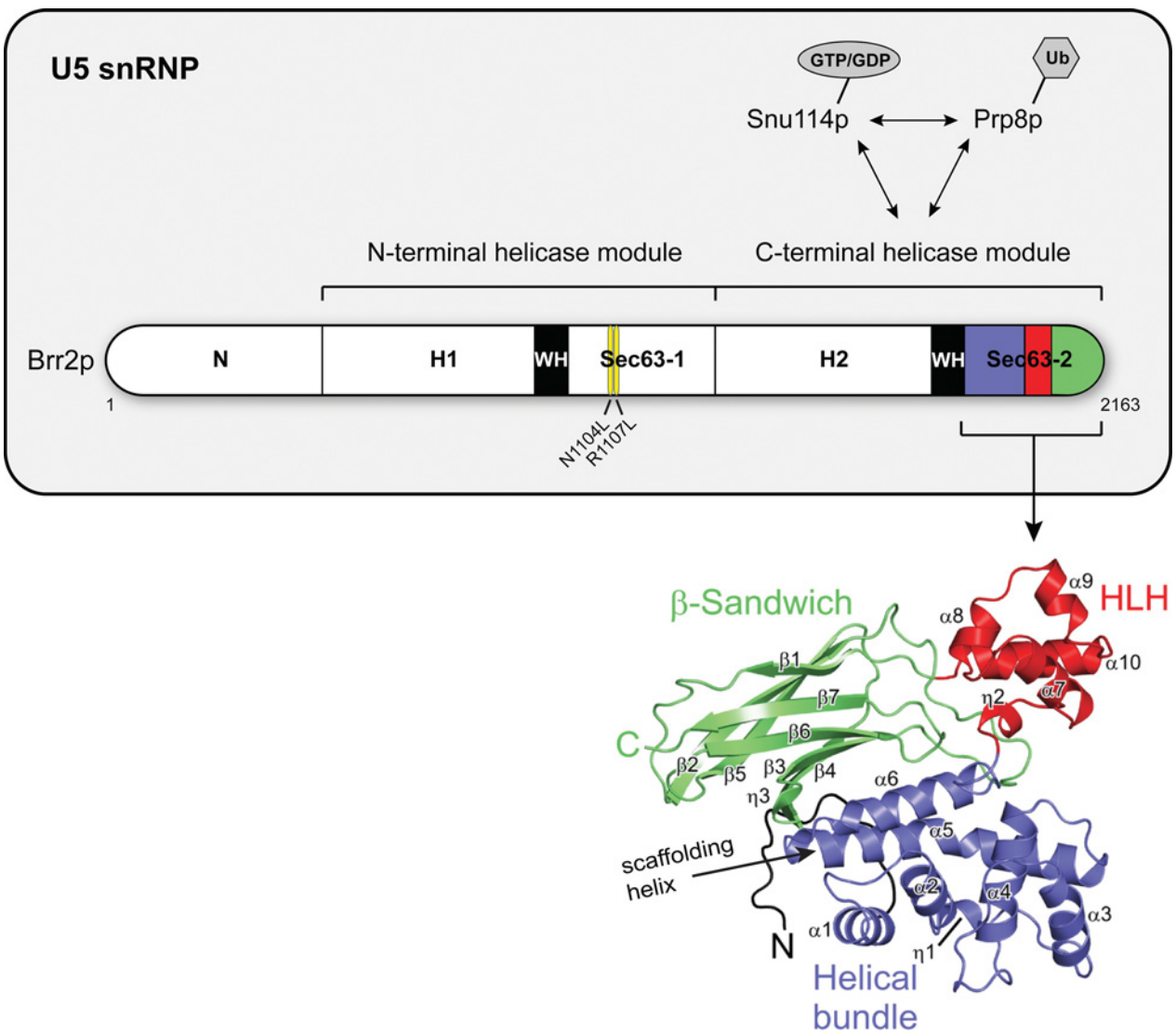
To achieve intermittent stimulation and repression of Brr2p activity, different modes of regulation have been suggested. The GTPase Snu114p is believed to regulate Brr2p activity dependent on its guanine-nucleotide state. In its GTP-bound state Snu114p promotes Brr2p activity, but when bound to GDP it represses Brr2p activity [16]. Prp8p is another suggested regulator of Brr2p activity [17,18]. Periodic ubiquitination of Prp8p was suggested to contribute to Brr2p regulation [19,20]. Furthermore, a recent study found that the presence of a CTF (C-terminal fragment) of Prp8p (referred to as Prp8-CTF) stimulates Brr2p helicase activity *in vitro*, although it suppresses Brr2p ATPase activity [21]. The mechanism by which Prp8-CTF modulates Brr2p activity remains unknown. Further studies will be required to understand how GTP hydrolysis by Snu114p and the (de)ubiquitination of Prp8p can be co-ordinated to allow dynamic control of Brr2p helicase activity.

Brr2p architecture and the helicase mechanism

Brr2p is a large 246 kDa protein. Apart from an N-terminal domain, of unknown function, Brr2p consists of two

Figure 1 | **Domain organization of yeast Brr2p**

Brr2p consists of an N-terminal domain (N) and two structurally similar, but functionally distinct helicase modules. Each helicase module is composed of a DExH box helicase-like domain (H1 and H2), a WH domain, and a Sec63-like domain (Sec63-1 and Sec63-2). Snu114p and Prp8p, which are components of the U5 snRNP, interact with the C-terminal region of Brr2p. The GTP/GDP state of Snu114p and the ubiquitination state of Prp8p modulate Brr2p activity. The Sec63-2 domain comprises three structural domains: the helical bundle (blue); the HLH (red); and the β-sandwich (green). α-Helix 5 of the helical bundle domain is referred to as a 'scaffolding' or 'ratchet' helix. Substitutions corresponding to hBrr2 adRP mutations (N1104L and R1107L in yeast) fall into the predicted analogous ratchet helix within Sec63-1 and are indicated in yellow. See the text for details. The crystal structure is reprinted from [25] with permission from Elsevier.



putative helicase domains, each connected at its C-terminus to a Sec63-like domain (Figure 1, abbreviated as N, H1, Sec63-1, H2 and Sec63-2). Notably, this unusual tandem repeat domain organization is conserved amongst Brr2p orthologues and can also be found in at least one other helicase in *Saccharomyces cerevisiae*, Slh1p [22]. The N-terminal helicase domain of Brr2p shares high sequence similarity to the conserved signature motifs of DExH-box RNA helicases. In yeast Brr2p these motifs were shown to be essential for cell viability, ATPase activity and Brr2p's function in U4/U6 unwinding [14,15,23]. The C-terminal helicase-like domain motifs of Brr2p are more degenerate and deviate from the consensus [4–6]; mutations that were predicted to be functionally deleterious are tolerated with little consequence [23]. The function of the Sec63-like domains is unknown. They are defined by homology to Sec63p, a component of the ER (endoplasmic reticulum) translocon complex [24].

Recently, two reports have presented crystal structures of the Brr2p C-terminal Sec63-like domain [12,25]. It consists of three interconnected structural domains that are arranged in a triangular fashion (Figure 1). The helical domain features a long α-helix (helix α5) at its core, which spans the entire length of this domain; it is referred to as a scaffolding or ratchet helix and is suggested to be of crucial functional importance (see below). The second helical domain adopts an HLH (helix-loop-helix) fold. The third domain consists of β-strands only and forms an immunoglobulin-like β-sandwich (Figure 1) [12,25].

Structural similarities have been recognized between the Brr2p C-terminal Sec63-like domain and domains 4 and 5 of the DExH-box DNA helicase Hel308, despite there being no obvious sequence similarity [12,25–27]. On the basis of sequence comparisons and structural modelling it was concluded that structural similarity to Hel308 also extends to the helicase-like domain [12,25]. Pena et al. [25] observed a further similarity to the Hel308 structure and found that a WH (winged helix) domain functions as a connector to link and position the helicase and Sec63-like domains (Figure 1). On the basis of these observations a structural model was generated in which the Brr2p C-terminal helicase, WH and Sec63-like domains form a functional unit, or helicase module, resembling Hel308. Owing to high sequence conservation the Brr2p N-terminal helicase, WH and Sec63-like domains were also predicted to form a helicase module, so that Brr2p probably consists of a unique N-terminal domain plus two consecutive helicase modules (Figure 1) [12,25]. The two helicase modules are predicted to have a similar structure and organization, in which the Sec63-like domain is positioned opposite the helicase domain, forming a central channel through which a single-stranded nucleic acid molecule can be threaded.

The structural analogy between Brr2p's 'active' N-terminal helicase module and Hel308 gave reason to speculate that their helicase mechanisms bear resemblance too. It has been suggested that Hel308 uses a β-hairpin loop that inserts between the DNA strands, thereby separating them [26]. Mutational analysis of the analogous structure in the Brr2p N-terminal helicase module revealed growth phenotypes or lethality, underscoring the importance of this structure within Brr2p [12,25]. Furthermore, Buttner et al. [26] proposed that Hel308 can achieve processivity by means of a ratchet helix that allows coupling of ATPase activity with nucleic acid translocation. The ratchet helix uses aromatic or positively charged residues to directly interact with the DNA. Conformational rearrangements triggered by ATP binding and ATP hydrolysis push the ratchet helix, and with it the separated product strand, forwards. In this way unidirectional ($3'\rightarrow5'$) translocation can be achieved. A corresponding putative ratchet helix within the Brr2p N-terminal helicase module was predicted to be located in the Sec63-like domain, more precisely in helix α5 of the helical bundle domain [12,25]. The inner surfaces of the Brr2p N-terminal helicase module feature an electrostatic-surface-potential appropriate for nucleic acid interaction. In addition, mutations in aromatic or positively charged residues of the putative ratchet helix resulted in growth defects in *S. cerevisiae* [12,25]. One mutation that falls in the putative ratchet helix (*brr2* R1107A) has been reported previously to confer a cold-sensitive growth defect, a U4/U6 unwinding defect and an intron release defect [16]. Zhang et al. [12] show that *brr2* R1107P lacks ATPase activity and fails to unwind U4–U6 in the presence of Prp8-CTF *in vitro*. These findings argue that the Brr2p N-terminal helicase module and Hel308 have similar functional properties. Brr2p might require a processive mode of unwinding, considering the extensive base-pairing and stability of the U4/U6 snRNA duplex [28], its suggested substrate. However, with respect to alternative, less stable substrates during spliceosome disassembly [16], processive unwinding might not be required. Ultimately, knowledge of Brr2p's natural RNA substrates is essential, as it will help in understanding both its mode of activity and its function(s).

The function of Brr2p's C-terminal helicase module is less understood. It is unlikely to have ATPase or helicase activity [23]. In addition, it seems unlikely that the C-terminal helicase module participates in RNA interactions, due to the partial absence of positively charged or aromatic residues in the scaffolding helix and an electrostatic surface potential unsuitable for nucleic acid interactions [25]. Indeed a recombinant Brr2p fragment consisting of the C-terminal helicase-like and Sec63-like domains showed no binding to arbitrary single- or double-stranded RNA 13-mers or to U4/U6 *in vitro* [12]. Nevertheless, *in vivo* deletion of both the C-terminal helicase-like and the Sec63-like domains is detrimental and leads to protein instability [12]. Only deletion of the C-terminal Sec63-like domain is tolerated, although it does affect cell growth, results in a global splicing defect, and reduces protein interactions with Prp8p and Snu114p [12]. Furthermore, Brr2p devoid of the C-terminal Sec63-like domain lacks ATPase activity and fails to be stimulated by Prp8-CTF to unwind U4/U6 *in vitro* [12]. Therefore it was suggested that the Brr2p C-terminal helicase module has adapted to function as a protein interaction domain that regulates the activity of the N-terminal helicase module [9,10,12,25].

To date the mechanisms by which the protein interactions at the Brr2p C-terminus modulate the helicase activity of its N-terminal helicase module remain unclear, as does how regulation can be realized *in vivo*. It will be interesting to learn more about how the two helicase modules fold with respect to one another in the full-length protein and how this contributes to communicating regulatory signals between the C- and N-termini. In addition, what is the advantage of a protein interaction domain with a helicase-like design? Although the Brr2p C-terminal helicase module is unlikely to have ATPase activity, it might retain the ability to bind a nucleotide. The helicase-like design might facilitate conformational flexibility, which could contribute to modulation of protein interactions.

hBrr2 and RP (retinitis pigmentosa)

adRP (autosomal dominant RP) is a heritable eye disease that leads to progressive retinal degeneration, ultimately resulting in blindness. Surprisingly, RP-related alleles were found in

genes encoding pre-mRNA splicing factors. Initially mutations in the human genes *PRPF31* (pre-mRNA processing factor 31), *PRPF3*, *PAP1* (also *RP9*), as well as *PRPF8*, were identified (reviewed in [29]). However, it remains poorly understood how mutations in splicing factors, whose functions are required ubiquitously, lead to retina-specific degenerations. In order to understand the disease mechanism, the effects of adRP mutations on the splicing machinery were studied. As the loci of adRP mutations are often conserved from yeast to human, yeast frequently served as a model system.

hBrr2 was suggested to play indirect, as well as direct, roles in relation to the molecular mechanism underlying adRP. adRP mutations in *PRPF8*, the human orthologue of *S. cerevisiae PRP8*, alter amino acids at the extreme C-terminus of the protein and interfere with the interactions between Brr2p and Prp8p [9–11,21,30]. However, different mechanisms were suggested for how this interaction defect can induce adRP. One study suggested the molecular mechanism is a U5 snRNP maturation defect; impaired protein interactions between Brr2p and Prp8p lead to the formation of an alternative U5 snRNP precursor particle, reducing the level of functional tri-snRNPs, and thus reducing splicing efficiency [30]. On the basis of *in vitro* experiments that tested the effects of the *PRP8* adRP mutations on the Brr2–Prp8-CTF interaction, a complementary or alternative disease mechanism was suggested. If Prp8-CTF carries adRP alleles, the normally strong enhancement it has on Brr2p-driven U4/U6 unwinding is lost. This lack of stimulation was observed even when mutant Prp8-CTF was present in molar excess, thus it is unlikely to be simply due to a weakened Brr2p–Prp8p interaction [21]. It is difficult to fully separate the Brr2p unwinding defect from the Prp8p–Brr2p interaction defect; however, the rationale is still that adRP may result from deregulated activation of spliceosomes, causing reduced splicing efficiency [21].

An immediate connection between hBrr2 and adRP comes from two recent reports that added hBrr2, encoded by *SNRNP200* (also known as *ASCC3L1*), to the list of splicing factors that can carry adRP-causing alleles [31,32]. The identified mutations cause substitutions S1087L and R1090L in hBrr2, which in yeast Brr2p correspond to N1104L and R1107L. Interestingly, both mutations locate to the N-terminal Sec63-like domain of hBrr2/Brr2p, and more precisely to the putative ratchet helix (helix α5) of the helical bundle domain (see above). Functional characterization of the mutations in yeast Brr2p established that neither N1104L nor R1107L shows tri-snRNP assembly defects, precluding a U5 snRNP maturation defect as a likely cause of this form of adRP. Instead both mutations lead to defective U4–U6 unwinding in native tri-snRNPs [31]. These observations support the structural predictions that assign functional importance to a ratchet helix in the Brr2p N-terminal helicase module. They also implicate a U4/U6 unwinding defect as a molecular basis for adRP; again concluding that adRP associated with splicing factors might stem from insufficient activation/regulation of hBrr2 helicase activity during spliceosome activation [21,31].

There is much to be learned about the mechanism(s) underlying adRP. Further investigation will be required to address if the hBrr2 adRP mutations compromise the protein's helicase activity directly, or if they interfere with regulation of its helicase activity instead. Do mutations in the N-terminal Sec63-like domain interfere with Prp8p and Snu114p interaction? Are hBrr2 adRP mutations limited to the N-terminal Sec63-like domain, or can mutations elsewhere in the protein that impair U4/U6 unwinding also be causative of adRP? In addition, given that another mutation of the same residue in the Brr2p putative ratchet helix (*brr2* R1107A, see above) affects both U4/U6 dissociation and spliceosome disassembly [16], it is conceivable that *brr2* R1107L will affect both processes. Hence, does a defect in spliceosome disassembly play a role in adRP? The same question applies to *PRP8* adRP-causing alleles. If they affect Brr2p activity during spliceosome activation, do they also affect Brr2p activity during spliceosome disassembly?

Conclusions

Brr2p plays an essential role in pre-mRNA splicing and over the past years it has become the focus of an increasing number of studies. The recent discovery that mutations within hBrr2p can be linked to adRP emphasized further the significance of hBrr2/Brr2p function. The unusual domain organization of Brr2p, and the intricate interaction with Snu114p and Prp8p at the centre of the U5 snRNP have raised many questions regarding the precise function(s) of Brr2p and the regulation of its enzymatic activity. The advances made by recent structural and biochemical analyses have broadened our understanding of the Brr2p architecture and provided the basis for future mechanistic studies. With the continued efforts of increasingly sophisticated structural analyses, and targeted biochemical and genetic approaches, a fuller understanding of the structure and mechanism of this unusual RNA helicase is beginning to emerge.

Acknowledgements

We thank Dr O. Cordin for helpful discussions and critical reading of the manuscript prior to submission.

Funding

D.H. is supported by the Darwin Trust of Edinburgh; J.D.B. is the Royal Society Darwin Trust Research Professor.

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Received 26 February 2010
doi:10.1042/BST0381105