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Superfamily 2 helicases

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1. ABSTRACT

Superfamily 2 helicases are involved in all aspects of RNA metabolism, and many steps in DNA metabolism. This review focuses on the basic mechanistic, structural and biological properties of each of the families of helicases within superfamily 2. There are ten separate families of helicases within superfamily 2, each playing specific roles in nucleic acid metabolism. The mechanisms of action are diverse, as well as the effect on the nucleic acid. Some families translocate on single-stranded nucleic acid and unwind duplexes, some unwind double-stranded nucleic acids without translocation, and some translocate on double-stranded or single-stranded nucleic acids without unwinding.

2. INTRODUCTION

Helicases are a ubiquitous group of enzymes that use the energy of nucleoside triphosphate (NTP) hydrolysis to catalyze the separation of double-stranded nucleic acids (dsNA). The resulting single-stranded nucleic acids (ssNA) are substrates for numerous cellular reactions. Consequently, helicases are involved in essentially every step in DNA and RNA metabolism, including replication, DNA repair, recombination, transcription, translation, chromatin rearrangement, ribosome synthesis, RNA maturation and splicing, nuclear export, Holliday junction movement, and displacement of proteins from DNA and RNA (reviewed in (1, 2, 3, 4). Helicases were originally identified as proteins that could separate double-stranded

Table 1. Members and enzymatic activities of superfamily 2 helicase families

Family	Family members discussed in this review	Activities
DEAD-box	Mammalian eIF4A(37)	dsRNA unwinding
	S. cerevisiae Mss116p (41, 164, 37)	
	E. coli DbpA (50, 49)	
	S. cerevisiae Ded1p (37)	
	Neurospora crassa CYP-19 (44)	
DEAH/RHA	*S. cerevisiae* Prp16p(77)	ssRNA translocase
	S. cerevisiae Prp22p(78)	dsRNA unwinding
	S. cerevisiae Prp43p (74, 79, 81)	
RecQ-like	human BLM (90)	ssDNA translocase
	human WRN (91, 24)	dsDNA unwinding
	human RecQ1 (23, 161, 165)	triplex and quadruplex unwinding
	human RecQ4 (92)	branched DNA unwinding
Rad3/XPD	archaeal XPD (97)	ssDNA translocase
	human XPD (100, 95)	dsDNA unwinding
Swi/Snf	human CSB (111)	dsDNA translocase
	human ATRX (116, 114)	
	S. cerevisiae INO80(108)	
	S. cerevisiae ISWI (19)	
	S. cerevisiae Rad54(113)	
	S. solfataricus SWI2/SNF2 (166)	
RIG-I-like	archaeal Hef (167)	dsRNA translocase
	human Dicer (123, 124)	
	human RIG-I(17, 126)	
Type I Restriction Enzyme	*E. coli* EcoR124I(168, 132)	dsDNA translocase
Ski2-like	*S. cerevisiae* Ski2p (52)	ssRNA translocase
	S. cerevisiae Mtr4 (56)	dsRNA unwinding
	archaeal Hel308 (85)	
RecG-like	*E. coli* RecG (152, 147, 155)	dsDNA translocase
	T. maritima RecG (162)	branched DNA unwinding
	E. coli PriA (158, 147, 160)	
NS3/NPH-II	Dengue Virus NS3(86, 62)	ssRNA translocase
	Vaccinia Virus NPH-II(59, 60)	dsRNA unwinding
	Hepatitis C Virus NS3 (63, 71, 69, 58)	

nucleic acids based on 7 conserved sequence motifs (5) and were later classified into superfamilies (SF) (6, 4). However, only a subset of these enzymes have dsNA unwinding activity. The helicase motifs, instead, are characteristic of all nucleic acid dependent NTPases, of which helicases are a subset (7, 1). Some helicases have been shown to be translocases (ie: utilize the energy of NTP hydrolysis for directional translocation on NA), including PcrA (8, 9, 10), NS3 (11, 12), NS3h (13), Rep (14), and UvrD (15). However, not all translocases have helicase activity, including EcoR124I (16) RIG-I (17), SWI/SNF (18), and ISW2 (19), and not all helicases have translocase activity, such as Ded1 (20, 21). Therefore, not all proteins possessing the helicase motifs and the helicase core structure are helicases (able to unwind dsDNA or dsRNA in an ATP dependent manner); examples are the Swi/Snf family and the type I restriction enzymes (Table 1).

Of the conserved sequence motifs, only the Walker A and B motifs are common to all helicases (22). These are involved in NTP binding and hydrolysis. Superfamily (SF) 1 and SF2 are the largest of the superfamilies and the conserved motifs are similar (6). The SF1 and SF2 helicases appear to function as monomers or dimers (3) for unwinding. Some specialized activities such as Holliday junction resolution and strand annealing require larger oligomers (23, 24). Each monomer contains two RecA-like domains (4). SF3-SF6 helicases show little similarity to SF1 and SF2 helicases. They have fewer conserved motifs (6, 4), contain one RecA-like domain per monomer (4), and function as hexamers or double hexamers (4, 25). These hexameric rings encircle the DNA, resulting in a highly processive helicase. The replicative helicases involved in chromosomal DNA replication are members of these superfamilies (26, 4).

3. SUPERFAMILY 2 HELICASES

Superfamily 2 is the largest and most diverse of the helicase superfamilies. It has been further divided into families including RecQ-like, RecG-like, Rad3/XPD, Ski2-like, type I restriction enzyme, RIG-I-like, NS3/NPH-II, DEAH/RHA, DEAD-box, and Swi/Snf families based on sequence homology (Table 1) (1, 27, 25). It also includes smaller groups, such as type III restriction enzymes and Suv3 (1). Although they are classified as helicases, some have not been shown to separate the strands of duplex NA or translocate on nucleic acids (16, 17, 18, 19, 28). Some unwind DNA or RNA while translocating on the NA, some unwind without translocation, and some translocate without unwinding. All have nucleic acid stimulated ATPase activity (25). SF2 helicases are involved in transcription, DNA repair, chromatin rearrangement, (29, 30, 31) and all aspects of RNA metabolism (25, 3). Since SF2 helicases function in diverse parts of nucleic acid metabolism, defects are associated with a variety of diseases including predisposition to cancer, premature aging, immunodeficiency, and mental retardation (32, 33).

4. FAMILIES

Based on recent work by the Jankowsky lab there are 10 families within SF2, in addition to the smaller type III restriction enzyme group and helicases such as Suv3

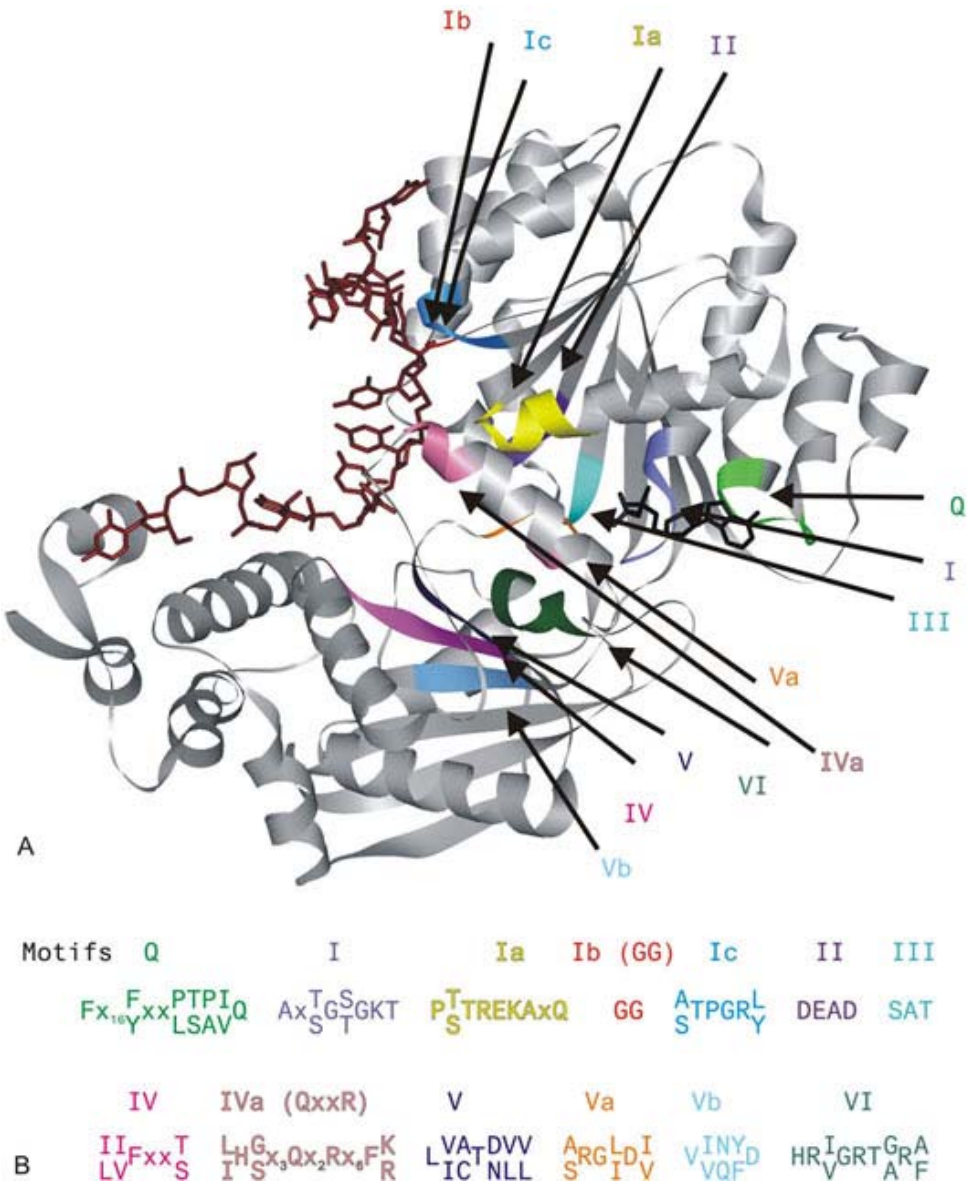

Figure 1. Structure of DEAD-box helicase Mss116p. A. The crystal structure (Protein Data Bank code 3I61 (41)) of the DEAD-box helicase Mss116p bound to ssRNA and the ATP transition state analog, ADP-BeF_3^-, illustrates the bending of the nucleic acid substrate by DEAD-box helicases. The helicase motifs are in the cleft formed between the two RecA-like domains. B. The consensus sequence for the conserved helicase motifs (1, 34) in DEAD-box family members is shown.

which belong to SF2, but not to any of the families or groups (1, 27, 25). They are collectively referred to as DExH/D helicases. However, the structures, mechanisms, and biological functions of the members of each of the families within this SF vary widely. This review will summarize available information about each of the families within SF2.

4.1. DEAD-box

The DEAD-box family is the largest in SF2 and is conserved from bacteria to humans (25). They are required for all aspects of RNA metabolism including transcription, splicing, transport, ribosome biogenesis, translation, RNA/protein complex assembly, and degradation (34, 25, 7). These enzymes are named for the conserved sequence of amino acids in the Walker B motif. They function exclusively on RNA as ATP-dependent chaperones that reconfigure the RNA. Diverse substrates are utilized by these enzymes, but they are most efficient when the RNA binding domain, separate from the unwinding active site, is also bound to RNA (35, 20). It can be ssRNA, dsRNA, or even structured RNA (36). DEAD-box proteins bind to RNA in an ATP dependent manner, but they don't translocate. Instead, they manipulate structured RNAs and RNA protein complexes (RNPs) by disrupting local secondary and tertiary structures and RNA-protein interactions (34). ATP-dependent unwinding of RNA by DEAD-box proteins

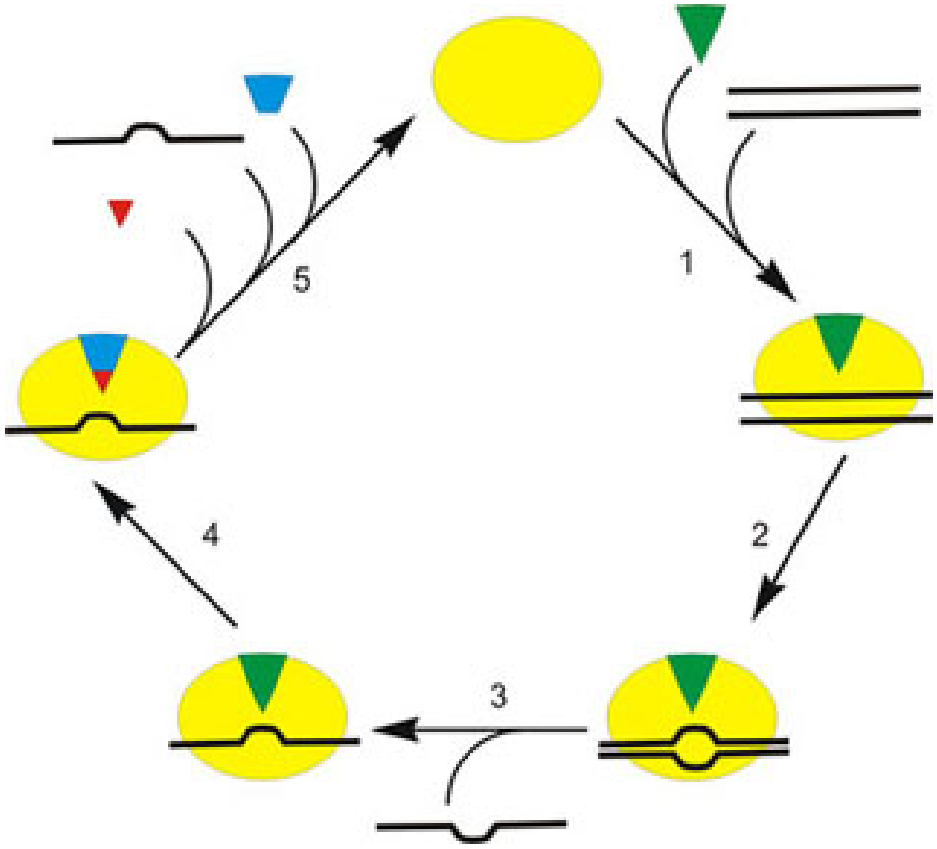

Figure 2. Proposed destabilization mechanism for unwinding by DEAD-box helicases (34, 37). The helicase (yellow oval) binds to the ATP (green triangle) and dsRNA (black lines) (step 1). Following a rearrangement (step 2) one strand of RNA can dissociate (step 3). ATP hydrolysis occurs after unwinding (step 4), and the cycle is completed with the release of phosphate (red triangle), ssRNA, and ADP (blue trapezoid) (step 5).

occurs by binding to the dsRNA and prying the strands apart instead of by translocation on nucleic acid (21). This allows unwinding to occur without directionality in some cases (37). It also limits the DEAD-box helicases to unwinding short duplexes, normally less than 2 helical turns (21).

The helicase motifs are clustered in the cleft between the two RecA-like domains (Figure 1). They form the ATP and RNA binding sites. The Q motif (38) contacts the nucleotide base, providing a specificity for ATP (7). The N-terminal RecA-like domain of all DEAD box helicases contains motifs I-III. Motifs IV-VI are in the C-terminal domain (34). When ATP and RNA are absent, the helicase is in an open conformation and the two RecA-like domains do not interact (39). Upon binding of RNA and ATP, the helicases domains close (40). In the structures of DEAD-box proteins bound to ssRNA, the phosphate backbone is kinked (Figure 1) (41, 40, 42, 43). This may aid in duplex destabilization, thereby providing a mechanism for unwinding short duplexes. Many contacts are made between the DEAD-box proteins and the RNA backbone, but little or no interactions with the bases are observed in the structures (40, 42, 43). Hydrogen bonding between the ribose 2'-OH and helicase motifs Ia, Ib, and IV confers specificity for RNA (42, 43).

ATP binding, but not hydrolysis, is required for strand separation (37, 44). *S. cerevisiae* DEAD-box proteins Ded1p and Mss116, and mammalian eIF4A can unwind dsRNA with the non-hydrolyzable ATP analog ADP-BeF_3, but not with ADP-AlF_4^- or ADPNP (37). These results suggest that ATP hydrolysis is needed for protein recycling, not strand separation. When bound to ATP, the helicase has a high affinity for RNA, but the ADP bound and free enzymes have low affinity for RNA (7, 45), resulting in release of the RNA after hydrolysis of ATP. Interestingly, although Mss116p functions differently with various ATP analogs, the structures of Mss116p bound to AMP-PNP, ADP-BeF_3, and ADP-AlF_4^- are all similar (41). Comparisons of the kinetic parameters for ATPase and unwinding reactions also suggest that ATP binding results in unwinding (44). ATP hydrolysis is not required for unwinding, but it is possible that ATP hydrolysis occurs after the dsRNA is melted due to ATP binding, but before the strands have completely separated. Helicase dissociation increases after ATP hydrolysis, but unwinding is faster than helicase dissociation, resulting in strand separation upon ATP hydrolysis. This could

explain the reduced unwinding rates with ADP-BeF_3 compared to ATP (37). Local unwinding, whether or not it is accompanied by ATP hydrolysis allows the remainder of short duplexes to spontaneously melt. Due to this unwinding mechanism, the unwinding rate constants decrease as duplex length and stability increase (21). With longer duplexes, the enzyme is likely to dissociate following ATP hydrolysis before the strands are completely separated, resulting in nonproductive ATP hydrolysis (44).

DbpA appears to be an exception. ATP and RNA bind cooperatively to most DEAD-box proteins (45, 46, 47, 48), and this has been accepted as a characteristic of DEAD-box proteins (34). However, kinetic studies on DbpA indicate no cooperativity in binding (49). Also, when the equilibrium and rate constants of each step in the ATPase cycle of DbpA were measured, it was found that the high affinity RNA binding state is ADP-bound (50), in contrast to other DEAD-box proteins which have high affinity for RNA when bound to ATP. Upon release of phosphate from the ADP-P_i bound state, the DbpA loses its high affinity for RNA and returns to the low affinity state. This results in unwinding of an 8 nucleotide nucleic acid strand after ATP hydrolysis, but before phosphate release (50). This is in contrast to Ded1p, Mss116p, and eIF4A which all unwind dsRNA before ATP hydrolysis, as shown in Figure 2 (37).

4.1.1. Destabilization mechanism

Since unwinding can occur in the absence of ATP, a destabilization mechanism has been suggested (Figure 2) (7, 34). ADP-bound and the free protein have low affinity for RNA for most DEAD-box proteins (37, 44). Helicase bound to ADP and P_i (49) or bound to non-hydrolyzable ATP analogs (37) has high affinity for RNA. The rate limiting step in unwinding is phosphate release (49). This is in agreement with unwinding occurring in the presence of ADP-BeF_3 for some DEAD-box proteins (37). The kink in the ssRNA bound in the active site disrupts base pairing and causes separation of a few base pairs of the dsRNA substrate (step 2 in Figure 2), which has been suggested to be the initial step in unwinding (43). Strand separation occurs before ATP hydrolysis, but ATP hydrolysis is required for enzyme recycling (37) (step 5 in Figure 2). Since the substrates unwound are short duplexes, destabilization of a small portion of the duplex may be sufficient for unwinding as the remainder of the duplex may spontaneously melt. Since AMP-PNP and ADP-AlF_4^- binding also produce a kink in the RNA, but not unwinding, a rearrangement of the protein/ATP complex before hydrolysis has been suggested (34). This is consistent with two phase nucleotide binding (49). Based on these data, a model where the protein binds to ATP and dsRNA rearranges to a hydrolysis competent form has been proposed (7, 34, 41). Rearrangement can occur when ADP-BeF_3 is bound, so unwinding can occur. Rearrangement does not take place when ADP-AlF^-_4 or AMP-PNP is bound, so no unwinding occurs. ATP hydrolysis (step 4 in Figure 2) occurs after dissociation (unwinding) of the first RNA strand (step 3 in Figure 2) (37). The hydrolysis of one ATP molecule either nearly or completely unwinds a short helix due to a kink that distorts the duplex RNA. For longer duplexes, the dsRNA may not be separated by the local distortion of the duplex, resulting in ATP hydrolysis while duplex RNA is bound to the enzyme (no unwinding) (44). After ATP hydrolysis, the enzyme is bound to ssRNA (or dsRNA if unwinding did not occur due to a long or stable duplex), ADP, and P_i (step 4 in Figure 2). The ADP-P_i bound helicase has high affinity for RNA, so phosphate likely dissociates before RNA. This causes the enzyme to return to the open conformation, where ADP and RNA are released (step 5 in Figure 2) (49, 45).

4.2. Ski2-like

Ski2 family members are RNA helicases essential for removal of polyadenylated RNA from the cell (51, 52), and are thought to unwind secondary structure in and displace proteins from the RNA targeted to the exosome (53). mRNA is degraded in eukaryotes in the 5'-to-3' direction by the exonuclease XRN1 and in the 3'-to-5' direction by the exosome, a complex of exonucleases and the Ski complex which includes a Ski2 helicase (54, 55). Ski2 helicases translocate on ssRNA and unwind dsRNA in the 3'-to-5' direction (56). Eukaryotes have nuclear and cytosolic exosomes. XRN1, the cytosolic exosome, and the Ski complex are also a part of the nonsense-mediated decay (NMD) pathway that degrades mRNAs with premature translation termination codons and the nonstop decay (NSD) pathway that eliminated mRNAs without stop codons (55). The nuclear exosome interacts with the TRAMP (Trf4-Air1-Mtr4) complex which recognizes polyadenylated RNA substrates. Trf4 is a poly(A) polymerase, Air1 is a Zn knuckle protein, and Mtr4 is a member of the Ski2-like RNA helicase family (53).

4.3. Viral NS3/NPH-II

Viral NS3/NPH-II helicases are DExH helicases encoded by many positive strand RNA viruses that unwind substrates with a 3'-ssNA overhang (57, 58). NPH-II requires a RNA loading strand (59). It translocates along the loading strand through an interaction with the sugar-phosphate backbone (60). NPH-II has been proposed to unwind RNA by strand exclusion (wire-stripper or wedge mechanism) (60). Nicks in the displaced strand do not affect unwinding by NPH-II or NS3, but both are halted by nicks in the loading strand (60, 61), indicating that these enzymes track along one of the strands.

A number of the *Flaviviridae* family of viruses encode a SF2 helicase, including hepatitis C, dengue virus, West Nile virus, yellow fever virus, and Japanese encephalitis virus (62). Hepatitis C virus (HCV) nonstructural protein 3 (NS3) is a dual function helicase/protease. The C-terminal portion forms a SF2 helicase (3, 1) while the N-terminal domain forms the protease. The HCV nonstructural proteins replicate and package the viral genome, and NS3 is required for viral replication (58).

Several structures of the helicase domain of NS3 (NS3h) (63, 64) and full length NS3 (65) from Hepatitis C have been solved. The structures suggest that translocation of 1 nucleotide per ATP hydrolyzed occurs in a ratcheting or inchworm mechanism due to several conformational changes that occur upon ATP binding and hydrolysis (64). NS3 has been reported to have a large kinetic step size of 11-18 base pairs (66, 67, 68) composed of smaller steps of 3 base pairs (69) and 1 base pair (63, 64, 69). The large kinetic step size has been proposed to be due to slow dissociation of the displaced strand from an as yet unidentified site on the enzyme (70). Using single-molecule FRET, Myong *et al* (69) observed unwinding in three base pair steps, with smaller translocation steps of one nucleotide (69). A spring-loaded inchworm mechanism was proposed based on this data in which three translocation steps of one nucleotide each produce strain in the enzyme's structure. Release of the strain occurs when the trailing edge of the enzyme springs forward to melt three base pairs. This model received support from recent crystal structures (71) which indicated that the leading edge of NS3 could translocate one nucleotide while the trailing edge remained bound to the same RNA bases of the 3'-end of the RNA (71). It is possible that some form of 'scrunching' of RNA might also account for the single molecule FRET data as has been reported for the SF1 helicase UvrD (15).

4.4. DEAH/RHA

The DEAH family of RNA helicases is found in eukaryotes (72) and prokaryotes (73). It is distinct from the NS3/NPH-II (viral DExH) family of helicases (74). It is named for human RNA helicase A (RHA) and for the conserved sequence of the Walker B box. DEAH/RHA helicases have two conserved domains C-terminal to the two RecA-like helicase domains (72). One is a helicase-associated domain and the other has unknown function. These domains are required (73) and are specific to DEAH/RHA helicases; viral NS3/NPH-II helicases do not have these conserved domains (74).

DEAH/RHA helicases are involved in ribosome biogenesis (Dhr1p and Drh2p in yeast, and DHX32 and DHX37 in humans) and mRNA splicing (Prp2p, Prp16p, Prp22p, and Prp43p in yeast and DHX8, DHX16, and DHX38 in humans) (72). In bacteria, DEAH/RHA helicases are also involved in RNA processing (73). Helicases in the human RHA subfamily (DHX9, DHX29, DHX30, DHX36, and DHX57) are involved in nuclear import and export, RNA localization, translational regulation, and splicing (75). RHA knockout mice were not viable (76). During splicing, DEAH/RHA helicases appear to remodel structural RNAs. Prp16p melts the U2/U6 helix in the spliceosome after cleavage of the 5'-exon (77). Prp22p catalyzes mRNA release from the spliceosome by translocating on the mRNA (78). Prp43p is required for synthesis of both subunits of the ribosome (79, 80) and releases the lariat intron from the spliceosome in an ATP dependent process (81, 82, 83, 84).

The structure of Prp43p is similar to the Ski2-like DNA helicase Hel308 (74). Like Hel308, Prp43p has a ratchet domain. Stacking interactions with amino acids of the helix and the nucleic acid are proposed to pull the ssNA into the active site and allow the helicase to translocate along the NA in a processive manner (85, 74). However, unlike Hel308, C-terminal to the RecA-like domains, Prp43p has an oligonucleotide/oligosaccharide-binding (OB)-fold that is characteristic of DEAH/RHA proteins. The OB-fold is required for ATPase activity, interaction with protein partners, and increases its affinity for RNA (74). The helicase interacts with the nucleic acid through the phosphate backbone. ATP is bound in a conformation similar to that of NS3/NPH-II helicases (86), not like it is typically bound in DEAD-box helicases (43) or Ski2-like helicases (85). Since DEAH/RHA and Ski2-like helicases share a similar structure, it suggests that the catalytic mechanisms are similar between these two families. Ski-2-like helicases translocate in the 3'-to-5' direction along the ssNA, with a beta-hairpin (Figure 3) causing strand separation (74).

4.5. RecQ-like

RecQ-like helicases are involved in DNA recombination, telomere maintenance, and DNA damage signaling (87). They reduce illegitimate recombination by unwinding branched DNA structures (88). Cells lacking RecQ proteins have increased recombination and chromosome missegregation, in addition to defects in meiosis. There are five human RecQ-like helicases (BLM, WRN, RecQ1, RecQ4, and RecQ5) (29). Mutations in three are associated with predispositions to cancer and premature aging (33, 89, 87, 32). Mutations in BLM are associated with Bloom's syndrome (90), WRN with Werner's syndrome (91), and RecQ4 with Rothmund-Thomson syndrome (92). RecQ helicases interact with the recombination and replication complexes to remove intermediates during recombination and to stabilize replication forks, thereby aiding in maintenance of genomic integrity (29).

RecQ family members are 3'-to-5' DNA helicases. In addition to duplexes, they can unwind triplexes, quadruplexes, and 3- and 4-way junctions (29, 93). The beta-hairpin (Figure 3) is required for unwinding, HJ resolution, dimer and tetramer formation. The oligomeric properties may regulate some functions of these helicases. Monomers unwind DNA, although dimers are preferred; tetramers are required for HJ resolution by RecQ1 (23) and hexamers of WRN are needed for strand annealing (24).

4.6. Rad3/XPD

Rad3 family members in humans include: XPD, involved in nucleotide excision repair (NER) and RNA transcription, FancJ, involved in recombinational repair, Rtel1, involved in homologous recombination (HR) by

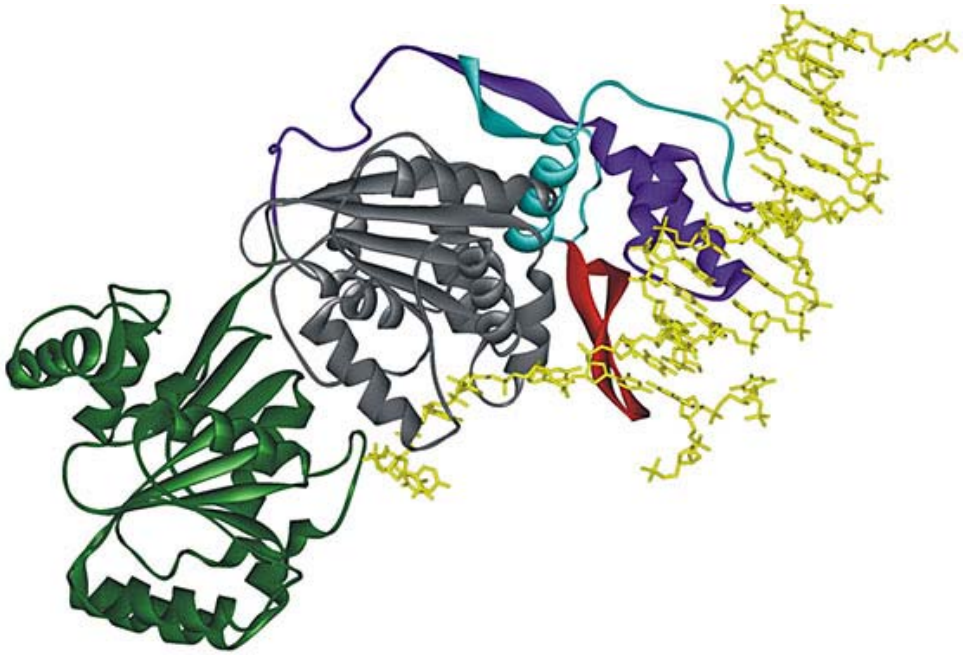

Figure 3. The crystal structure of the human RecQ1 (Protein Data Bank code 2WWY (23)) shows the beta-hairpin separating the strands of duplex DNA. The two RecA-like domains are colored in green and gray. The Zn domain is purple. The winged helix domain is cyan, and the beta-hairpin is red.

unwinding toxic recombinational intermediates, and ChlR1, involved in sister chromatid cohesion (94). XPD is part of the transcription factor II H (TFIIH) complex which initiates transcription of genes regulated by RNA polymerase II promoters. The helicase activity of XPD is required in NER, but only its presence, not its activity, is required for transcription initiation (95). Mutations in *XPD* affect nucleotide excision repair, resulting in photosensitivity and an increased risk of skin cancer (32). Three distinct disorders can result, *Xeroderma pigmentosum* (XP), a predisposition to cancer, and the aging disorders: trichothiodystrophy (TTD) and Cockayne Syndrome (CS), depending on whether the helicase activity, interactions with TFIIH or both are affected (96). All have photosensitivity, but only XP has increased risk of skin cancer. CS and TTD have developmental disorders and premature aging. CS is more severe with patients exhibiting mental retardation (96).

All members of the Rad3 family that have been studies are 5'-to-3' DNA helicases involved in DNA repair, and genome maintenance. They translocate on ssDNA and unwind dsDNA (97). Two insertions into helicase domain 1 distinguish Rad3 family helicases from other SF2 helicases: an Arch domain (98, 99, 100) and an iron-sulfer (FeS) cluster (101). A mutation in the FeS domain of XPD causes TTD (102). A mutation in the FeS domain of FancJ causes Fanconi anemia (103) and a predisposition to early-onset breast cancer (102, 104). The FeS domain forms a secondary ssDNA binding site and couples ATP hydrolysis to translocation on ssDNA (97, 101).

Honda *et al.* (97) used a single molecule approach to simultaneously monitor translocation of the XPD helicase from *Ferroplasma acidarmanus* in the presence of ssDNA binding proteins (SSB) RPA1 and RPA2. Both SSBs have similar DNA binding affinities, but had different effects on XPD translocation. RPA1 competed with XPD for binding, and RPA2 did not interfere with XPD binding to ssDNA, but slowed down XPD translocation. RPA2 facilitates XPD binding to DNA by bending the DNA. RPA1 and competes with XPD for DNA binding by extending the DNA. When XPD encountered RPA1, it displaced it from the DNA. However, RPA2 was not displaced from ssDNA during translocation. XPD bypassed RPA2 without displacing it from DNA. Simultaneous visualization of both the helicase and its obstacle brought them to the conclusion that XPD can translocate on the protein-coated ssDNA without disrupting the protein-nucleic acid complex. SF2 helicases translocate along the phosphodiester backbone of nucleic acids (4), and RPA binding to ssDNA primarily involves the bases (105, 106). Since the helicases contacts the DNA backbone while the SSB interacts with bases, this allows both proteins to be bound simultaneously to the same region of ssDNA and allows the helicase to move by the SSB. Translocation over the bound protein and displacement of the protein both provide mechanisms for these helicases to bypass ssDNA binding proteins (97).

4.7. Swi/Snf

Swi/Snf complexes are involved in diverse processes in the cell, including replication, DNA repair,

regulation of RNA polymerase II and III, cell signaling, cell cycle progression, metamorphosis, and tumor suppression (107, 108). Many of these processes involve their ability to remodel chromatin. This occurs by a variety of mechanisms, including repositioning histone octamers, unwrapping the DNA around an octamer, ejection of a histone octamer, or dimer, or exchange of a histone dimer (108, 107).

Chromatin remodeling complexes are large, multisubunit complexes that change the structure of nucleosomes to vary the accessibility of the DNA (109). They all contain a member of the Swi/Snf family of helicases, but the other components of the complex vary, and can be used to subdivide the family (31, 110). Swi/Snf helicases are subdivided into Snf2, ISWI, CHD, INO80, CSB, RAD54, and DDM1 subfamilies of chromatin remodeling proteins (109, 108). The INO80 subfamily is involved in DNA repair and activation of transcription (108). It is the only member of the family which has been shown to have helicase (unwinding) activity (31). Snf2 subfamily members disrupt nucleosomes and ISWI subfamily members can assemble nucleosomes, resulting in repression of transcription (31). CDH subfamily members have been implicated in chromatin remodeling and transcription activation (108, 31). Cockayne Syndrome protein B (CSB) is involved in NER and remodels chromatin (111). DDM1 is required for maintaining proper DNA methylation in the plant *Arabidopsis thaliana* (112). Rad54, along with Rad51, is involved in HR (31, 113). Mutations in ATRX, a Rad54 family member, result in ATR-X syndrome, characterized by alpha-thalassemia and mental retardation (114). The majority of the mutations that have been linked to the disease occur in the helicase domains and the histone H3 binding domain (115). ATRX localizes to telomeres and other repetitive DNA sequences, in particular sequences that have the potential to form quadruplexes (116, 114).

Swi/Snf helicases have a high affinity for nucleosomes and are able to recognize histone modifications. The translocation activity of the helicase can reposition or eject histones from the DNA. This activity is modulated by other associated subunits of the remodeling complexes (108, 107). Several mechanisms have been proposed for nucleosome sliding (117). In the twist diffusion model (118), a single base pair is shifted from the linker to wrapped around the nucleoseome core with an accompanying twist to accommodate an extra base pair. Because a rotation of ~35° would be required for each base pair, this is not likely to be the mechanism of histone repositioning by Swi/Snf (117). Another model is the histone core swiveling model. It proposes that the nucleosome rotates relative to the DNA (117). Two variations of the loop or bulge propogation model have been proposed. In one, the remodeling protein pulls the DNA from the nucleosome entry or exit site, resulting in a bulge. In the second, the protein binds to an internal site and pulls DNA from the linker. They propose that the helicase binds to the DNA and upon ATP hydrolysis, the dsDNA is translocated, without being unwound, while the remodeling complex remains bound to the nucleosome (108, 109). This results in formation of a loop of DNA on the surface of the nucleosome where the histone-DNA contacts are broken (19, 119, 120, 18). This loop moves around the nucleosome, repositioning the nucleosome. Loops are visible in single molecule experiments, and the direction of translocation has been observed to switch (18, 121). It is unknown whether the helicases can translocate in either direction on DNA or whether the nucleosome rebinds in the opposite orientation. In addition to repositioning of nucleosomes, small DNA loops can also allow replacement of dimer with a modified dimer or ejection of dimers or nucleosomes by remodelers or localized unwrapping (108).

4.8. RIG-I-like

RIG-I-like helicases are involved in the antiviral immune response (122). Dicer has RNase activity for dsRNA (123) and a RIG-I like helicase domain. The helicase is required for efficient processing of pre-miRNA, and may allow Dicer to cleave structured viral RNAs (124, 125). RIG-I serves a sensor of viral RNA to initiate an immune response that leads to production of interferon (IFN) (126). Activation of two N-terminal caspase activation and recruitment domains (CARDs) occurs by recognition of 5'-triphosphate (127, 128) or dsRNA (126). 5'-triphosphates and dsRNA are present during viral replication but not during most cellular processes (129). In the presence of viral RNA, CARD ubiquitination results in IFN expression (130). RIG-I also has a C-terminal regulatory domain (RD) and is a DExH box RNA helicase. The RD inhibits signaling when viral RNA is absent. The ATPase activity of the helicase is required for signaling (126). The helicase has dsRNA translocase activity, but does not unwind the RNA (17). The CARDS prevent translocation of RIG-I in the absence of 5'-triphosphate recognition by the RD (17). In the presence of viral triggers, RIG-I tranlsocates on the RNA strand in a RNA/DNA heteroduplex or on dsRNA (17).

4.9. Type I restriction enzymes

Restriction enzymes or endonucleases are part of the restriction-modification system in bacteria (131, 132). They protect the bacterial genome against cleavage by methylating target sequences and restriction of foreign DNA. They are classified into three groups (types I-III) based on their recognition sequence, subunit composition, cleavage position, and cofactor requirements (133, 134). Type I restriction enzymes (T1RE) are pentamers made up of three different subunits: specificity (S), methylase (M), and restriction (R) with R2M2S stoichiometry (135, 131). They are encoded by the Host Specificity for DNA (*hsdS, hsdM*, and *hsdR* genes (136). A dimer of two R2M2S holoenzymes, with each bound to a target sequence, is the active form of the enzyme for restriction of the DNA (132).

Bacterial DNA is methylated, and T1RE dissociate upon binding to fully methylated DNA (137); therefore T1RE have no effect on host DNA. Hemi-methylated DNA is methylated at the target sequence (137). HsdM and HsdS are sufficient for methylation (136). When the target sequence is unmethylated, HsdR restricts the foreign DNA (132).

All T1RE utilize S-adenosyl methionine (SAM) as the methyl donor for the methylation reaction, catalyzed by HsdM (138). It is also required for DNA restriction for most T1RE, EcoR124I being the exception (138, 139). The HdsS subunit recognizes and binds to a non-methylated DNA sequence containing two 3-5 base pair domains separated by a 6-8 base pair spacer (138). After binding, the enzyme translocates dsDNA in an ATP dependent manner toward the enzyme while it remains bound to the recognition sequence (140), resulting in formation of dsDNA loops (141). HsdR contains both a helicase domain, and an endonuclease domain (138). T1RE are not known to unwind dsNA (138) but appear to function as a dsDNA translocases (142). After translocation of 400 to 7000 basepairs (138), while remaining bound to the target sequence, the DNA is cleaved by nicking of each strand by one HsdR subunit (143). The cleaved DNA can then be degraded by exonucleases (ie: RecBCD).

A model describing T1RE was proposed by Szczelkun (144). The enzyme binds to the DNA at the target sequence, upon binding of ATP. Two holoenzymes bind to non-methylated target sequences and associate to form a dimer. ATP dependent dsDNA translocation occurs, while remaining bound to the target sequence, resulting in formation of loops. Eventually, translocation is impeded, possibly due to a collision with another protein, and the DNA is cleaved, resulting in enzyme dissociation.

4.10. RecG-like

RecG-like helicases are involved in resolution of recombination intermediates through translocation on dsDNA. In prokaryotes, Mfd removes RNA polymerase from stalled replication forks by destabilizing its interaction with the transcription complex during translocation (145, 146). PriA recognizes and binds to D-loops formed during recombination and loads the replisome onto the branched DNA to allow restart of replication (147, 148). RecG limits origin independent DNA replication (149, 150).

Until recently, RecG was believed to catalyze Holliday junction intermediate branch migration in a pathway that overlaps functionally with the RuvABC pathway (151). However, it now seems likely that RecG may function to limit replication at sites remote from *oriC* initiated by PriA (152). RecG translocates on dsDNA and catalyzes Holliday junction branch migration (153), in addition to unwinding various branched DNA substrates, *in vitro* (154). RecG decreases replication by unwinding D (147) and R (155) loops, which prevents PriA from loading DnaB helicase at the branch, leading to assembly of the replisome and replication (156, 157). By resolving these loops, RecG limits replication to *oriC* (152).

PriA, on the other hand, binds to and stabilizes stalled replication forks, eventually leading to replication restart (158). PriA has a 3'-terminus binding pocket that binds specifically to the 3'-end of the invading strand in the D loop (147) or the nascent leading strand (159) and displaces the nascent lagging strand (160). Primasome assembly at stalled replication forks is dependent upon PriA (148).

5. CONCLUSIONS

Superfamily 2 is a diverse group of helicases. Although some sequence motifs are conserved among all families, there are motifs that are unique to separate families (1, 25). All SF2 helicases are capable of binding nucleic acids and have nucleic acid stimulated NTPase activity (3). However, some families, such as type I restriction enzymes and RIG-I do not perform the canonical helicase reaction of unwinding duplex NA (132). DEAD-box family members unwind RNA, but without translocation (34). In some cases, DEAD-box helicases even unwind dsRNA without ATP hydrolysis (44).

Crystal structures of Hel308 (85), an archaeal Ski2-like helicase, and RecQ1 (23, 161), a RecQ-like helicase, complexed with a single-strand/double-strand junction contain a beta-hairpin loop in a position where it could separate the strands of dsNA (Figures 3 and 4). Interestingly, HCV NS3 and *S. cerevisiae* Prp43p, which also unwind duplex nucleic acids in a translocation dependent process, also contain a prominent beta-hairpin (Figure 4A). XPD also unwinds dsNA and translocates on NA, but it contains a wedge made of two alpha-helices instead (Figure 4B). Another way that helicases couple translocation to unwinding is through a formal wedge domain, such as in the case of *T. maritima* RecG. It has a beta-hairpin on one side of the three-way or four-way junction and a wedge domain on the other which separate the dsDNA on each side of the junction simultaneously (162). The DEAD-box helicase mss116p unwinds dsRNA without translocation, and its structure complexed with a single-strand/double-strand junction does not appear to contain a beta-hairpin (Figure 4C). Structures of SWI2/SNF2, RIG-I-like Hef, and the type I restriction enzyme EcoR124I also do not appear to have a beta-hairpin (Figure 4C). These enzymes are known to translocate on nucleic acids, but not unwind dsNA. Thus, the beta-hairpin may be a conserved feature among helicases that translocate on dsNA to unwind the duplex. Pin-like structures have been proposed to serve the purpose of splitting the duplex in SF1 helicases PcrA (161) and UvrD (85) and RecD2 (163). The lack of such a structure in some SF2 helicases may serve to further distinguish

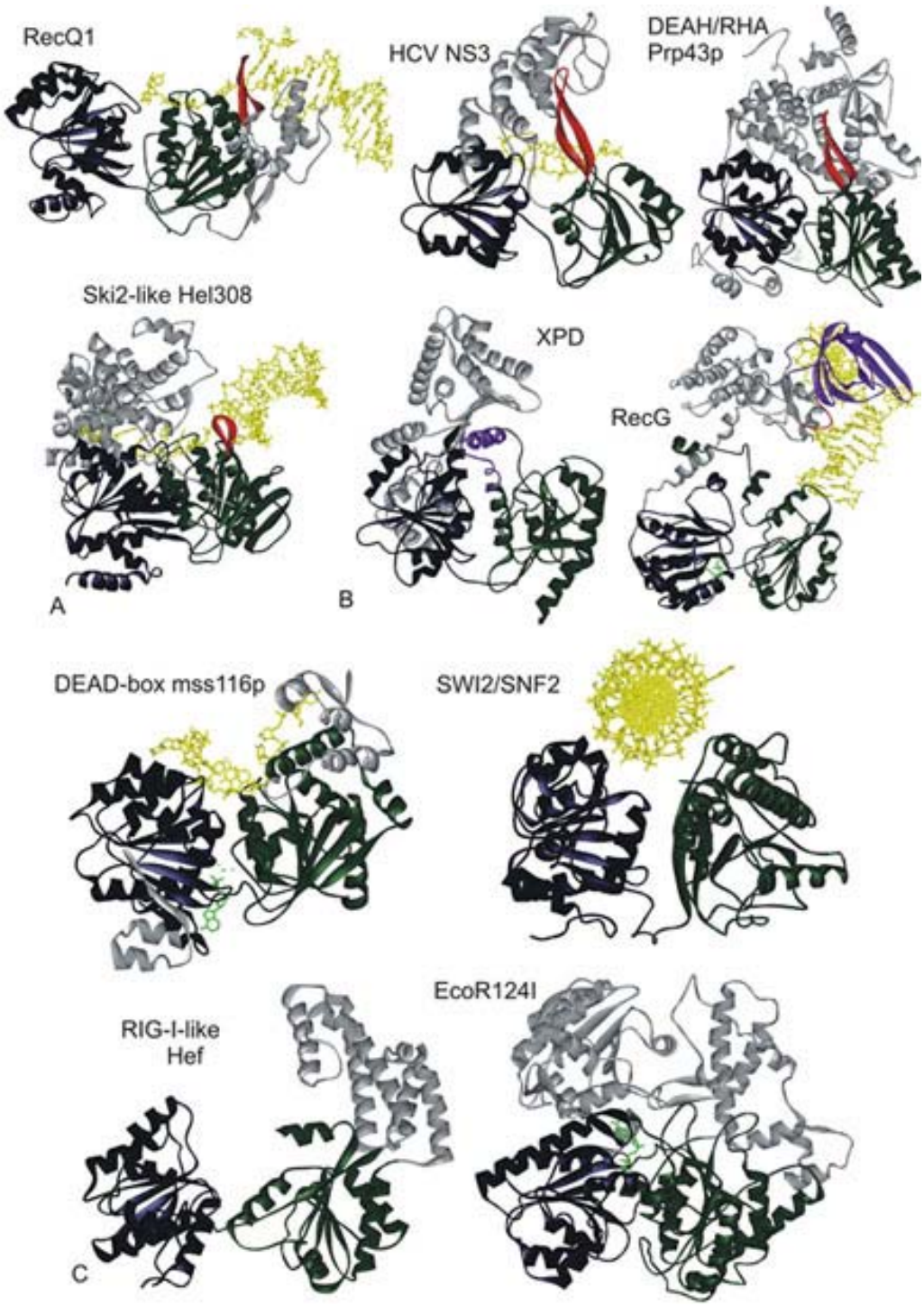

Figure 4. A. Families containing helicases that unwind duplex nucleic acids using a mechanism dependent on translocation upon the substrate contain a beta-hairpin. The Protein Data Bank codes are RecQ1: 2WWY (23), NS3: 1A1V (63), Hel308: 2P6R (85), and Prp43p: 2XAU (74). B. XPD (Protein Data Bank code 2VSF (100)) has translocase and helicase activity, but does not have a beta-hairpin. Instead, the wedge appears to be formed from two alpha-helices (100). RecG (Protein Data Bank code 1GM5 (162)) has a beta-hairpin and a wedge domain which simultaneously separate two arms of a DNA fork. C. Families which either do not unwind nucleic acids, or unwind without translocating, do not have the beta-hairpin. The Protein Data Bank codes are Mss116p: 3I61 (41), SWI2/SNF2: 1Z63 (166), Hef: 1WP9 (167), and EcoR124I: 2W00 (168). In each of the structures, the N-terminal RecA-like domain is navy and the C-terminal RecA-like domain is green. Accessory domains are gray, except the beta-hairpin, which is red and wedge domains are purple. Nucleic acid is yellow and nucleotide is green.

structure-function relationships among this large, diverse class of enzymes.

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Abbreviations: NTP, nucleoside triphosphate, ss, single-stranded, NA, nucleic acid, ds, double-stranded, SF, superfamily, RNP, RNA-protein complexes, Pi, inorganic phosphate, HCV, hepatitis C virus, DENV, dengue virus, SAM, S-adenosyl methionine, T1RE, type I restriction enzyme, HJ, Holliday junction, TFIIH, transcription factor IIH, NER, nucleotide excision repair, HR, homologous recombination, XP, Xeroderma pigmentosum, TDD, trichothiodystrophy, CS, Cockayne's Syndrome, Pi, inorganic phosphate, RHA, RNA helicase A, CARD, caspase activation and recruitment domains, RD, regulatory domain

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