BOX 2 - BLM, WRN, Sgs1 and Srs2 helicases -

The RecQ protein family are 3'-5' helicases and involved in recombination. Mutations in three of the human orthologs, BLM, WRN, and RTS cause Bloom's, Werner's and Rothmund-Thomson syndromes, respectively, and are characterized by genetic instability, due to hyperrecombination, and cancer.

Studies reveal that BLM forms foci upon HU treatment, which co-localize with its heterodimeric partner TOPO IIIα and also with RAD51, PCNA, γ-H2AX and ATR (by which it can be phosphorylated). Also, BLM deficient cells fail to recover from S-phase arrest (88) and BLM is required for HU induced co-localization and association of p53 with RAD51 (391).

Equally, the WRN mutation leads to sensitivity to DNA damage. Suppression of RAD51-dependent recombination leads to increased survival of the WRN mutant following DNA damage (380). Furthermore, the mutant could be rescued by over-expression of RusA, suggesting that WRN functions in resolving recombination structures (HJs).

The yeast RecQ homologues are called Rqh1 in *S. pombe* and Sgs1 in *S. cerevisiae*. Both mutants display genomic instability and are deficient in DNA repair (128). Sgs1 is involved in proper S-phase checkpoint functioning upon perturbed DNA replication via interaction with Rad53 (116) and forms a heterodimer with topoisomerase Top3.

Another 3'-5' helicase in budding yeast is Srs2. The double mutant Sgs1-Srs2 is synthetically lethal, but can be rescued by an additional deletion of *RAD51* (or *RAD55, RAD57*). Both Sgs1 and Srs2 are involved in DNA replication (and transcription) and suppress crossovers during DSB repair (128, 238, 485). Srs2 is also involved in proper S-phase checkpoint functioning (467). As the synthetic lethality suggests, both helicases may (partially) substitute for each other when a cell is challenged with compounds interfering with DNA replication, but there are also differences.

Srs2 disrupts the pre-synaptic Rad51 nucleoprotein filament by removing Rad51 (218, 468). On the other hand, Sgs1 will probably function as its mammalian homologue BLM, acting at a later stage of recombination. BLM can resolve recombination intermediates with dHJs by reversing the branch migration and its partner TOPO IIIα resolves the junction by strand passage (485).