

Gene Section

Review

RAD52 (RAD52 homolog (*S. cerevisiae*))

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Abstract

Review on RAD52, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

HGNC (Hugo): RAD52

Location: 12p13.33

DNA/RNA

Note

The human and murine RAD52 gene is composed of 12 exons.

Kito et al. identified three RAD52 isoforms designated RAD52 β (226 amino acids), RAD52 γ (139 amino acids), and RAD52 δ (118 amino acids) which were able to bind ssDNA and dsDNA much like reference RAD52 (RAD52 α). However, these isoforms lacked the ability to associate with RAD52 α (Kito et al., 1999).

Thorpe and colleagues describe two splice variants that conferred increased homology-directed repair in the murine RAD52 gene RAD52 Δ exon4 and RAD52+intron8 (Thorpe et al., 2006).

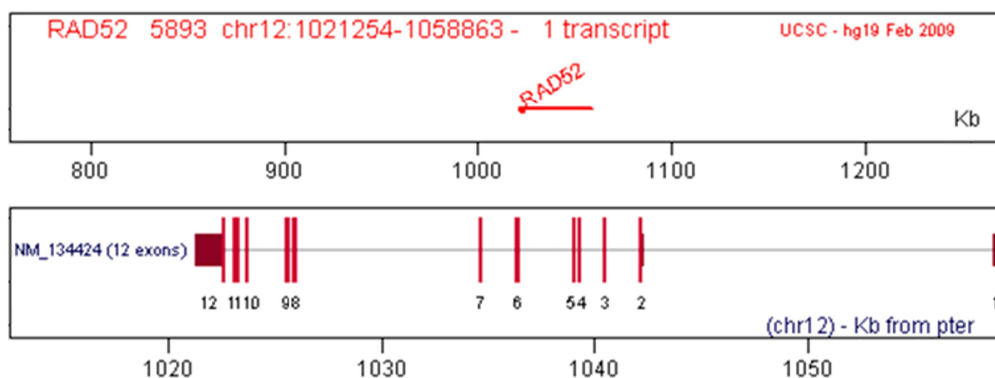
Protein

Note

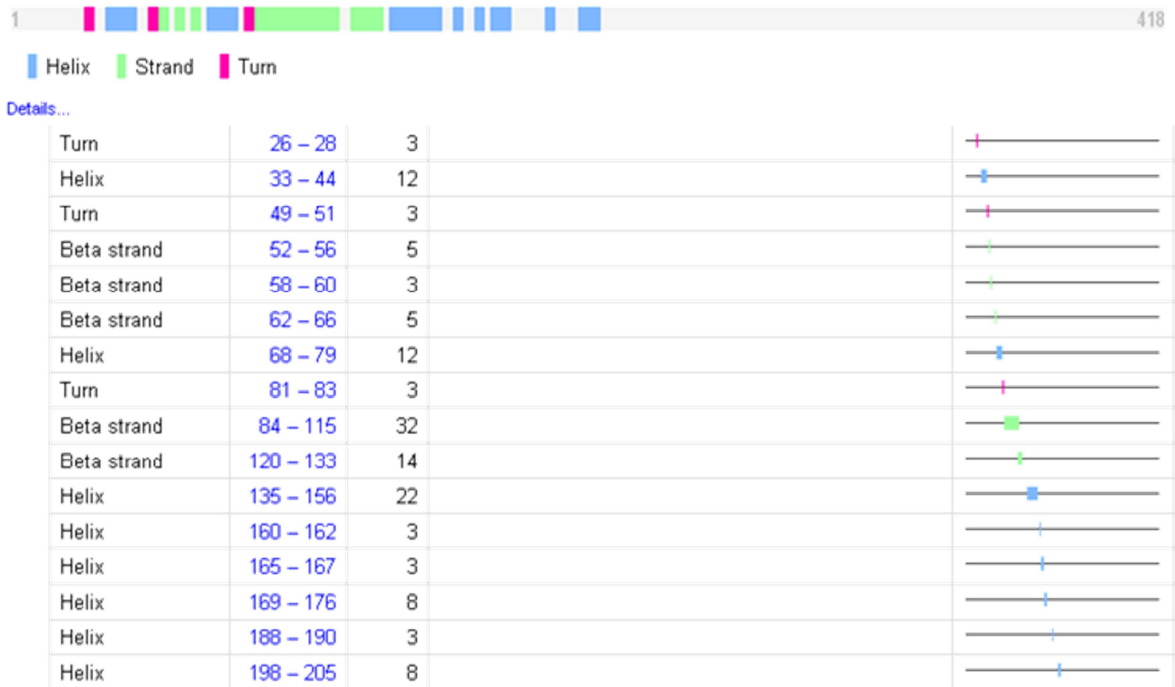
The human RAD52 (hRAD52) protein is similar to the *Saccharomyces cerevisiae* RAD52 protein (ScRAD52) both structurally and biochemically. However the phenotypic properties of RAD52, particularly in mediating homologous recombination varies amongst the evolutionary spectrum.

Description

hRAD52 protein is comprised of 418 amino acids and forms a heptameric ring (Stasiak et al., 2000), which is mediated by the N-terminus (Ranatunga et al., 2001). This N-terminal portion binds ssDNA (Mortensen et al., 1996).



Secondary structure



Secondary structure of the hRAD52 protein. From Uniprot.org (Creative Commons License).

The well-studied hRAD52₁₋₂₁₂ is the N-terminal portion which forms an undecameric ringed polymer (Kagawa et al., 2002).

DNA binding properties are linked to various amino acids, including, Arg-55, Tyr-65, Lys-152, Arg-153, Arg-156. Arg-55 and Lys-152 are necessarily for ssDNA binding, whereas Tyr-65, Arg-152, and Arg-156 are essential for binding both ssDNA and dsDNA (Kagawa et al., 2002).

Phe-79 and Lys-102 have also shown a role in ssDNA and dsDNA binding, respectively (Lloyd et al., 2005).

Interfering with the Phe-79 of hRAD52 was recently demonstrated to disrupt the RAD52-DNA interaction leading to an accumulation of DNA double-strand breaks (DSBs) particularly in BRCA1/2 deficient cells (Cramer-Morales et al., 2013).

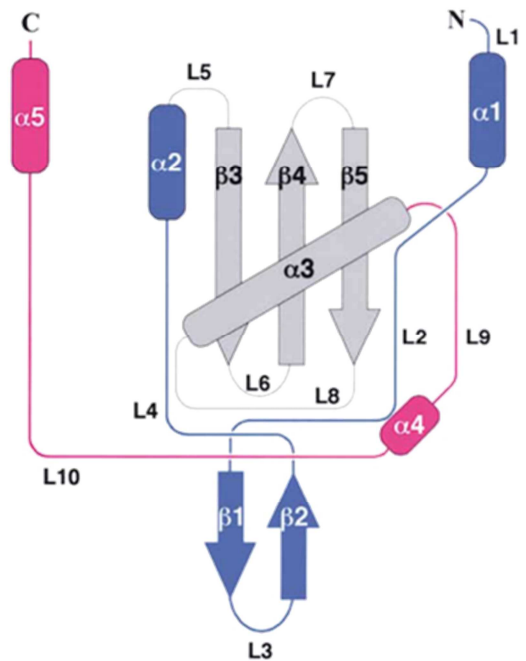
Further study is required to decipher the hierarchy of these respective sites and study additional novel binding sites.

Please see the following diagram for the location of several of these amino acid sites.

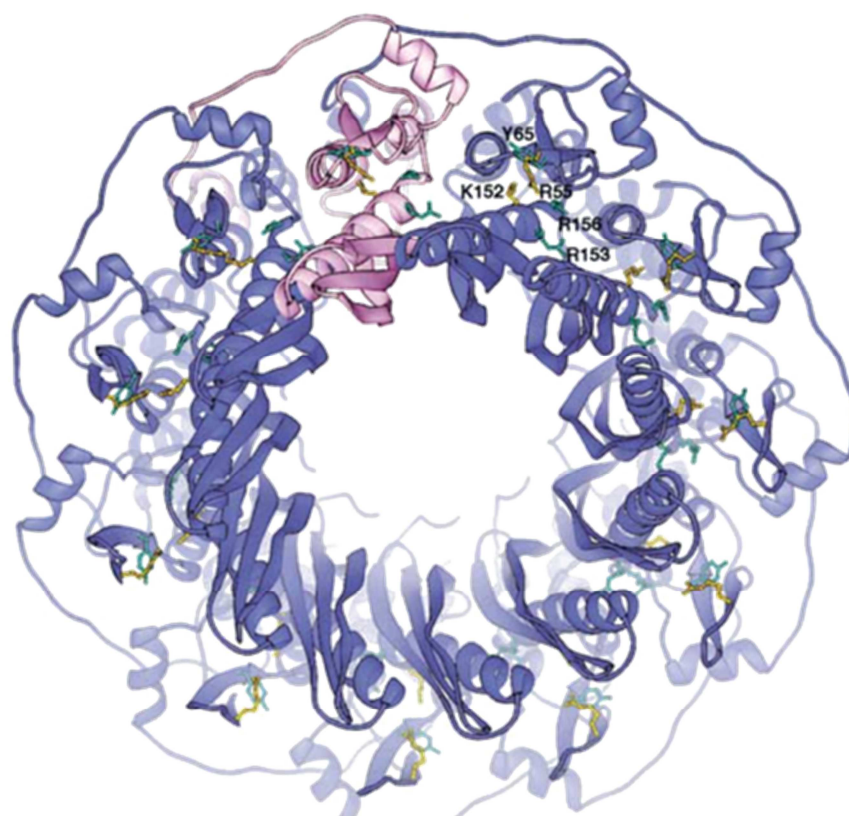
Localisation

ScRAD52 is a nuclear protein and predominantly recruited into sub-nuclear foci during the S-phase of the cell cycle (Lisby et al., 2001).

hRAD52 sub-nuclear foci formation after exposure to ionizing radiation is dependent on c-Abl-mediated phosphorylation (Kitao and Yuan, 2002).



Secondary structure of the hRAD52 protein. From Kagawa et al. 2002, with permission from Elsevier.



The hRAD52₁₋₂₁₂ undecameric polymer with principal DNA binding amino acid residues labeled residing in the predominantly positively charged groove. From Kagawa et al. 2002, with permission from Elsevier.

Function

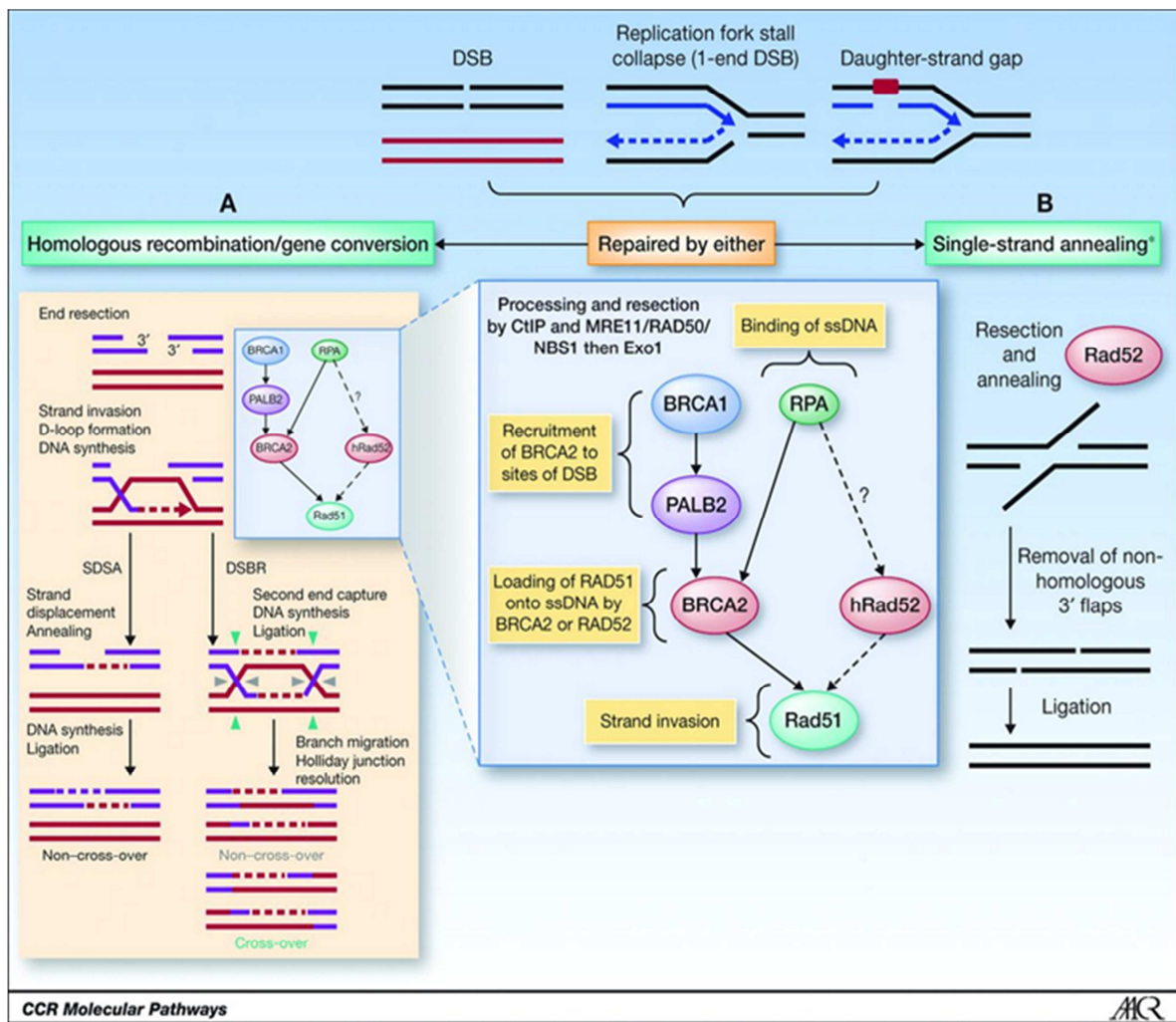
ScRAD52 mediates RAD51 recombination activity and thus homology-directed repair (Milne and Weaver, 1993). hRAD52 also demonstrates this ability to stimulate homologous pairing by hRAD51 (Benson et al., 1998). The interaction of ScRAD52 and hRAD52 with replication protein A (RPA) is important for the binding with ssDNA by RAD52 (Hays et al., 1998; Shinohara et al., 1998; Jackson et al., 2002). hRAD52 binds directly to DSBs, protects them from exonuclease resection, and facilitates end-to-end interaction (Van Dyck et al., 1999). Furthermore, capture of the second DNA end in homologous recombination appears to involve RAD52-mediated annealing of RPA-ssDNA strands in biochemical reactions (Sugiyama et al., 2006).

Although, ScRAD52 and hRAD52 does not stimulate RAD51 DNA strand exchange with RPA-ssDNA complexes in biochemical assays (Jensen et

al., 2010), under certain conditions, hRAD52 does promote RAD51-mediated homologous DNA pairing (Baumann and West, 1999).

hRAD52 mediates RAD51 recombination function in human cancer cells deficient in BRCA1 (Cramer-Morales et al., 2013; Lok et al., 2013), PALB2 (Lok et al., 2013) or BRCA2 (Feng et al., 2011). RAD52 is able to mediate RAD51-mediated homology-directed repair when the predominant BRCA1-PALB2-BRCA2 homologous recombination pathway is perturbed (see figure below). The RAD52-RAD51 pathway also appears to function independently of the RAD51 paralogs RAD51B/RAD51C/RAD51D-XRCC2 (Chun et al., 2013).

ScRAD52 is required for RAD51-independent single-strand annealing (SSA) (Singleton et al., 2002; Symington, 2002) and break-induced replication (BIR) (Malkova et al., 1996; Ira and Haber, 2002; McEachern and Haber, 2006).



The BRCA and RAD52 pathways of DNA double-strand break repair. *There is currently no well-defined evidence that single-end DSBs or daughter-strand gaps are repaired by single strand annealing. From Lok and Powell, 2012.

Species	Official gene name	Location
Homo sapiens (Human)	RAD52, H.sapiens RAD52 homolog (<i>S. cerevisiae</i>)	Chromosome 12
Pan troglodytes (Chimpanzee)	RAD52, P.troglodytes RAD52 homolog (<i>S. cerevisiae</i>)	Chromosome 12
Macaca mulatta (Monkey)	RAD52, M.mulatta RAD52 homolog (<i>S. cerevisiae</i>)	Chromosome 11
Canis lupus (Dog)	RAD52, C.lupus RAD52 homolog (<i>S. cerevisiae</i>)	Chromosome 27
Bos Taurus (Cow)	RAD52, B.taurus RAD52 homolog (<i>S. cerevisiae</i>)	Chromosome 5
Mus musculus (Mouse)	Rad52, M.musculus RAD52 homolog (<i>S. cerevisiae</i>)	Chromosome 6
Rattus norvegicus (Rat)	Rad52, R.norvegicus RAD52 homolog (<i>S. cerevisiae</i>)	Chromosome 4
Gallus gallus (Chicken)	RAD52, G.gallus RAD52 homolog (<i>S. cerevisiae</i>)	Chromosome 1
Danio rerio (Zebrafish)	rad52, D.rerio RAD52 homolog (<i>S. cerevisiae</i>)	Chromosome 25

Modified from HomoloGene.

Mutations

Note

Currently, there are no known mutations of RAD52 that lead to human disease, including none associated with breast cancer (Bell et al., 1999), ovarian cancer (Tong et al., 2003; Beesley et al., 2007) or chronic lymphocytic leukemia (Sellick et al., 2008).

Implicated in

Resistance to platinum-based chemotherapy

Prognosis

There is a report of uncertain significance by Shi et al. that may link certain RAD52 variants and RAD52 protein expression levels to resistance to platinum-based chemotherapy (Shi et al., 2012), however no other published studies have demonstrated a similar association.

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