Article

Interactome analysis and docking site prediction of DNA X-ray repair cross-complementing protein (XRCC) in *Arabidopsis thaliana*

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Abstract

There are seven homologs in eukaryotic RAD51 gene family which are conserved among animals and plants, and those are RAD51, DMC1, RAD51c, XRCC3, RAD51b, RAD51d and XRCC2. The first four of them are important in the process of homologous recombination, but also the DNA repair mechanism, while the other three show normal meiosis. RAD51, DMC1, RAD51c and XRCC3 have lineages that are divergent from the other three paralogs, showing potential functional redundancy. The repair mechanism also includes single- or double-strand break rejoining during replication, recombination and DNA damage, which is made by the DNA ligase enzymes. There are many DNA ligase enzymes, and the sequenced genome of Arabidopsis thaliana showed a homologue XRCC4 of the human DNA ligase IV binding protein. Arabidopsis thaliana encoded also homologues for the other six vertebrate Rad51 proteins. Our Results showed the XRCC2 and XRCC3 are interacting with Rad51c. Tow complexes will be formed; BCDX2 (RAD51B-RAD51C-RAD51D-XRCC2) and CX3 (RAD51C-XRCC3). The two complexes have a function at two distinct stages of homologous recombinational DNA repair.

Keywords DNA damage; DNA repair mechanism; interactome; domain; XRCC protein; RAD51.

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1 Introduction

The genome stability is a very important parameter of the cellular homeostasis. Each living organism has to be able to repair a damaged DNA by different repair mechanisms. One of the very common DNA damages, are the double-strand DNA breaks. They can be caused by ionizing radiation, different toxic chemicals or errors occurring during DNA replication. If an organism, a cell, fails to repair the damage in DNA breaks, this will cause mutations, genome instability, cell cycle arrest and it can also lead to cell death. Two major pathways for DNA double-strand break repair are the homologous recombination (HR) and non-homologous end-joining

(NHEJ). HR is more accurate than NHEJ, because NHEJ requires a template of similar sequence in order to repair the break, which can make insertions or deletions, while HR relies on the homologous DNA sequence. HR has also a big role in maintaining normal meiosis, taking care of right association of chromosomes (Wang et al., 2013).

The genes that are part of the HR pathway belong to the RAD52 group, which contains the RAD 51 family. On the other hand, the RAD51 family genes have a crucial role in HR and DNA repair mechanism (Jing et al., 2019). Those genes are DMC1, RAD51 and the paralogs RAD51B, RAD51C, RAD51D, XRCC2 and XRCC3. Mutations in those genes lead to DNA sensitivity as well as to cell death, which implies that those genes are an important part of the DNA repair in the mitotic cycle (Bleuyard and White, 2004).

To repair a double strand DNA break, a DNA ligase is needed. A homologue to the DNA ligase IV is found in the plant *Arabidopsis thaliana*, the XRCC4.

The homologues of the RAD51 have been studied in different animals, plants, fungi etc. The Arabidopsis thaliana genome sequence showed homologs of the five Rad51 genes: AT2G28560 (RAD51B), AT2G45280 (RAD51C), AT1G07745 (RAD51D), AT5G64520 (XRCC2) and AT5G57450 (XRCC3) (Bleuyard and White, 2004).

In the plant Arabidopsis thaliana, the RAD51 homologues function in the HR pathway for DNA repair in somatic and meiotic cells. Like in vertebrates, in *Arabidopsis thaliana*, there are seven homologs, which are separated into two subfamilies, RAD alpha (RAD51 and DMC1) and RAD beta (RAD51B, RAD51C, RAD51D, XRCC2 and XRCC3). One of our genes of interest, the XRCC3, has a non-redundant role in the meiotic HR. XRCC2 and XRCC3 both have a function in somatic DNA repair. Any mutation in those genes, shows increased sensitivity of DNA to damages (Wang et al., 2013).

The main goal and aim of this study was to demonstrate the analysis of the XRCC group of proteins and to get an understanding of their sequence structure and function in A. thaliana through a series of bioinformatic tools, we did the multiple sequence alignment, predicted and confirmed the 3D structure of XRCC2, XRCC3 and XRCC4, as well as showing protein – protein interactions with interacting proteins. The last step was the identification of docking sites between our protein of interest and interacting proteins in *Arabidopsis thaliana*.

2 Material and Methods

2.1 Retrieving protein sequences and multiple sequence alignment

The sequence of the XRCC2, XRCC3 and XRCC4 proteins were obtained from the National Center for Biotechnology Information (NCBI) Database. The ID/Accession numbers of XRCC2, XRCC3 and XRCC4 are shown in Table 1. Additionally, The Arabidopsis Information Resource (TAIR) Database was used to obtain the ID of the proteins. The same databases were used to obtain the ID/Accession numbers of the interacting proteins, as shown in Table 2.

For the multiple sequence alignment (MSA), Clustal Omega software was used, located on the website of the European Bioinformatics Institute (EBI). This software applies default parameters and executes aligned sequences (Chenna et al., 2003).

2.2 3D structure prediction and validation

In order to predict the 3D structure of our proteins, Phyre2 was used for protein structure and function prediction. This is a highly intuitive and user-friendly web-based tool and we used it to make our 3D models for the proteins of interest (proteins and interacting proteins) (Kelley et al., 2015). PyMOL gave the visualization of the models. PyMOL is a very popular molecular graphics program which makes it possible to visualize small and bigger molecules.

The validation of the 3D structures of our proteins was made through the software RAMPAGE. This is an

online server that makes a structural evaluation analysis and makes a Ramachandran plot. This plot is used to compare ψ/φ angle couples, in order to give us information about residues in this polypeptide of protein structure (Rhee et al., 2003).

2.3 Identification of domains

The software Simple Modular Architecture Research Tool (SMART) was used to identify and analyze the domains of XRCC2, XRCC3 and XRCC4 proteins. Besides that, the PFAM domain search was done (Schultz et al., 2000).

2.4 Subcellular localization of proteins

Subcellular localization of the three proteins, was done by using the Plant Subcellular Localization Integrative predictor (PSI – predictor). This is a relatively new, but highly reliable and integrative subcellular location predictor. SMART combines 11 individual prediction tools: cello, mPloc, Predator, mitoProt, MultiLoc, TargetP, Wolf PSORT, subcellPredict, iPsort, Yloc and PTS1. Thanks to these tools, the software gives accurate prediction of the location of the protein in all subcellular compartments (Tanz et al., 2012).

2.5 Prediction of the interactome

The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) contains currently proteins from 2000 organisms, and contains known and predicted protein – protein interactions. This software was used to see which proteins interact with our XRCC proteins and give us the information how strong the interactions are.

2.6 Docking site prediction

ClusPro 2.0 software was used to predict the docking sites for our XRCC proteins. It is a web based tool for protein – protein interaction prediction. After the software rotates the ligand protein 70 000 times, it chooses only 1000 combinations with lowest scores (Comeau et al., 2004).

3 Results

3.1 Multiple sequence alignment

First step in our protein analysis was the establishment of the amino acid sequences of our proteins of interest, namely the XRCC2, XRCC3 and XRCC4, which were taken from the NCBI database. The obtained sequences and their accession numbers from NCBI and ID numbers from TAIR are shown in Table 1. For further analyses and later determination of the docking sites, we also found the sequences of the interacting proteins, listed in Table 2. To be able to multiple align our sequences in the Clustal Omega online tool, we used the FASTA format sequences of XRCC2, XRCC3 and XRCC4 from the NCBI database and aligned the sequences. The tool has reported conserved regions between the three sequences.

Table 1 Accession numbers of XRCC2, XRCC3 and XRCC4 proteins.

Protein	TAIR ID	NCBI
XRCC2	At5g64520	OAO93797
XRCC3	At5g57450	OAO96242
XRCC4	At3g23100	OAP04777

Table 2 Names and accession numbers of the selected interacting proteins.

Protein	TAIR ID	NCBI
DMC1	At3g22880	OAP03373
RAD51c	At2g45280	OAP09768
RECQ4A	At1g10930	OAP12301
RAD50	At2g31970	OAP10613
MRE11	At5g54260	OAO95209
At1g52650	At1g52650	AAR24665
ARV1	At1g01020	AAV92715

3.2 Predicted 3D Structure models and Ramachandran plot confirmation

In order to be able to determine the function of a given protein, we have to know its structure. One of the ways to obtain an image of the structure of a protein is, generating its 3D image. This can be done using the Phyre2 online tool. 3D images of our proteins of interest are given in Fig. 1, Fig. 2 and Fig. 3. RAMPAGE validated the structures and in the mentioned Figures are the Ramachandran plots of our proteins. Results of the Ramachandran plot validation are also shown in Table 2.

3.3 Domain identification

The next step was annotation of the domains of our proteins in the SMART software, which predicted two domains of XRCC3 and one domain of XRCC4. Those are Pfam: Rad51, Pfam: AAA_25 and Pfam: XRCC4, respectively. Table 4 shows the domain sequences.

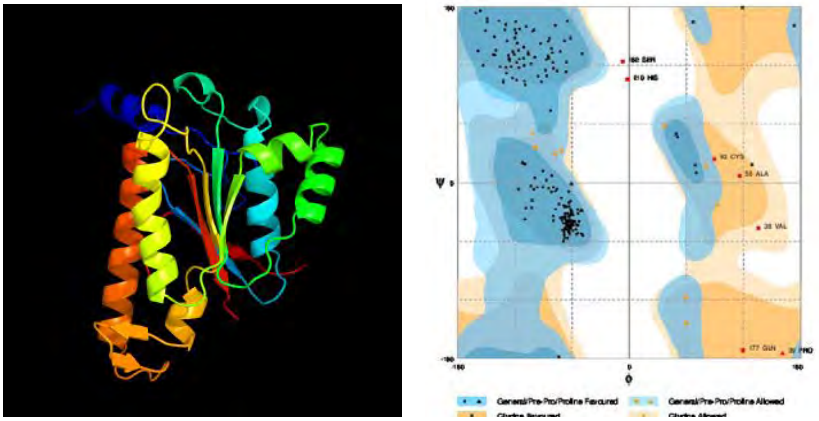


Fig. 1 Predicted 3D structures of XRCC2 and respective Ramachandran plot.

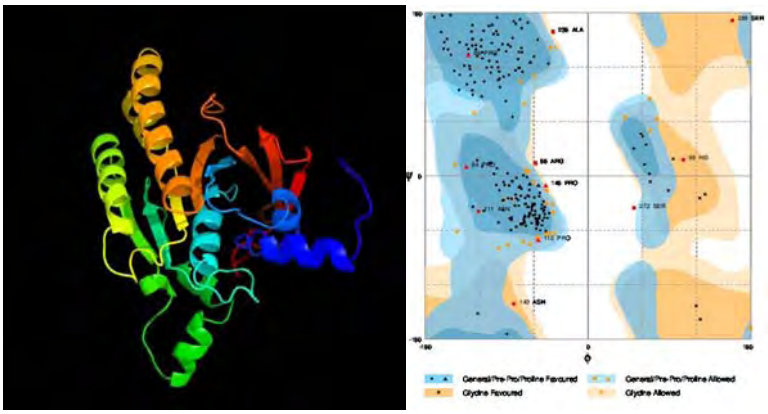


Fig. 2 Predicted 3D structures of XRCC3 and respective Ramachandran plot.

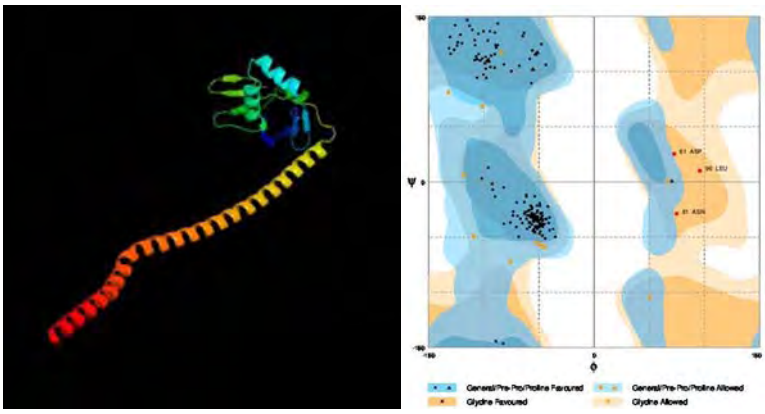


Fig. 3 Predicted 3D structures of XRCC4 and respective Ramachandran plot.

Table 3 Ramachandran plot results showing number of residues in favored, allowed and outlier region for XRCC2, XRCC3 and XRCC4 proteins.

	XRCC2	**XRCC3**	**XRCC4**
Number of residues in favored region	191 (92.3%)	201 (82.0%)	174 (92.6%)
Number of residues in allowed region	9 (4.3%)	33 (13.5%)	11 (5.9%)
Number of residues in outlier region	7 (3.4%)	11 (4.5%)	3 (1.6%)

Table 4 Confidently predicted domains of XRCC2, XRCC3 and XRCC4 proteins.

Protein	Domain	Start	End
XRCC3	Pfam: Rad51	4	214
	Pfam:AAA_25	7	203
XRCC4	Pfam: XRCC4	38	263

3.4 Subcellular localization

Through the PSI predictor, we obtained results showing our protein placed mainly in the cytosol, nucleus and the mitochondria. The protein XRCC2 is mainly located in the cytosol and nucleus, as well as the protein XRCC4, while XRCC3 besides cytosol and nucleus, is also placed in the mitochondria. Table 5 shows the score of the protein subcellular localization. The normal range is between 0 and 1, and everything above 0.5 is considered high content, and under this number it is low content.

3.5 Interactome

One of the aims of this study was to show the protein – protein relation of our proteins of interest and other interacting proteins. Our interactome analysis results are showing different proteins that interact with our three. We couldn't take all the interactions into consideration, so we choose just those with the highest confidence values. The results are demonstrated in Table 6. Figs 4, 5 and 6 also show the result of our interactome analysis.

3.6 Docking site prediction

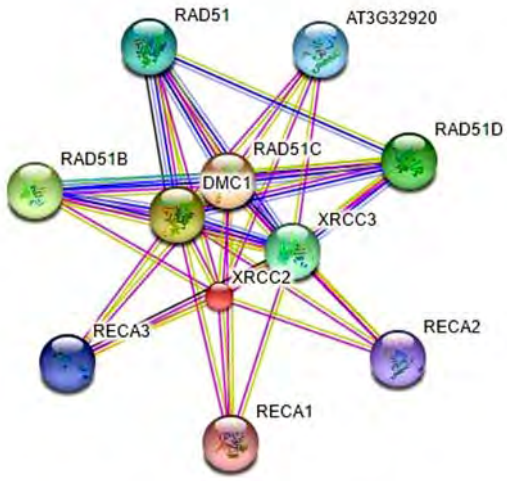
The final step in our study was the docking site investigation. According to the interactome analysis, we identified the proteins for the docking site investigation, and the results are given in the Figs 7 to 12.

Table 5 PSI predicted subcellular localization for XRCC2, XRCC3 and XRCC4 proteins.

Proteins	Subcellular localization	Score
XRCC2	Cytosol	0.76
	Nucleus	0.09
XRCC3	Cytosol	0.57
	Mitochondria	0.19
	Nucleus	0.12
XRCC4	Cytosol	0.62
	Nucleus	0.35

Table 6 Interactome of XRCC proteins and functions of interacting proteins.

XRCC	Interactome	Interlog Confidence	Function of interacting protein
XRCC2	Rad51c	Highest confidence (0.999)	Involved in the homologous recombination repair (HRR) pathway of double-stranded DNA breaks arising during DNA replication or induced by DNA-damaging agents.
	DMC1		May participate in meiotic recombination, specifically in homologous strand assimilation, which is required for the resolution of meiotic double-strand breaks.
XRCC3	Rad50		Implicated in double-strand breaks (DSBs) repair by non-homologous end joining (NHEJ).
	RECQ4A		Required for maintenance of genome stability by modulation of the DNA damage response and repression of crossovers.
	MRE11		Involved in DNA double-strand break repair (DSBR). Also involved in meiotic DSB processing (By similarity).
XRCC4	At1g52650		F-box/LRR-Repeat protein.
	ARV1		Arv1 like protein.



Your Input:

		Neighborhood	Gene Fusion	Cooccurence	Coexpression	Experiments	Databases	Textmining	(Homology)	Score
XRCC2	DNA repair protein XRCC2-like protein; Involved in the homologous recombination repair (HRR) pathway of double-stranded DNA, thought to repair chromosomal fragmentation, translocations and deletions (By similarity) (372 aa)									

Predicted Functional Partners:

RAD51C	DNA repair protein RAD51-like 3; Involved in the homologous recombination repair (HRR) pathway of double-stranded DNA ...					•		•		0.999
DMC1	DISRUPTION OF MEIOTIC CONTROL 1; May participate in meiotic recombination (344 aa)					•		•		0.997
RAD51B	DNA repair protein RAD51-like 2; May be involved in the homologous recombination repair (HRR) pathway of double-strand...					•		•		0.997
RAD51D	homolog of RAD51 D; Involved in the homologous recombination repair (HRR) pathway of double-stranded DNA breaks aris...					•		•		0.996
XRCC3	DNA repair protein XRCC3-like protein; Plays essential roles in DNA damage repair in both somatic and meiotic cells. It is im...					•		•		0.992
RAD51	DNA repair protein RAD51-like 1; Binds to single and double stranded DNA and exhibits DNA-dependent ATPase activity. Un...					•		•		0.989
AT3G32920	P-loop containing nucleoside triphosphate hydrolase-like protein; Involved in recombination ability and DNA strand transfer...					•		•		0.901
RECA3	RECA homolog 3; Involved in recombination ability and DNA strand transfer activity (By similarity) (389 aa)					•		•		0.901
RECA2	A. thaliana recA homolog 2; Involved in recombination ability and DNA strand transfer activity (By similarity) (430 aa)					•		•		0.901
RECA1	homolog of bacterial RecA; Involved in recombination ability and DNA strand transfer activity (439 aa)					•		•		0.901

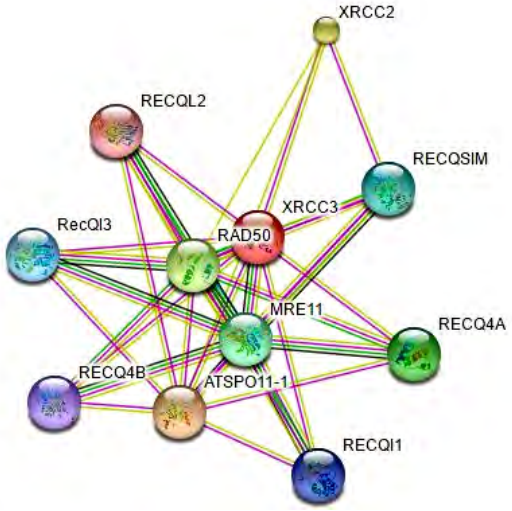
Your Current Organism:

Arabidopsis thaliana

NCBI taxonomy Id: 3702

Other names: A. thaliana, Arabidopsis thaliana, Arabidopsis thaliana (L.) Heynh., mouse-ear cress, thale cress, thale-cress

Fig. 4 Interactome visualization by STRING program, showing only high CV interactions for XRCC2.



Your Input:

		Neighborhood	Gene Fusion	Cooccurence	Coexpression	Experiments	Databases	Textmining	[Homology]	Score
XRCC3	DNA repair protein XRCC3-like protein; Plays essential roles in DNA damage repair in both somatic and meiotic cells. It is important for postsynaptic events following pachytene in meiosis. It is also required for DNA cross- links repair and is involved in double strand breaks (DSBs) repair (304 aa)									

Predicted Functional Partners:

ATSPO11-1	meiotic recombination protein SPO11-1; Required for meiotic recombination. Mediates DNA cleavage that forms the double-...					•		•		0.997
XRCC2	DNA repair protein XRCC2-like protein; Involved in the homologous recombination repair (HRR) pathway of double-stranded D...					•		•		0.992
RAD50	DNA repair protein RAD50; Implicated in double-strand breaks (DSBs) repair by non- homologous end joining (NHEJ). Involve...					•		•		0.990
RECQ4A	ATP-dependent DNA helicase Q-like 4A; 3'-5' DNA helicase that may play a role in the repair of DNA. Required for maintenanc...					•		•		0.986
MRE11	MEIOTIC RECOMBINATION 11; Involved in DNA double-strand break repair (DSBR). Possesses single-strand endonuclease a...	•				•		•		0.985
RECQSIM	RECQ helicase SIM; Plant specific 3'-5' DNA helicase that may play a role in the repair of DNA (858 aa)					•		•		0.985
RecQI3	ATP-dependent DNA helicase Q-like 3; 3'-5' DNA helicase that may play a role in the repair of DNA. Exhibits an ATP or dATP-d...					•		•		0.985
RECQI1	RECQ helicase I1; 3'-5' DNA helicase that may play a role in the repair of DNA (By similarity) (606 aa)					•		•		0.985
RECQ4B	RECQ helicase L4B; 3'-5' DNA helicase that may play a role in the repair of DNA (By similarity). Required to promote but not to...					•		•		0.985
RECQL2	RECQ helicase L2; Component of the Mediator complex, a coactivator involved in the regulated transcription of nearly all RNA...					•		•		0.985

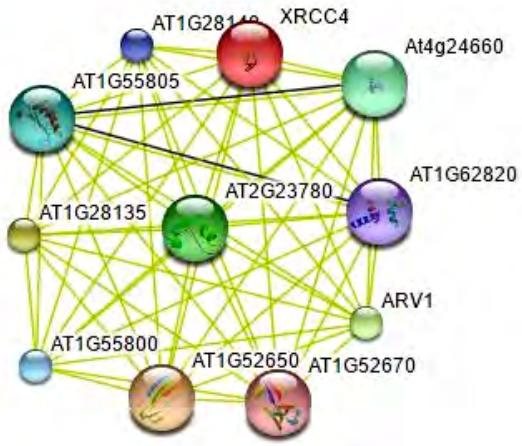
Your Current Organism:

Arabidopsis thaliana

NCBI taxonomy Id: 3702

Other names: A. thaliana, Arabidopsis thaliana, Arabidopsis thaliana (L.) Heynh., mouse-ear cress, thale cress, thale-cress

Fig. 5 Interactome visualization by STRING program, showing only high CV interactions for XRCC3.



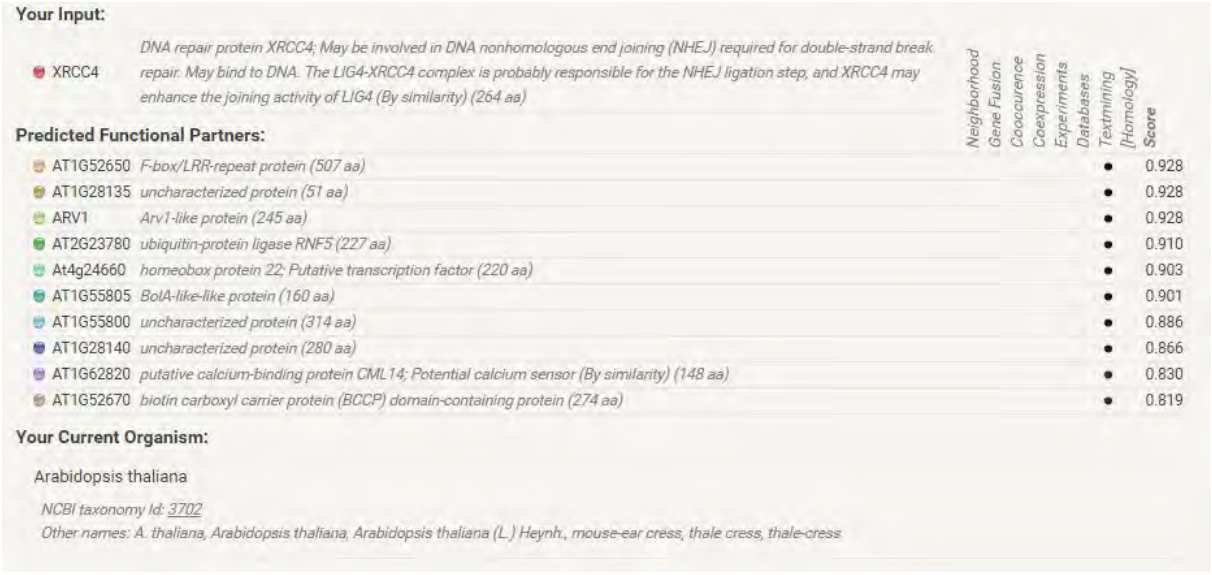


Fig. 6 Interactome visualization by STRING program, showing only high CV interactions for XRCC4.

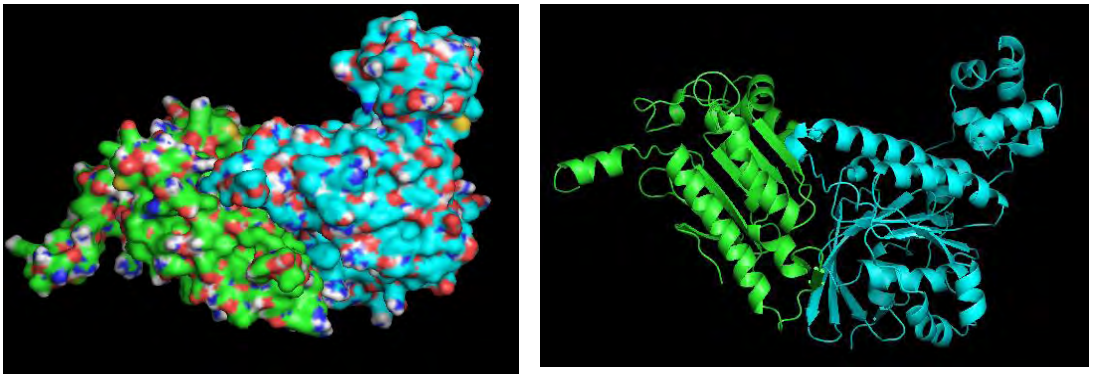


Fig. 7 Cluspro generated model of XRCC2 – DMC1 interaction, visualized by PyMol. XRCC2 is represented as a green molecule and DMC1 as a blue molecule.

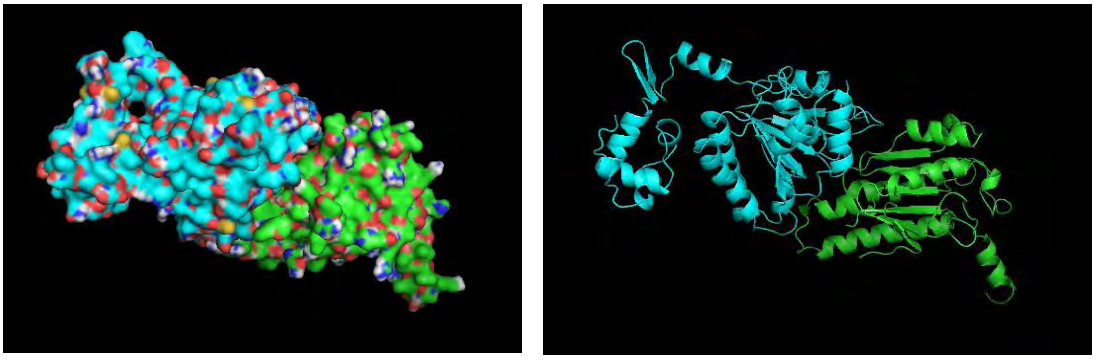


Fig. 8 Cluspro generated model of XRCC2 – Rad51c interaction, visualized by PyMol. XRCC2 is represented as a green molecule and Rad51c as a blue molecule.

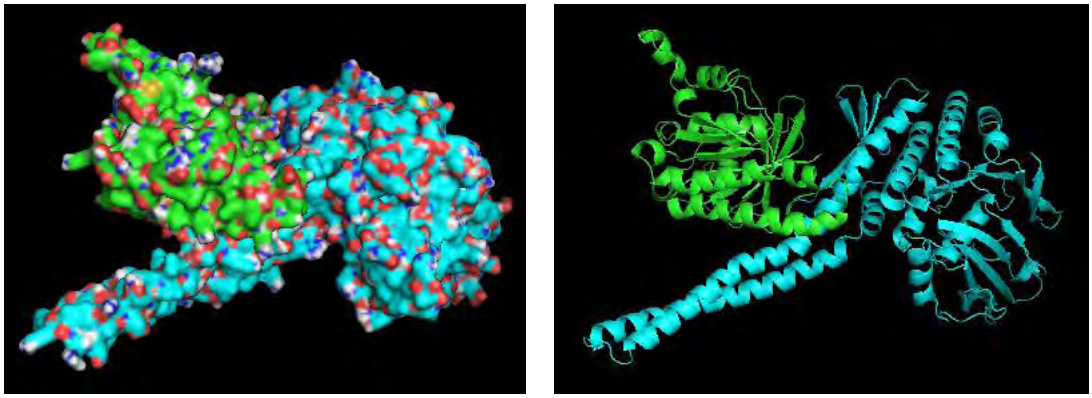


Fig. 9 Cluspro generated model of XRCC3 – Rad50 interaction, visualized by PyMol. XRCC3 is represented as a green molecule and Rad50 as a blue molecule.

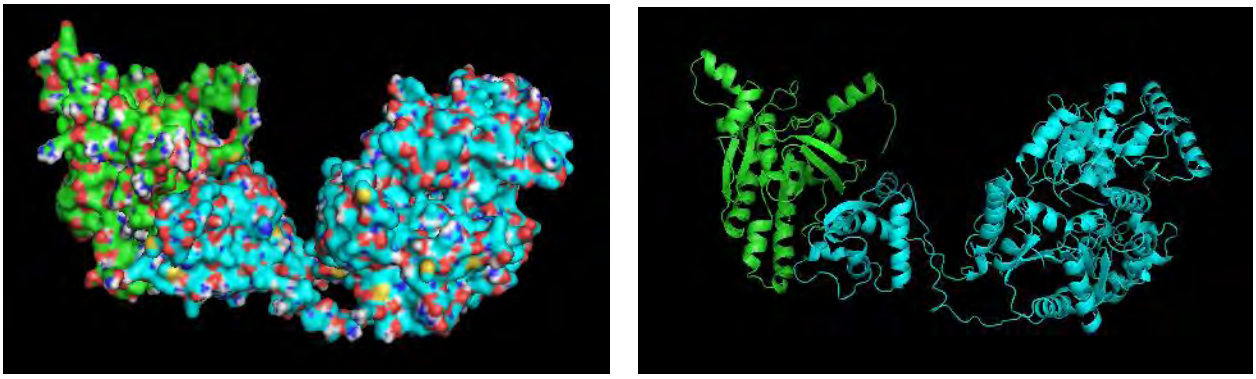


Fig. 10 Cluspro generated model of XRCC3 - RECQ4A interaction, visualized by PyMol. XRCC3 is represented as a green molecule and RECQ4A as a blue molecule.

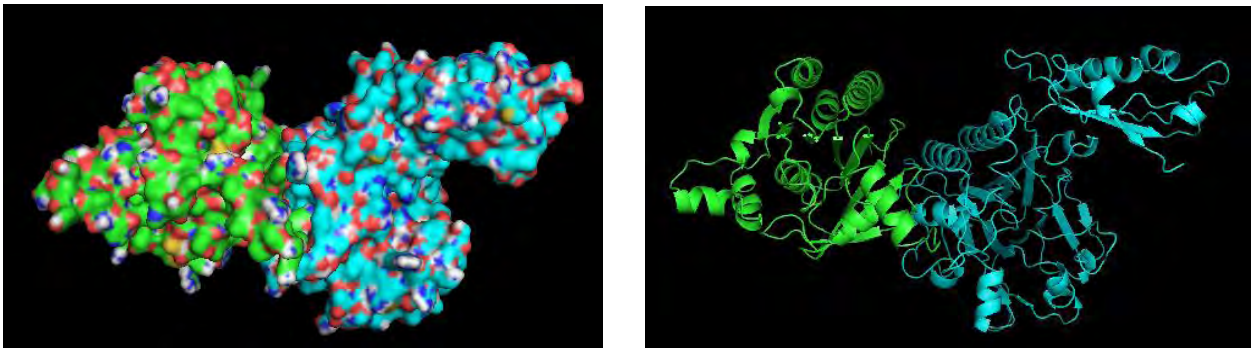


Fig. 11 Cluspro generated model of XRCC3 – MRE11 interaction, visualized by PyMol. XRCC3 is represented as a green molecule and MRE11 as a blue molecule.

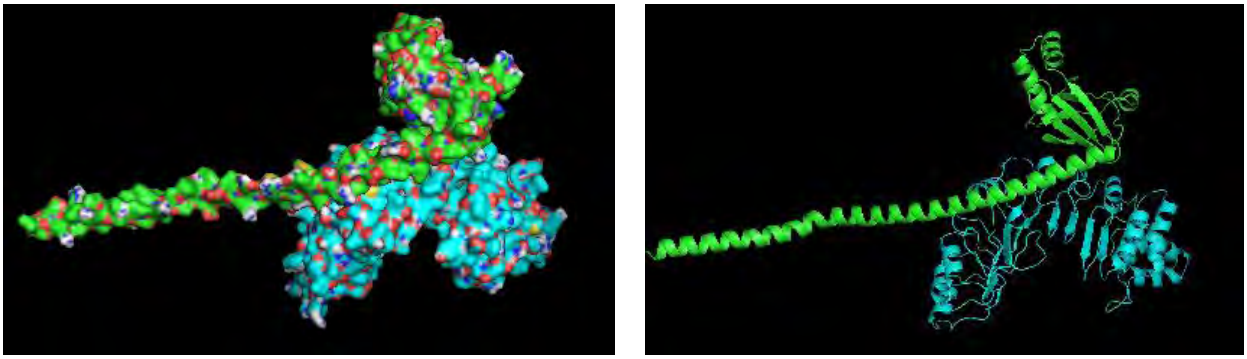


Fig. 12 Cluspro generated model of XRCC4 – At1g52650 interaction, visualized by PyMol. XRCC4 is represented as a green molecule and At1g52650 as a blue molecule.

4 Discussion

XRCC functional analysis is still an important field for the understanding of DNA double-strand break repair mechanisms and processes of genetic instability (Thacker and Zdzienicka, 2005). XRCC2 and XRCC3 are RAD51 paralogs which have a function in the DNA double-strand break repairs mechanism by homologous recombination (HR). XRCC4 on the other hand is homolog of the DNA ligase, having a function in the repair system too. Breaches in the DNA backbone can be made during DNA recombination, replication and excision repair, but it can also be a consequence of different DNA damaging agents. The mutations that occur during the double strand breaks in DNA cause chromosomal and genomic instability, and specifically mutations in the XRCC gene family show altered HR functions with increased gene conversion tract length, local rearrangement and increased frequencies of discontinuous tracts in HR (Brenneman et al., 2002).

The Arabidopsis thaliana genome sequence has shown genes related to the five Rad51 paralogs: AT2G28560 (RAD51B), AT2G45280 (RAD51C), AT1G07745 (RAD51D), AT5G64520 (XRCC2) and AT5G57450 (XRCC3). The predicted proteins have 14.2–26.7% sequence identity to AtRad51 and to each other, and 20.1– 36.4% sequence identity to their human counterpart (Bleuyard and White, 2004).

The multiple sequence alignment in our paper of XRCC2, XRCC3 and XRCC4 has shown some sequence homology between those three proteins, mostly located in the cytosol and especially in the nucleus. The domain analysis of XRCC3 identified two domains of which one is the Pfam: AAA_25 domain, ATPases Associated with diverse cellular Activities. The protein exerts its activity through the energy-dependent remodeling or translocation of macromolecules. It is involved in processes such as DNA replication, protein degradation, membrane fusion, microtubule severing, peroxisome biogenesis, signal transduction and the regulation of gene expression (Lupas and Frickey, 2004).

Interactome analysis showed that each of the homologues of XRCC protein, interacts with different proteins, while XRCC2 and XRCC3 are closely associated. XRCC2 is interacting with Rad51c and DMC1. Rad51c makes two different complexes with other related homologs: BCDX2 (RAD51B-RAD51C-RAD51D-XRCC2) and CX3 (RAD51C-XRCC3). The two complexes have a function at two distinct stages of homologous recombinational DNA repair. The first one, BCDX2 complex, has a function of RAD51 recruitment and the stabilization of damaged parts of the DNA (Kurzbauer et al., 2012). Meiosis makes sure that the genome will be reduced before generative cell formation and promotes information exchange. For this processes DNA double strand breaks are essential making single-stranded DNA overhangs, which together with RAD51 and DMC1, mediate the search for homologous sequences (Chun et al., 2013).

XRCC3 is interacting with Rad50 which is implicated in double-strand breaks (DSBs) repair by non-homologous end joining (NHEJ), RECQ4A - a DNA helicase which has a function in the maintenance of genome stability by triggering the DNA damage response and suppression of homologous recombination (Schropfer et al., 2013). MRE11 is part of the Mre11/Rad50/Nbs1 complex. This complex is involved in many parts of the chromosome metabolism. Failure and damaged function of this complex is connected with defects in the DNA double-strand break repair, checkpoint, meiosis, and telomere maintenance, while XRCC4 interacts with the homologs At1g52650 and ARV1 (Puizina et al., 2004).

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