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Molecular mechanic and monte carlo study of polymorphism effects on biophysical chemistry properties of XRCC1 BRCT2 domain

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Key words: XRCC1, BRCC2, polymorphism, molecular dynamic, Monte Carlo, potential energy, QSAR, dE.

Abstract

DNA repair is one of the most important process that maintains genomic integrity and cell survival. X-ray repair cross-complementing group 1 (XRCC1) is one of proteins that involves in this process. XRCC1 encompasses two BRCT domains (BRCT1and BRCT2). Any change in XRCC1 residues can alter function and its stability. One of the normal substitutions in XRCC1 BRCC2 domain is Arg560Trp. Molecular mechanic (MM) and Monte Carlo (MC) was used for investigation biophysical chemistry properties for any type of XRCC1 BRCC2 domain (wild type or mutant) in any temperatures (290,292,294,296,298,300,302,304,306,308,309,310,311,312,313,314, and 315 K), and any mediums (vacuum or water).Assessments of potential energy (Kcal/mol) and Quantitative structure–activity relationship (QSAR) of XRCC1 BRCC2 domain revealed that polymorphism (Arg560Trp) is caused it become unstable. Therefore mutant type (Trp560) of this protein cannot interact with Lig3 as well as wild type (Arg560) and then DNA repair is defected. Furthermore with determination of $dE= (\frac{\partial E}{\partial T})v\ dT+(\frac{\partial E}{\partial V})T\ dV$ equations specified best temperature for normal activity of XRCC1 BRCC2 domain is in confine of body natural temperature(310K).

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Introduction

DNA repair means a collection of processes by which a cell identifies and corrects damage to the DNA molecules. In human cells, both normal metabolic activities and environmental factors such as some chemical molecules, radiation and other agents can cause DNA damage, resulting in as many as 1 million individual molecular lesions per cell per day (Lodish *et al.,* 2004). Several proteins (XRCC1, XPD, XRCC4, ERCC1) involved in DNA repair processes (Caldecott *et al.,* 2003; Hayden *et al.,* 2007; Clarkson *et al.,* 2005). The XRCC1 encoded by X-ray repair cross-complementing group 1 gene (XRCC1) involve in the efficient repair of DNA single-strand breaks (SSBs) formed by exposure to ionizing radiation, alkylating agents, or other agents. This scaffold protein interacts with DNA ligase III, polymerase beta and poly (ADP-ribose) polymerase to participate in the base excision repair (BER) pathway (Caldecott *et al.,* 2003). It also plays a role in DNA processing during meiogenesis and recombination in germ cells. XRCC1 through its N-terminal domain (NTD) and breast cancer susceptibility protein-1 C-terminal (BRCT) domains bind to DNA intermediates in BER, and this binding could play a role to guaranty the accurate repair of damaged bases (Zhanna *et al.,* 2006). XRCC1 encompasses two BRCT domains (BRCT1and BRCT2) with independent and important roles (Kubota *et al.,* 2003; Richard *et al.,* 2002). The BRCA1 C Terminus (BRCT) domain is found predominantly in proteins involved in cell cycle checkpoint functions responsive to DNA damage (Bork *et al.,* 1997), for example as found in the breast cancer DNA-repair protein BRCA1, PARP-1 and XRCC1 (Xiaodong *et al.,* 1998; Paul *et al.,* 2011). The BRCT2 domain of XRCC1 that is attended in this basic investigation interacts with DNA ligase III (Lig III). The interaction is required to maintain normal levels of DNA ligase activity and DNA ligation is defective in the absence of an XRCC1/L3a complex (Caldecottn *et al.,* 1994; Taylor *et al.,* 1998). The pathways utilization by cells for SSBR can be divided into four basic steps, involving damage detection, end processing, gap filling, and DNA ligation (Richard *et al.,* 2002; Caldecott, 2001). DNA ligation is achieved by DNA ligase IIIα (Lig3α). There are several DNA polymorphisms in XRCC1(Arg560Trp, Arg194Trp, Arg280His, Arg399Gln), resulting in non-synonymous amino acid changes, which could alter its conformational stability, and binding or regulatory activities and then alter the ability of XRCC1 to repair damaged DNA (Duell *et al.,* 2000). Some studies have shown genetic polymorphisms of the XRCC1 are associated with colorectal cancer, lung cancer and cervical cancer (Camilla *et al.,* 2006; Chih-Ching *et al.,* 2005; Dai et al., 2012; Zhang *et al.,* 2012) and response to platinum-based chemotherapy in non-small-cell lung cancer, colorectal cancer, and breast cancer (Stoehlmacher *et al.,* 2001; Gurubhagavatula *et al.,* 2004). Arg560Trp occur in BRCC2 domain, thus it may influence stability and activities of the XRCC1. Therefore by means of computational method was investigated stability and behavior wild type BRCC2 (Arg560) and mutated type BRCC2 (Trp560).

We also know any temperature changes or different dielectric can alter protein structure and its stability. Hence, affects of these cases were verified too.

Methods and computation

In the present study, X-ray structure of wild type BRCC2 domain of XRCC1 obtained from protein data bank (PDB).The PDB entry code of the BRCC2 is 1CZD. Simulation and computation was performed by Hyper Chem 8.1.81 software (Weiner *et al.,* 1984). From this software, molecular mechanic method , Monte Carlo (MC) simulation , and amber 99 force field was used for computation of potential energy for any type of BRCC2 (wild type or mutant) in any temperature(290,292,294,296,298,300,302,304,306, 308,309,310,311,312,313,314, and 315 K), and any environments (vacuum or water). The mutation (Arg560Trp) was made with Swiss-PDB Viewer _4.04_PC. Geometry optimization of BRCC2 domain (wild type and mutant) implemented before computation of single point, or Monte Carlo simulation. In this investigation also were calculated

Quantitative structure–activity relationship (QSAR) properties (volume and surface) of BRCC2 domain (wild type and mutant) after Monte Carlo run in any temperatures in vacuum.

$dE= (\frac{\partial E}{\partial T})v\ dT+(\frac{\partial E}{\partial V})T\ dV$ equations of wild type and mutant of BRCC2 are determined by computation of partial derivatives of potential energy (∂E) and partial derivatives of volume (∂V) at different temperatures (E is potential energy of protein and V is its volume and T is temperature of system).

∂E =Emax – En and ∂T =TEmax – Tn .

E= f (T, V) and V= g (T) therefore:

$$\frac{\partial E}{\partial V}=\frac{\partial E}{\partial T}\times\frac{\partial T}{\partial V}=\frac{\partial E}{\partial T}\Big/\frac{\partial V}{\partial T}.$$

$\frac{\partial E}{\partial T}$ and $\frac{\partial V}{\partial T}$ at any temperature can calculate by equations exist in Fig. 5,6,7 and 8.

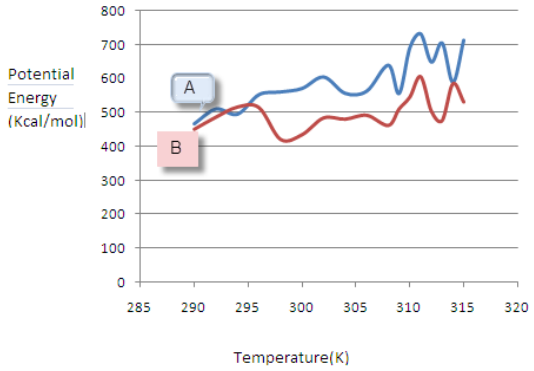

Fig. 1. Comparison of potential energy A) mutant BRCT2 domain of XRCC1, B) wild type BRCT2 domain of XRCC1; in different temperatures in vacuum.

Results and discussion

The present study shows different energy of wild type BRCC2 domain of XRCC1and its mutant type (Arg560Trp) in different temperatures and different dielectrics (Fig. 1 and Fig. 2). As we have shown in figure 1 with substitution Arg560 (fig 1B) by Trp (fig 1A) in vacuum, potential energy level were increased, therefore BRCC2 domain become unstable and then will have not a stable interaction with Lig3. In water medium (fig 2) is same vacuum medium, however as it is observed in figure 2 XRCC1 BRCT2 domain is more stable in water than in vacuum.

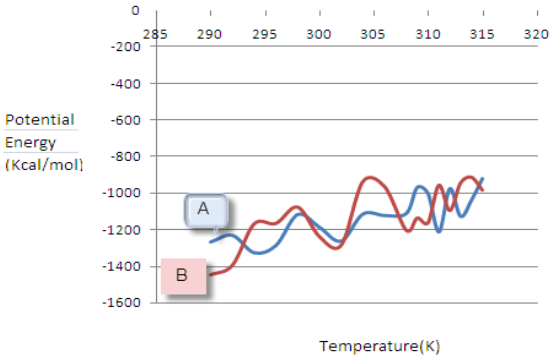

Fig. 2. Comparison of potential energy A) wild type BRCT2 domain of XRCC1, B) mutant BRCT2 domain of XRCC1; in different temperatures in water.

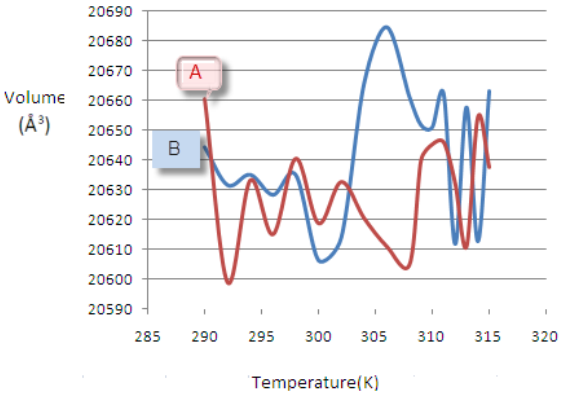

Fig. 3. Comparison of volume A) mutant BRCC2 domain of XRCC1 B) wild type BRCC2 domain of XRCC1; in different temperatures in vacuum.

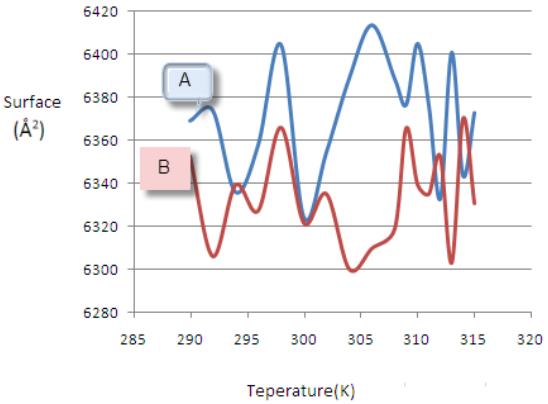

Fig. 4. Comparison of surface A) wild type BRCC2 domain of XRCC1 B) mutant BRCC2 domain of XRCC1; in different temperatures in vacuum.

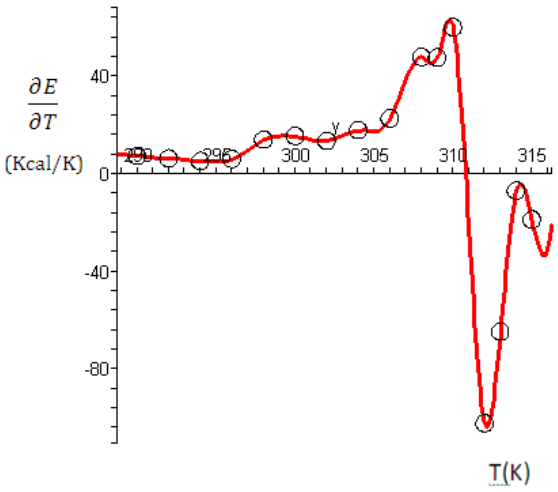

Fig. 5. Alterations of $\frac{\partial E}{\partial T}$ versus temperature (T) for wild type BRCC2 domain of XRCC1.The equation of this curve is:

f(y)=0.9295234657×10^{26}y - 0.2145122618×10^{25}y^{2}+0.3064405267×10^{23}y^{3}-0.3030523858×10^{21}y^{4}+0.1069181760×10^{-2}y^{13}-0.5032541561×10^{-6}y^{14}-854646.5002×y^{10}+432230136.6×y^{9}-1.406106468×y^{12}+1280.154679×y^{11}+0.2197702634×10^{-19}y^{5}-0.1207325916×10^{17}y^{6}+0.5116278271×10^{14}y^{7}-0.1686233290×10^{12}y^{8}+0.1105371935×10^{-9}y^{15}-0.1879548838×10^{28}

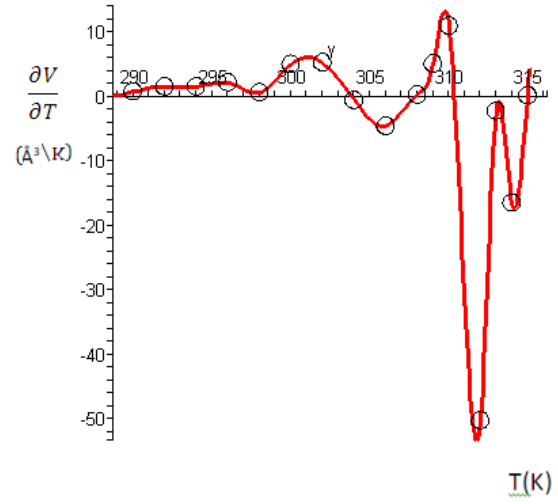

Fig. 6. Alterations of $\frac{\partial V}{\partial T}$ versus temperature (T) for wild type BRCC2 domain of XRCC1.The equation of this curve is:

f(y)=0.3607007640×10^{26}y+0.1189965429×10^{23}y^{3}+0.8540049109×10^{18}y^{5}+0.4310661190×10^{-10}y^{15}-0.7291053711×10^{27}-0.4693191801×10^{16}y^{6}+0.1989531132×10^{14}y^{7}-332693.4571y^{10}-0.5477541436y^{12}+0.4166530360×10^{-3}y^{13}+498.5110893y^{11}-0.6559451153×10^{11}y^{8}+168197140.3y^{9}-0.8327014369×10^{24}y^{2}-0.1177219013×10^{21}y^{4}-0.1961852612×10^{-6}y^{14}

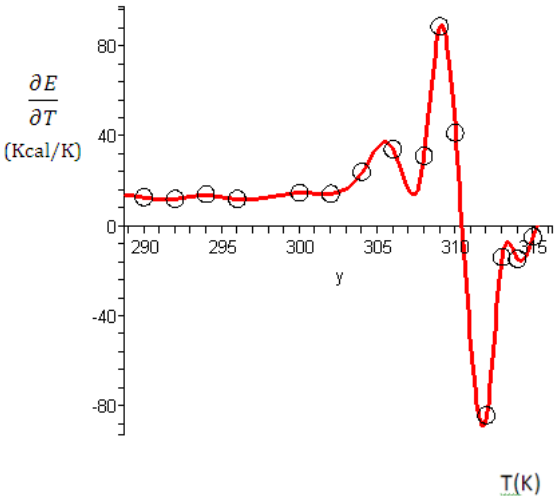

Fig. 7. Alterations of $\frac{\partial E}{\partial T}$ versus temperature (T) for mutant type BRCC2 of XRCC1 domain .The equation of this curve is:

f(y)=0.4123654163×10^{25}y-13298.82643y^{10}-0.1050089099×10^{20}y^{4}+0.6909039114×10^{17}y^{5}+0.1160663732×10^{22}y^{3}-0.8819293777×10^{23}y^{2}+8087401.084y^{9}+15.90338689y^{11}+0.6613912162×10^{-5}y^{13}-0.3409140598×10^{15}y^{6}-0.1553329549×10^{-8}y^{14}-0.8951387219×10^{26}+0.1281584931×10^{13}y^{7}-0.3688421488y^{8}-0.1307414619×10^{-1}y^{12}

QSAR properties (volume and surface) of wild type and mutant XRCC1 BRCT2 domain after Mont Carlo run in any temperatures in vacuum have been shown in figures 3 and 4.The QSAR properties of BRCC2 same potential energy alter by mutation and are notable. Volume of mutant XRCC1 BRCC2 domain (Fig 3B, Fig 4B) is lower than wild type (Fig 3A, Fig 4A) ,thus mutant cannot interact with lig3 as well as

wild type of XRCC1 BRCT2 domain, therefore cannot worthily interact with damaged DNA for repair it.

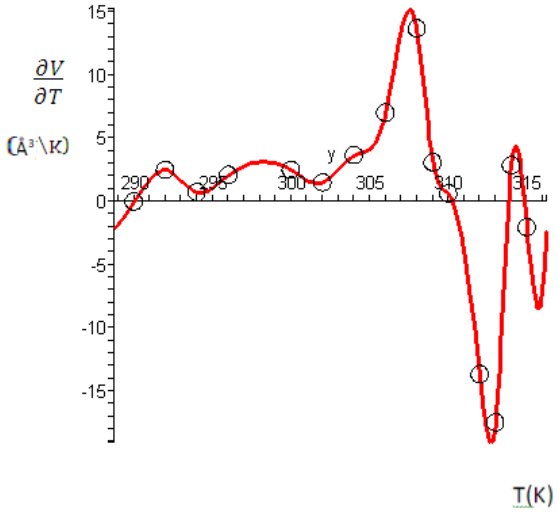

Fig. 8. Alterations of $\frac{\partial V}{\partial T}$ versus temperature (T) for mutant type BRCC2 domain of XRCC1 .The equation of this curve is:

$f(y)=-0.7244779198\times10^{24}y-0.2039783863\times10^{21}y^{3}+0.1572412261\times10^{26}-0.1214595667\times10^{17}y^{5}+0.5994151695\times10^{14}y^{6}-0.2253716748\times10^{12}y^{7}+2339.779451y^{10}+0.2301000111\times10^{-2}y^{12}-0.1164214898\times10^{-5}y^{13}-2.798477925y^{11}+648727021.6y^{8}-1422657.359y^{9}+0.1549686851\times10^{23}y^{2}+0.1845745708\times10^{19}y^{4}+0.273470287210^{-9}y^{14}$

Curves of $\frac{\partial E}{\partial T}$ and $\frac{\partial V}{\partial T}$ versus temperature (T) and its equations for wild type and mutant XRCC1 BRCC2 domain also have been shown in figures 5,6,7 and 8.These figures show $\frac{\partial E}{\partial T}$ and $\frac{\partial V}{\partial T}$ alterations in confine of body natural temperature (310 K or 37 ċ) is more than of another temperatures. Hence, best temperature for normal activity of XRCC1 BRCC2 domain is in confine of body natural temperature.

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