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Computational studies on PLK1 delta gene in cancer diseases

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ABSTRACT

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Polo-like kinases (Plks) are a family of conserved serine/threonine kinases involved in the regulation of cell cycle progression through G2 and mitosis. One of them being PLK1, it's over expression leads to a variety of cancers. Plk1 delta, an uncharacterized protein sequence found in UniProt was studied and found to consist of the N-terminal portion of plk1gene. The 3D protein structure of PLK1 delta was modeled and then the predicted structure was validated. Molecular dynamics simulation was performed to find the stability of the protein. The modelled protein was docked to BI 2536, an inhibitor of Plk1 to obtain conformation of least binding energy. The interacting sites between the protein and inhibitor were also analyzed.

INTRODUCTION

Cancer research has generated a rich and complex body of knowledge, revealing cancer to be a disease involving dynamic changes in the genome. The foundation has been set in the discovery of mutations that produce oncogenes with dominant gain of function and tumour suppressor genes with recessive loss of function (Hanahan *et al.* 2000). Cancer has become the leading cause of death in many Asian countries. There is an increasing trend in breast, prostate and colon cancers, which are considered as typical of economically developed countries. Although breast and prostate cancer rates are still lower than in western countries, they are particularly rapidly increasing (Park *et al.* 2008). The important lifestyle factors that affect the incidence and mortality of cancer include tobacco, alcohol, diet, obesity, infectious agents, environmental pollutants, and radiation (Anand *et al.* 2008). Studies published since the 1986 IARC Monograph on "Tobacco smoking" provide sufficient evidence to establish a causal association between cigarette smoking and cancer of the nasal cavities and paranasal sinuses, nasopharynx, stomach, liver, kidney (renal cell carcinoma) and uterine cervix, and for adenocarcinoma of the oesophagus and myeloid leukaemia (Sasco *et al.* 2004). Although genetic susceptibility influences the risk of cancer, most of the variation in cancer risk across populations and among individuals is due to factors that are not inherited. Behaviors such as avoiding exposure to tobacco products, maintaining a healthy weight, staying physically active throughout life, and consuming a healthy diet can substantially reduce one's lifetime risk of developing, or dying from cancer (Kushi *et al.* 2012). Primary prevention through lifestyle and environmental interventions remains the main way to reduce the burden of cancers (Danaei *et al.* 2005). Polo-like kinases (Plks) are a family of conserved serine/threonine kinases involved in the regulation of cell cycle progression through G2 and mitosis. Polo-like kinases (Plks) are important regulators of the cell cycle. Plks are involved in the formation of and the changes in the mitotic spindle and in the activation of CDK/cyclin complexes during the M-phase of the cell cycle. The discovery of the polo kinase in Drosophila was made by Sunkel and Glover in 1988, following the observation that mutant polo results in abnormal spindle formation. In 1993, Clay and colleagues determined the nucleotide sequence of a cDNA encoding the mammalian protein kinase that was closely related to the enzyme encoded by the Drosophila mutant polo and designated it as Plk. Today, the mammalian homolog family of Plks consists of five described members, Plk1–5, which are characterized by the presence of an N-terminal kinase and C-terminal polo-box domain. The Plk family is a group of highly conserved serine/threonine kinases that is typically associated with cell-cycle progression and mitosis; however, recent studies have suggested involvement of this kinase family in cancer (Cholewa *et al.* 2013).

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Serine/threonine-protein kinase PLK1, also known as polo-like kinase 1 (PLK-1) or serine/threonine-protein kinase 13 (STPK13), is an enzyme that in humans is encoded by the *PLK1* (polo-like kinase 1) gene. PLK1 consists of 603 amino acids and is 66kDa.The Polo-Like Kinase 1 (PLK1) acts as a central regulator of mitosis and is over-expressed in a wide range of human tumors where high levels of expression correlate with a poor prognosis. PLK1 comprises two structural elements, a kinase domain and a polo-box domain (PBD) (Huggins *et al.* 2010).Plk1 has emerged as a key mitotic regulator and is most commonly known for being a critical component of centrosome maturation, kinetochore–microtubule attachment, bipolar spindle formation, and cytokinesis. Polo-like kinase-1 (PLK1) is a crucial driver of cell cycle progression and its down-regulation plays an important checkpoint role in response to DNA damage (King *et al.* 2012). The protein kinase PLK1 plays a pivotal role in the maturation of centrosomes, entry into M phase, spindle formation and cytokinesis. Ectopic expression of PLK1 in cultured cells is oncogenic and, consistent with this observation, elevated PLK1 levels occur in various human tumour types (King *et al.* 2012).

Elevated Plk1 levels are found in numerous tumour types including breast cancer, colorectal cancer, endometrial carcinomas, head/neck squamous cell carcinomas, non–small cell lung cancer, ovarian cancer, and pancreatic cancer probably due to increased mitosis in these cancer tissues. Taken together, the critical role of Plk1 in mitosis and its overexpression in cancer makes it an attractive therapeutic target (Degenhardt *et al.* 2010). Thus, interfering with Plk1 function in human cells leads to a prominent prometaphase/metaphase-like arrest, which is dependent on the activation of the spindle assembly checkpoint (Mandal *et al.* 2013). The most striking feature of Plk1 is its changing localization to various subcellular structures during mitotic progression. Plk1 first associates with centrosomes in prophase, then also becomes enriched at kinetochores in prometaphase and metaphase, is afterwards recruited to the central spindle in anaphase, and finally accumulates in the midbody during telophase (Petronczki *et al.* 2008). Polo-like kinase 1 (Plk1) is an interesting molecule both as a biomarker and as a target for highly specific cancer therapy for several reasons. The expression of Plk1 in normal cells is not nearly as strong as that in cancer cells, which makes Plk1 a discriminating tartget for the development of cancer-specific small molecule drugs (WeiSz *et al.* 2012). PLK1 Delta is a protein sequence which is not fully characterised. In this study, we modelled the 3D structure of the protein and its stability of the protein was analysed. In addition to this, we also carried out the molecular docking with the plk1 inhibitor BI2536. The interaction between the modelled protein and the inhibitor were observed to understand the orientation and interactions.

MATERIALS AND METHODS

PLK1 Delta gene

The protein sequence of PLK1 Delta was obtained from Uniprot with the id Q58A51. The length of the protein sequence is 247 amino acids and the weight is about 27.3kDa. The sequence alignment between the PLK1 delta and PLK1 gene sequence was performed using global alignment program EMBOSS. It was found that PLK1 delta sequence aligns to the N-terminal region of the PLK1 gene with the identity is 36.6% as shown in the figure1.

Protein structure prediction

The 3-dimensional structure of PLK1 delta protein sequence was modeled using Swiss model server. The protein structure with a QMEAN score of -1.26 was selected for further analysis, more the QMEAN score is better the model. Qualitative Model Energy Analysis (QMEAN), is a composite scoring function describing the major geometrical aspects of protein structures (Benkert *et al.* 2008). The validation of the predicted protein structure was carried out using SAVES server. The molecular graphics of protein structure and the interaction sites are visualized using PyMOL(DeLano 2002).

Molecular dynamics simulation

MD simulations were performed with GROMACS 4.5.5(Berendsen *et al.* 1995).First it was made sure that there are no crystal waters in the PDB structure. The topology file (topol.top), position restraint file (posre.itp) and a post-processed structure file (processed.gro) were generated using the GROMACS tool pdb2gmx. The force field OPLS-AA/L all-atom was used and the system was simulated in A simple cubic box(which was the unit cell).

The system was solvated using Spc(simple point charge) water molecules. The spc216.gro model was used, which is a generic equilibrated 3-point solvent model. Adding ions to the simulation was done using genion that reads through the topology and replaces water molecules with the ions to neutralize the net charge on the protein. Energy of the system was first minimized using the steepest descent algorithm until it reached a tolerance of 1000kJ/mol/nm. Finally, the MD simulations were performed under constant temperature and pressure for 20.0ns using an integration time step of 2fs.

PLK1 BI-2536 Inhibitor

BI 2536, is a potent and selective inhibitor of Plk1 gene. The fact that BI 2536 blocks Plk1 activity fully and instantaneously enabled us to study controversial and unknown functions of Plk1. Cells treated with BI 2536 are delayed in prophase but eventually import Cdk1-cyclin B into the nucleus, enter prometaphase, and degrade cyclin A, although BI 2536 prevents degradation of the APC/C inhibitor Emi1. BI 2536 prevent Plk1's enrichment at kinetochores and centrosomes, and when added to metaphase cells, it induces detachment of microtubules from kinetochores and leads to spindle collapse (Lenart *et al.* 2007). The structure of BI 2536 was drawn using chemsketch (Li *et al.* 2004) as shown in figure2 and then it was converted into 3D coordinates using OpenBabel software (Olboyle *et al.* 2011).

```
PLK1_delta        1 MSAAVTAGKLARAPADPGKAGVPGVAAPGAPAAAPPAKEIPEVLVDPRSR     50
                    ||||||||||||||||||||||||||||||||||||||||||||||||||
PLK1              1 MSAAVTAGKLARAPADPGKAGVPGVAAPGAPAAAPPAKEIPEVLVDPRSR     50

PLK1_delta       51 RRYVRGRFLGKGGFAKCFEISDADTKEVFAGKIVPKSLLLKPHQREKMSM    100
                    ||||||||||||||||||||||||||||||||||||||||||||||||||||
PLK1             51 RRYVRGRFLGKGGFAKCFEISDADTKEVFAGKIVPKSLLLKPHQREKMSM    100

PLK1_delta      101 EISIHRSLAHQHVVGFHGFFEDNDFVFVVLELCRRRSLLELHKRRKALTE    150
                    ||||||||||||||||||||||||||||||||||||||||||||||||||||
PLK1            101 EISIHRSLAHQHVVGFHGFFEDNDFVFVVLELCRRRSLLELHKRRKALTE    150

PLK1_delta      151 PEARYYLRQIVLGCQYLHRNRVIHRDLKLGNLFLNEDLEVKIGDFGLATK    200
                    ||||||||||||||||||||||||||||||||||||||||||||||||||||
PLK1            151 PEARYYLRQIVLGCQYLHRNRVIHRDLKLGNLFLNEDLEVKIGDFGLATK    200

PLK1_delta      201 VEYDGERKKTLCGTPNYIAPAVPCLQCAPQPRWLGRAASSLQVGVAV---    247
                    ||||||||||||||||||.|           |.:...|.:|.|..
PLK1            201 VEYDGERKKTLCGTPNYIAPEV-----------LSKKGHSFEVDVWSIGC    239

PLK1_delta      248 --------------------------------------------------    247

PLK1            240 IMYTLLVGKPPFETSCLKETYLRIKKNEYSIPKHINPVAASLIQKMLQTD    289

PLK1_delta      248 --------------------------------------------------    247

PLK1            290 PTARPTINELLNDEFFTSGYIPARLPITCLTIPPRFSIAPSSLDPSNRKP    339

PLK1_delta      248 --------------------------------------------------    247

PLK1            340 LTVLNKGLENPLPERPREKEEPVVRETGEVVDCHLSDMLQQLHSVNASKP    389

PLK1_delta      248 --------------------------------------------------    247

PLK1            390 SERGLVRQEEAEDPACIPIFWVSKWVDYSDKYGLGYQLCDNSVGVLFNDS    439

PLK1_delta      248 --------------------------------------------------    247

PLK1            440 TRLILYNDGDSLQYIERDGTESYLTVSSHPNSLMKKITLLKYFRNYMSEH    489

PLK1_delta      248 --------------------------------------------------    247

PLK1            490 LLKAGANITPREGDELARLPYLRTWFRTRSAIILHLSNGSVQINFFQDHT    539

PLK1_delta      248 --------------------------------------------------    247

PLK1            540 KLILCPLMAAVTYIDEKRDFRTYRLSLLEEYGCCKELASRLRYARTMVDK    589

PLK1_delta      248 --------------    247

PLK1            590 LLSSRSASNRLKAS    603
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Fig. 1. Global alignment of Plk1 delta and Plk1 protein sequence. Plk1 delta consists of the N-terminal portion of Plk1.

Molecular Docking

The molecular docking was carried out using AUTODOCK (Morris *et al.* 2009). The target protein was prepared by deleting all water molecules from the protein structure and adding polar hydrogens and Kollman charges to it. The ligand file was initialized by adding gasteiger charges to it. The root of the ligand was detected, its torsions were chosen was saved in PDBQT format. The BI2536 inhibitor was docked to plk1 delta protein with a population size of 150 and 200 runs and the docked confirmation energies were obtained.

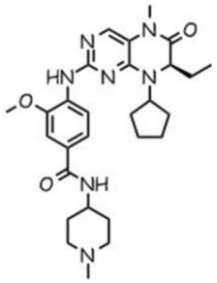

Fig. 2: Chemical structure of BI 2536 inhibitor.

RESULT AND DISCUSSION

Protein structure and validation

The protein Plk1 delta's PDB structure was obtained by modeling in SWISS MODEL. The model with the least QMEAN4 score was chosen for analysis. The template used by the server for modeling was 3fc2 and it had alpha beta structure. Its architecture was 2-layer sandwich. Its homology was like that of phosphorylase kinase, domain 1. The predicted protein structure with its two most important secondary structures alpha helix and the beta sheet are

displayed in figure 3a. The Ramachandran plot was obtained for the protein structure for its validation. The residue present in the allowed regions is around 88.6% as shown in figure 3b.

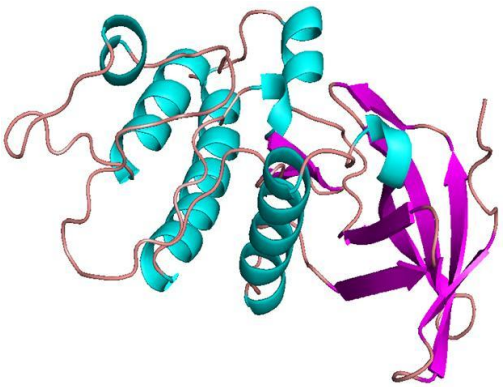

Fig. 3a 3-Dimensional structures of modelled Plk1 delta protein.
b) Ramachandran plot for the predicted structure.

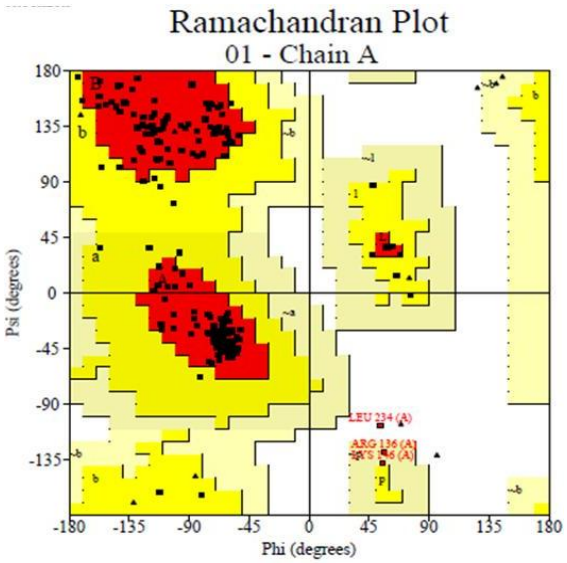

Fig. 3b: RMSD Plot of plk1 delta protein for 20ns.

Molecular dynamics simulation analysis

The root-mean-square deviation (RMSD) is the measure of the average distance between the atoms (usually the backbone atoms) of superimposed proteins. When a dynamical system fluctuates about some well-defined average position, the RMSD from the average over time can be referred to as the *RMSF* or root mean square fluctuation. The size of this fluctuation can be measured and can provide important physical information. For the MD simulation, the trajectories of the plk1 delta in the solvent were calculated. The RMSD values for the protein were plotted to obtain an estimate of the MD trajectory quality and convergence. The simulation indicate that after a rapid increase during the first 1.25 ns, the trajectory stabilized within the 0.2 to 0.25 nm range for up to 7.5ns as shown the figure4. Then it varies within the 0.15 to 0.2nm range for up to 7.5 to 12.5 ns. Finally the protein gets stabilized after 12.5ns within the range of 0.2 to 0.25nm. Thus the simulation confirms that the modeled protein PLK1 delta is in stabilized state.

Following phosphorylation of PICH on the Cdk1 site T1063, Plk1 is recruited to PICH and controls its localization (Morris *et al.* 2009). Studies propose that the balance of Evi5 and Polo-like kinase activities determines the timely accumulation of Emi1 and cyclin, ensuring mitotic fidelity (Eldridge *et al.* 2006). Polo-like kinase 1 phosphorylates cyclin B1 and targets it to the nucleus during prophase (Toyoshima-Morimoto *et al.* 2001).

Molecular docking analysis

Docking was done between the plk1delta protein and its inhibitor BI2536 to check the affinity and binding mode. Ten confirmations were obtained as shown in table1 and the binding energies were found to range from -2.12 to -5.56Kcal/mol.

Table 1: Binding energies for the docked inhibitor on to the active site of the plk1 delta protein.

Conformation	Binding Energy(kcal/mol)
1	-5.56
2	-3.3
3	-3.19
4	-2.94
5	-2.38
6	-2.3
7	-2.25
8	-2.2
9	-2.19
10	-2.12

Out of the 10 obtained conformations, the first one with the binding energy of -5.56 was considered the best, because lower energy indicates the higher stability. The best conformation between the protein and the inhibitor is represented in figure5 where the protein is displayed in tube structure and the ligand in stick model. Both animal and cell experiment suggest that BI 2536, a potent and selective inhibitor of polo-like kinase 1, inhibits the tumor growth in vivo (Steegmaier *et al.* 2007).

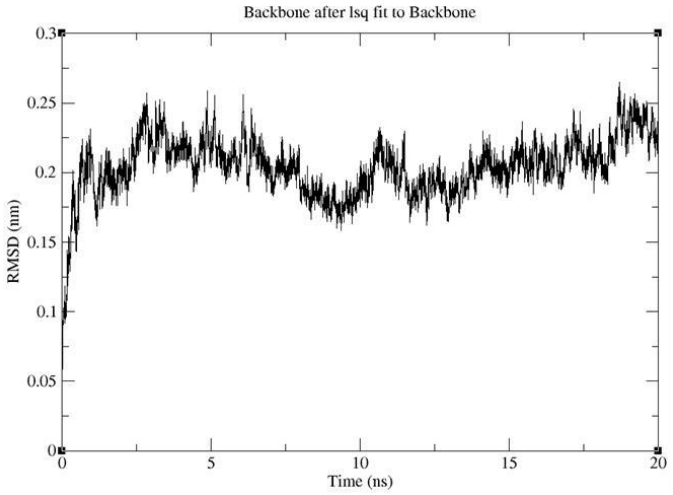

Fig. 4: The plk1 delta protein is represented as tube structure and the ligand in stick model.

Ligand interacting site

The ligand interacting residues are viewed in figure 6a using LigPlot (Wallace *et al.* 1995) and their 3D representation

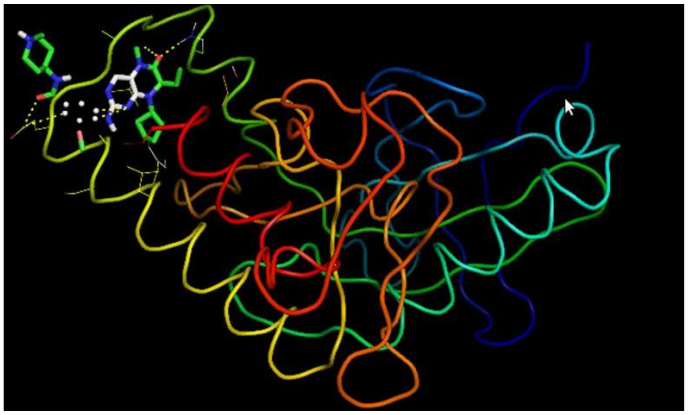

Fig. 5 Ligand interacting site of Plk1 delta with BI2536 in 2D. b) 3-dimensional representation of ligand interacting residues. Presence of hydrogen bond between protein and ligand is shown as a blue line.

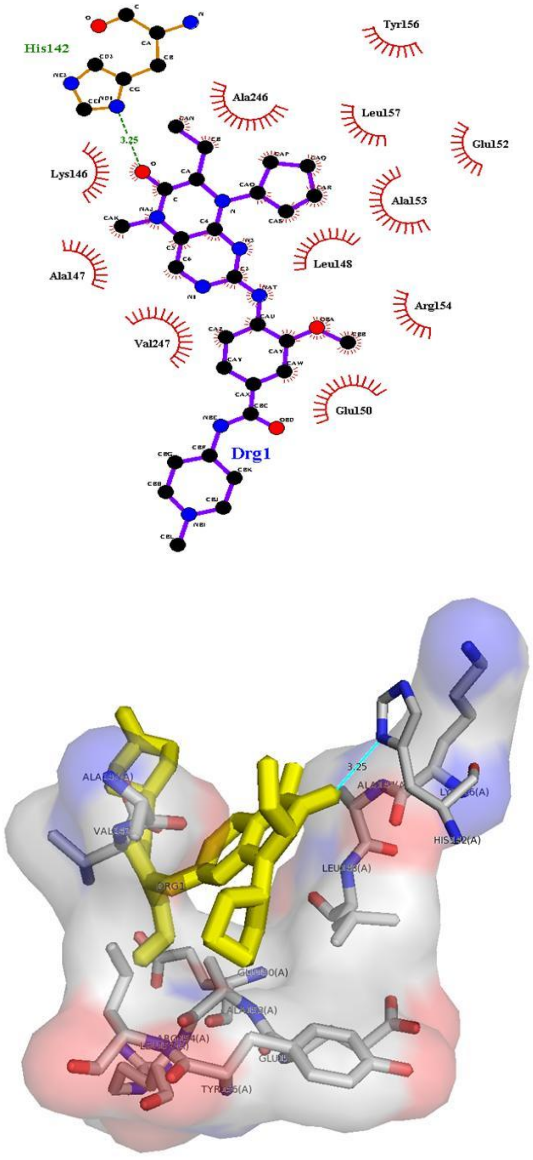

Fig. 6: a) Ligand interacting site of Plk1 delta with BI2536 in 2D. b) 3-dimensional representation of ligand interacting residues. Presence of hydrogen bond between protein and ligand is shown as a blue line.

was displayed in figure 6b. The methoxy-N-benzamide group was surrounded in a hydrophobic cage comprising Ala147, Leu148, Ala153, Leu157, Ala246 and Val247 amino acids. The hydrophilic amino acids Lys146, Glu150, Glu152, Arg154 and Tyr156 were also contributed to the stability of the protein-ligand complex.. One hydrogen bond was observed between HIS142 to the oxygen atom of the cyclopentyl group with a 3.25Å distance which may increase the affinity between the plk1 delta protein and the inhibitor. Similarly, Nitric oxide (NO) has been shown to down-regulate PLK1 and up-regulate p21/waf1 independent of cGMP (Zhang *et al.* 2007) and wortmannin, which was previously thought to be a highly selective inhibitor of phosphoinositide (PI) 3-kinases, is a potent inhibitor of mammalian PLK1 (Liu *et al.* 2005).

CONCLUSION

The polo-like protein kinases (Plks) are a conserved subfamily of Serine/Threonine protein kinases that play a variety of roles during M-phase progression. In this study, Plk1 delta, an unchararcterized protein sequence was modelled to obtain a PDB structure. It was then validated using Ramanchandran's plot and it was found that 88.6% of its residues are in allowed regions. The molecular dynamics simulation was performed and the protein structure was stable from 12.5ns upto 20ns within the range of 0.2 to 0.25 nm range. Molecular docking was performed to dock the protein to BI2536 and a conformation with the least binding energy was obtained. However further studies are required to study the structural and functional properties of Plk1 delta which may help in identify the remedies for cancer therapy.

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