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Resveratrol derivative-triacetyl-resveratrol interacts directly with the Gli-DNA zinc finger complex

Dhruv Kumar

Amity Institute of Molecular Medicine & Stem Cell Research (AIMMSCR), Amity University, India

Abstract

Sonic hedgehog (Shh) pathways have been shown to involve in many cellular processes including cancer cell proliferation and growth. Our studies show that triacetyl-resveratrol (TCRV)interacts with the Gli-DNA zinc finger complex which is a downstream target of Shh pathway. TCRV is a derivative of natural polyphenol compound resveratrol, grape polyphenol with cancer preventative activities in several cancers. TCRV interacted actively and specifically with Gli-DNA zinc finger complex through binding at the site targeted by the affinity (-8.0 Kcal/mol) with the VAL159, ARG162, HIS170, LEU184, GLU185, ASN186, DA14 AND DA15 residues. These studies could be helpful to understand the mechanism of TCRV and its chemo-theraputive effects for the prevention and treatment of cancers.

Keywords

TCRV, Gli-DNA, Cancer, Cancer Prevention

Introduction

Sonic hedgehog (Shh) is a secreted signaling protein that is essential for proper embryonic development [1-3]. AbnormalShh signaling drives initiation and maintenance of basal cell carcinoma.It has been associated with the progression of several cancers including gastrointestinal tumors,prostate cancer and pancreatic cancer [4,5]. When secreted Shh binds to its receptor patched (PTCH), the inhibition of smoothened (Smo), a G-protein-coupled receptor that activates downstream intracellular components of the pathway, by PTCH is relieved. The transcription of target genes (including PTCH and Gli) is subsequently activated by the Gli family of transcription factors [6]. The role of Gli activation through Shh in the growth of tumors has been studied and classified according to how the pathway is activated [7-9].

Dietary chemoprevention is an encouraging approach for cancer prevention and therapy. There are hundreds of dietary phytochemicals which have shown anticancer effects. Whereas the molecular mechanism (s) of cancer prevention and therapy through dietary phytochemicals are not very well understood. Previously published reports indicate a reduced cancer risk associated with the consumption of red wine, attributable mostly to higher resveratrol content [10,11]. Resveratrol is one of the best consideredstilbenes and is known to have a wide range of biological activities including anti-inflammatory activity,antioxidative cardiovascular protection, cancer preventive and therapeutic effects. Resveratrol has been shown to inhibit cell growth, cell proliferation and suppress tumor progression. Anti-proliferative activities of resveratrol have been reported in numerous cancer cells including human colorectal, murine epidermal and epidermoid carcinoma cells [12-17]. However, ambiguous suppression of proliferation has also been observed in several cancer cell lines including MDA-MB-231, MCF-7, MKL-F, KPL-1 and T47-D breast cancer cells, while low dose of resveratrol potentiated MCF-7 and T47-D proliferation [18-23]. Because of low bioavailability of resveratrol, and rapid metabolism has hindered its progression into clinical practice [24,25]. Other diet-derived stilbenes chemically related to resveratrol with the same backbone, but differing in the type, number, and position of substituents are of interest since they may possess greater biopotency [26]. For example, substitution of a hydroxyl (OH) group with a acetyl (COCH3) increases both the transport into cells and the metabolic stability of the molecule.

Here, we sought to study the *in silico* model of anticancer and chemo-preventive effects of TCRV through interacting with Gli-DNA zinc finger complex. Trimethoxy-resveratrol found in pterobolium hexapetallum has demonstrated anticancer effects through controlling apoptosis and cell cycle. Pterostilbene, naturally found in grapes and blueberries has therapeutic and anti-metastatic properties in hepatocellular carcinoma and melanoma. Among these new compounds, TCRV has been reported to show potential anticancer effects in cancer.

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*Corresponding author:

Dhruv Kumar
J3-112, Amity Institute of Molecular Medicine & Stem Cell Research (AIMMSCR)
Amity University Uttar Pradesh, Sec-125
Noida-20131, India
Tel: 7082436598
Email: dhruvbhu@gmail.com, dkumar13@amity.edu

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Materials and Methods

Molecular docking between TCRV and Gli-DNA zinc finger complex

Ligand (TCRV) was designed using ACD/ChemSketch Freeware software (http://www.acdlabs.com/resources/freeware/chemsketch/). Open Babel (An open chemical toolbox) software used to convert 3D structure of ligand (.MOL file) into .PDB file. Ligands were optimized by using Graphical User Interface program AutoDock Tools4 (ADT). Protein Gli-DNA zinc finger complex was downloaded from RCSB-Protein Data Bank (PDB-ID: 2GLI) and edited in.txt file. Protein was optimized by using ADT. Intermediary steps, such as .pdbqt files for protein and ligand preparation and grid box creation were completed using ADT. ADT assigned charges, solvation parameters and fragmental volumes to the protein. AutoDock saved the prepared file in .pdbqt format. AutoGrid was used for the preparation of the grid map using a grid box. The grid size was set to 110 × 80 × 94 xyz points with grid spacing of 0.375 Å and grid center was designated at dimensions (x, y, and z): -17.653, 10.415 and 7.117. AutoDock-Vina was employed for docking using protein and ligand information along with grid box properties in the configuration file. AutoDock-Vina employs iterated local search global optimizer. During the docking procedure, protein was considered as rigid and ligand was considered as flexible. The results less than 1.0 Å in positional root-mean-square deviation (RMSD) was clustered together and represented by the result with the most favorable free energy of binding. The pose with lowest energy of binding or binding affinity was extracted and aligned with receptor structure for further analysis.

Results and Discussion

In an *in silico* approach, we have focused on Gli-DNA zinc finger complex. Gli expressed as a nuclear protein in variety of cell types and shows binding to resveratrol derivative containing acetyl functional group. A molecular docking program Autodock-Vina [27] was employed to demonstrate the binding characteristics of TCRV to Gli-DNA zinc finger complex. This molecular docking strategy provides a theoretical calculation of the relative binding energies, indicative of the comparative conformation stability between a ligand with the pertinent interaction domain of a receptor. The docking results of the TCRV to Gli-DNA zinc finger complex were calculated and visualized using Autodock-Vina and AutoDock Tools 4 accessory programs. The results of the predicted binding of TCRV to the active site of Gli-DNA zinc finger complex are illustrated in Figure 1, which showed the calculated grid score (GS, representing overall binding energy), electrostatic energy, and the number of theoretically possible hydrogen bonds. TCRV can fit within the active site of Gli-DNA zinc finger complex. The binding energy calculations between TCRV and Gli-DNA zinc finger complex (-8.0 Kcal/mol) indicate the lowest binding and repulsive electrostatic energies (or the highest affinity). TCRV directly interacts with the VAL159, ARG162, HIS170, LEU184, GLU185, ASN186, DA14 AND DA15 residues of the Gli-DNA zinc finger complex. TCRV is theoretically capable of forming two hydrogen bonds with the Gli-DNA zinc finger complex. These hydrogen bonds and the specific amino acids may be involved in the spatial orientation and organization generated during interaction between TCRV and Gli-DNA zinc finger complex receptor. Docking results suggest that TCRV might be regulating some signaling pathways to induce cellular events by interacting with Gli-DNA zinc finger complex, which controls cancer cell growth.

Conclusion

The high expression of Gli andGli-DNA complex has been observed in the cancer cells. There are several signaling pathway and mechanism are involved upon binding to Gli-DNA zinc finger complex in the progression of cancer cells. As supported, by the molecular docking model, direct interaction between TCRV and Gli-DNA complex, this should expand the scope and framework of translational application of the TCRV in the prevention and treatment of cancer.

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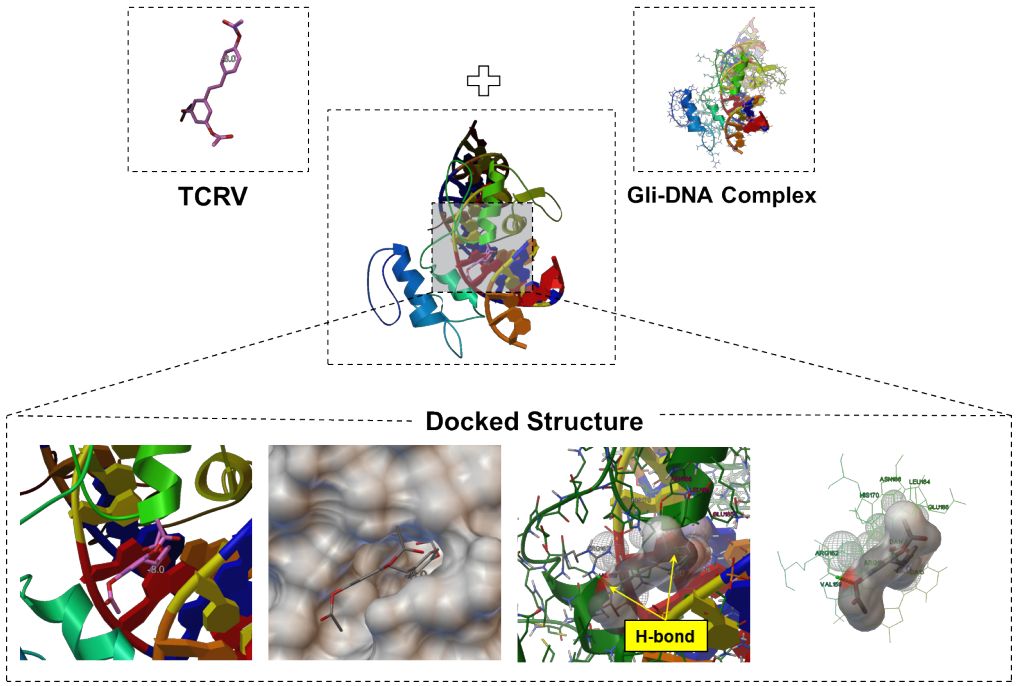

Figure 1: Molecular docking between Gli-DNA zinc finger complex (PDB-ID: 2GLI) and TCRV.
Binding conformations of top ranked docked poses of TCRV into Gli-DNA zinc finger complex. Binding activity of docked structure predicted by AutoDock-Vina is only showing important residues are displayed in CPK style. The inhibitors, and part of the amino acid residues in the background were visualized in New Ribbon style using the AutoDock Tools4.

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