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ELUCIDATION THE TOXICITY MECHANISM OF METAL OXIDE AND CARBON-BASED NANOPARTICLES WITH P53 PROTEIN USING MOLECULAR DOCKING APPROACH

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ABSTRACT

Metal oxide and carbon-based nanoparticles (NP) have a wide range of application in various fields, including paint, electroluminescent, pharmaceutical, and other industries. In the last decade, there is an exceeding demand of the applications using these particles in biomedical sciences such as in drug delivery system whereas these materials are also used widely in the environmental applications. Due to their extensive applications, these materials are the class of highest global annual production. The information of the potentially harmful effect of these nanoparticles lags behind their increased use in consumer products and therefore, the safety data on various nanoparticles applicable for risk assessment is urgently needed. The availability of less information of toxicity and harmful effects on the human biological system of these particles, there is a need to understand the toxicity of metal oxides and carbon-based nanoparticles. In the present study, we elucidate the toxic impact of the metal oxide and carbon-based nanoparticles on p53 DNA binding domain protein using molecular docking approach. Furthermore, we also explore the binding phenomenon between the p53 protein and nanoparticles (metal oxide and carbon-based NP) using the same molecular docking approach. The study illustrates that metal oxide based nanomaterial has a high binding affinity toward the DNA binding domain of p53 protein as compared to carbon-based nanoparticles, this happens because the metal oxide nanoparticles formed hydrogen and metal acceptor bonds whereas in the case of carbon-based nanoparticles only van der Waal interactions were identified in the molecular interaction. Due to the binding of these nanoparticles, DNA is unable to interact with binding domain site which may lead to deactivation of the tumor suppressing nature of the p53 protein.

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INTRODUCTION

In recent times, development in nanotechnology engineering has increased the prompt expansion of many applications for nanoparticles such as metal nanoparticles (gold, silver etc.), metal oxide nanoparticles (TiO_2, CuO, ZnO, fullerene etc.), C_{60} fullerenes nanocrystals, carbon nanotubes (CNTs) in various industries (Nel *et al*., 2006; Buzea *et al*., 2007; De Stefano *et al*., 2012; Oberdörster 2012). Principally, nanoparticles and nanofibers, depict advanced physical and chemical properties per unit weight, and these activities explain their vast application not only in industry but also in the scientific and medical researchers (Jain *et al*., 2015). Nanoparticles are unique with their dimensional and structural properties and extensively been used in various nanomedicine-related applications, which include cancer targeting, visualization, and destruction visualization in different biological systems (Suri *et al*., 2007; Cai *et al*., 2008). The application of nanoparticles as a biomaterial necessitates fully dissimilar assessments of safety, which include *in-silico* and *in-vivo* analysis, implantation tests, cytotoxicity tests and carcinogenicity tests, due to the research in last two decades has highlighted the toxicity and potential risks of their use for various applications (Hoet *et al*., 2004; Gangwal *et al*., 2011;

De Stefano *et al*., 2012). The toxicity of nanoparticles is more when they are minute (<10), that helps them to penetrate into the biological structures such as cells and cellular organelles, which are bigger than nanoparticles and interrupt the normal cell function and cause tissue inflammation, altered cellular redox balance toward oxidation, abnormal cell function or cell death (De Jong *et al*., 2008; Sonavane *et al*., 2008; Zhang *et al*., 2011). Nanoparticles of varied materials (e.g., gold, silica, titanium, carbon nanotubes, quantum dots) have shown their own unique mechanism of toxicity. Due to the proteins modifications, lipid peroxidation, DNA fragmentation reactive oxygen species (ROS) possibly lead to cellular damage, cancer and other several disorders (Oberdörster *et al*., 2005). Numerous studies have also shown the manifestation of DNA fragmentation and formation of oxidation induced DNA adducts on the exposure to the metal oxides nano-particles, and in retort the cells either start the DNA repair mechanism or initiate the cell cycle arrest or apoptosis (Karlsson *et al*., 2008; Lin *et al*., 2009; Bhattacharya *et al*., 2009). In this process, one of the main effector molecules p53 triggered in response to DNA damage, which plays a significant role in the DNA repair and cell cycle's arrest (Lane 1992; Khanna *et al*., 2015). In fact, the p53 protein plays an important role in the regulation of many critical cellular functions and biological process in living cells, however, the abnormal expression of p53 contributes to carcinogenesis. Cancer is generally linked with the abnormal cell cycle progression and imperfect apoptosis induction due to the activation of proto-oncogenes and/or inactivation of tumor suppressor genes (Hanahan and Weinberg 2000). In the year 1979 discovery of p53 was reported as an oncogene and after a decade of research, it was reported as a tumor suppressor gene in 1989 and located on chromosome 11 in the mouse and in human on chromosome 17 (17p13.1) (McBride *et al*., 1986; Vousden and Prives 2009; Levine and Oren 2009). p53 is a well-known tumor suppressor gene which acts biochemically as a transcription factor and controls the cell proliferation and apoptosis; whereas under normal, unstressed conditions, p53 protein persists imperceptible due to its short half-life and p53 also plays a critical role in keeping the genetic homogeneity of somatic cells and is most frequently affected in cancer. (Haupt *et al*., 1997; Almazov *et al*., 2007; Wang and Sun, 2010). In the present work, we have investigated the comparative binding and toxicity impact of metal oxide and carbon based nanoparticles on p53 DNA binding domain. The mechanism of interaction of metal oxide and carbon based nanoparticles and their effect on the p53 were elucidated using molecular docking approaches. The metal oxide based nanoparticles have a higher binding affinity as compared to the carbon based nanoparticles and their impact on the biological processes.

MATERIALS AND METHODS

Retrieval of p53 protein 3D Conformation

Three-dimensional coordinates of p53 protein were obtained from the Protein Data Bank (http://www.rcsb.org/pdb/home/home.do) PDB ID: 2AC0 (Kitayner *et al*., 2006a), which is a tumor suppressor protein encoded by the p53 gene. For molecular docking, the ligand and other heteroatoms (water, ions, etc.), were removed by using prepared protein protocol of Discovery Studio (D.S) 4.0.

Build 3D structure models of nanoparticles

Two different types of Nano-systems were built for this study (I) Carbon-based Nanoparticles Single wall carbon nanotube (SWCNT) and Fullerene (C_{60}) and (II) Metal oxide based Nanoparticles (TiO_2, ZnO and CuO) using build protocol of Material Studio 7.0 with a dimension of 1 nm. All the nano-systems were optimized using Material Studio protocol forcite geometry optimization.

Molecular docking of metal oxide and carbon-based nanoparticles with p53 protein

We identified the active sites of the protein molecule using experimental evidence from literature which ensured that blocking of p53 protein active site residues R273 and R248 may reduce functional properties of p53 protein (Kitayner *et al*., 2010; Petty *et al*., 2011; Paskulin *et al*., 2012). We defined the p53 protein active site residues to perform control docking with nanoparticles using AutoDock 4.0 (Morris *et al*., 1996). Protein structure was prepared by adding the hydrogen atoms, Kollman United charges and salvation parameters. Similarly, gasteiger charges were added to the metal oxide and carbon based nanoparticles and Lamarckian Genetic Algorithm (LGA) was used for flexible docking calculations (Goodsell *et al*., 1996) and grid box parameters were set to cover the maximum part the of active site in p53 protein. The values were set to 60 × 60 × 60 Å with a spacing of 3 Å. All top conformations of p53 docked complexes obtained were analyzed for the interactions and binding energy of the docked structure using Discovery Studio 4.0.

RESULTS

Molecular docking interaction plays a significant role in drug discovery. In our docking studies, we define the activation site residues which play an impotent role for the DNA binding to p53 for their proper functioning. The 3D structure of p53 core domain bound to DNA illustrate that the guanidinium groups of the ARG 273 residues (positively charged) plays a key role in docking (Cho *et al*., 1994; Olivier *et al*., 2002; Kitayner *et al*., 2006; Petitjean *et al*., 2007; Chen *et al*., 2010; Eldar *et al*., 2013). The p53 protein residue ARG 273 (positively charged) interaction with the DNA backbone (negatively charged) (Kitayner *et al*., 2010; Petty *et al*., 2011) and ARG 248 residues also participated in the DNA binding (Tomoda *et al*., 2008), which is supported by hydrogen bonding and salt-bridge interactions. In molecular docking Autodock generated 10 conformations of p53 protein with each nanoparticle, based on the binding energies we retrieved the best poses and analyzed. We further identified that metal oxide (TiO_2, ZnO, and CuO) and carbon-based nanoparticles (Fullerene, SWCNT) have best molecular interaction poses with p53 protein. The binding energies of metal oxides TiO_2, ZnO, and CuO were respectively (-7.94 kcal/mol, -5.90 kcal/mol and -5.57 kcal/mol), and carbon-based nanoparticles (Fullerene and SWCNT) binding energies were (-5.10 kcal/mol and -4.16 kcal/mol) as represented in Figure 1.

Different residues in DNA binding domain of p53 protein and their bonding with TiO_2-nanoparticle

The interaction between Tio_2 and p53 protein is basically based on the basic amino acid residues ARG 248, ARG 273, ARG 280 and 1 polar amino acid residue SER 241. The distance between the surfaces of the TiO_2 nanoparticle from the active site residues of p53 protein as given is 2.94, 2.97, 3.07 and 1.52 Å respectively. A total of four hydrogen bonds formed with SER 241, ARG 248, ARG 273 and ARG 280

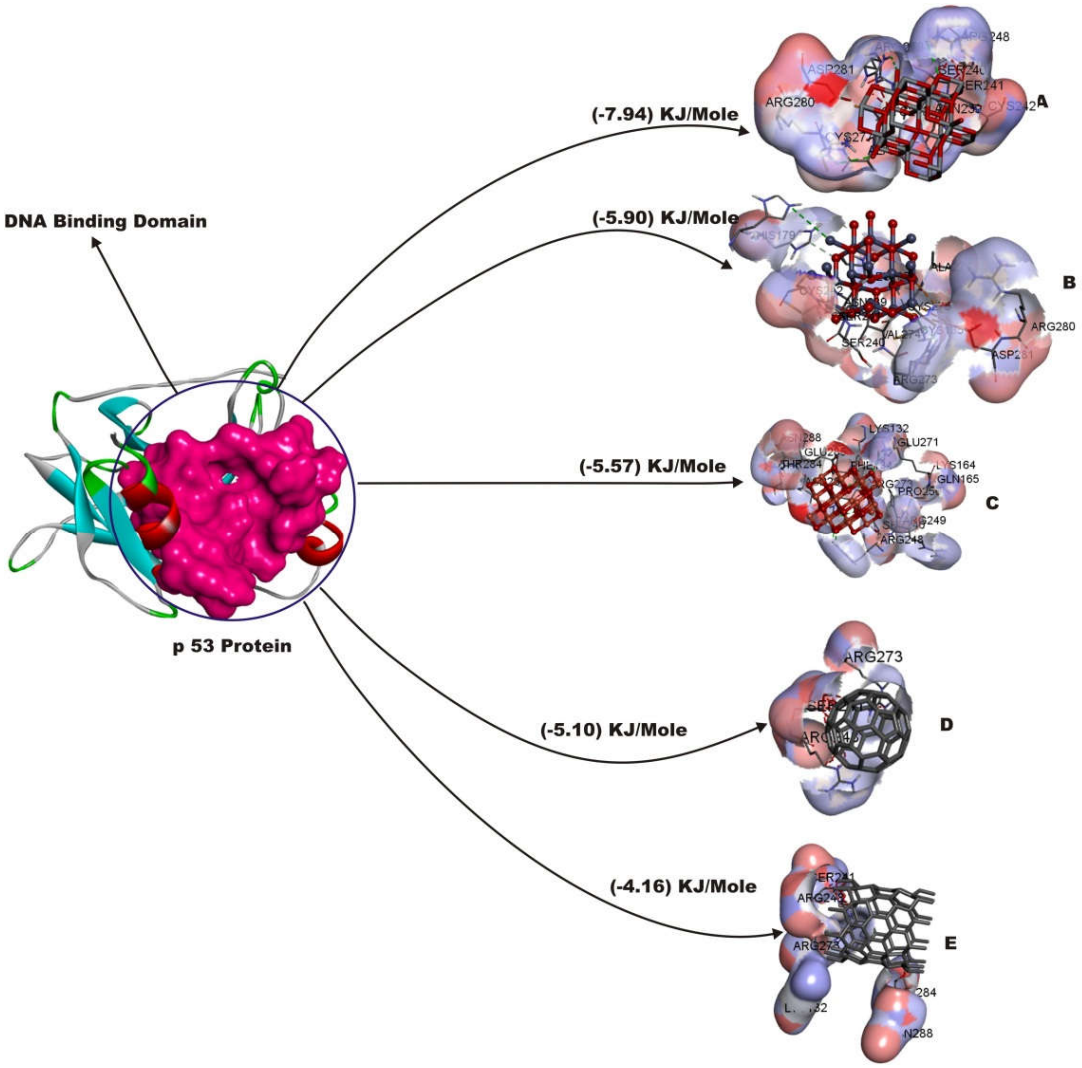

Figure . The interaction of nanoparticles with the DNA binding domain of p53 protein. The DNA binding domain was shown in pink color. In case A-E, the binding cavity and interacting residues of p53 with nanoparticles were shown. A) Tio_2 nanoparticle B) ZnO nanoparticle C) CuO nanoparticle D) Fullerene E) SWCNT, as well as binding energies and bonds with ---- lines, also highlighted

Table 1. Binding energies and interacting residues of p53 DNA binding domain and their distance from the nanoparticles

p53-ZnO Interaction			
Residues	Distance(Å)	Type	Energy(KJ/Mole)
p53: ARG273: HE - ZnO:O	2.88513	Conventional Hydrogen Bond	-5.90
p53: HIS179: CE1 - ZnO:O	2.72454	Carbon-Hydrogen Bond	
p53:CYS135:O - ZnO:Zn	3.237	Metal-Acceptor	
p53:CYS275:O -ZnO:Zn	2.30521	Metal-Acceptor	
p53- TiO_2 Interaction			
Residues	Distance(Å)	Type	-7.94
p53: SER241: HG - TiO_2:O	1.52922	Conventional Hydrogen Bond	
p53: ARG248: HH21 - TiO_2:O	2.94987	Conventional Hydrogen Bond	
p53: ARG273: HH12 - TiO_2:O	2.97795	Conventional Hydrogen Bond	
p53: ARG280: HH11 - TiO_2:O	3.07446	Conventional Hydrogen Bond	
p53-CuO Interaction			
Residues	Distance(Å)	Type	-5.57
p53: LYS132: HZ3 - CuO:O	2.46888	Conventional Hydrogen Bond	
p53:ARG248:HH22 - CuO:O	2.50651	Conventional Hydrogen Bond	
p53:ARG248:O - CuO:Cu	2.68922	Metal-Acceptor	
p53:GLU271:OE1 - CuO:Cu	3.35111	Metal-Acceptor	
p53-Fullerene Interaction			
Residues	Distance(Å)	Type	-5.10
p53:SER241:HG - full:C	1.06614	van der Waal	
p53:ARG248:HE - full:C	1.59328	van der Waal	
p53:ARG273:HH22 - full:C	1.50998	van der Waal	
p53-SWCNT Interaction			
Residues	Distance(Å)	Type	-4.16
p53:ARG248:HH11 - SWCNT:C	0.950406	van der Waal	
p53:ARG273:HH11 - SWCNT:C	1.02498	van der Waal	

amino acid residues of p53 protein with TiO_2. The docked energies indicate that TiO_2 formed more strong interaction with p53 with their active site residues due to more number of hydrogen bonds formed.

Different residues in DNA binding domain of p53 protein and their bonding with ZnO nanoparticle

ZnO nanoparticle and p53 protein interaction are mainly based on the basic and polar amino acids residues. HIS 179, ARG 273 belonged to basic and CYS 135, CYS 275 polar amino acid residues. The overall distance between the surfaces of the ZnO nanoparticle from the active site residues of p53 as given is 2.73, 2.88, 3.23 and 2.30 Å respectively shown in Table 1. The above mentioned amino acids would be the binding sites of p53 protein with ZnO nanoparticle. A total of two hydrogen bonds formed with HIS 179, ARG 273 and two metal acceptor bonds with CYS 135, CYS 275 amino acid residues of p53 protein. The docking energies indicate that ZnO formed strong interaction with p53 protein with their active site residues due to the hydrogen and metal acceptor bonds formed.

Different residues in DNA binding domain of p53 protein and their binding with CuO nanoparticle

In the case of CuO nanoparticle, the interaction residues are mostly basic in nature and also from two hydrogen and two metal acceptor bonds with LYS 132, ARG 248, ARG 248 and GLU 271 residues. The distance between the interacting residues of p53 protein with CuO is 2.46, 2.50, 2.68 and 3.35 Å respectively.

Different residues in p53 protein and their binding with Fullerene and SWCNT

Carbon-based nanomaterial, fullerene and SWCNT interact with p53 protein and formed weak interaction with active site amino acid residues. The binding energies indicated that carbon-based nanomaterial formed effective interaction due to hydrophobic surfaces adsorb a wide class of substances by van der waals interaction (Tirandai Hemraj-Benny *et al*., 2004; Banerjee *et al*., 2005; Bomboi *et al*., 2011). The nature of interacting amino acid residues in case of fullerene is basic and polar, SER 241 is polar and ARG 273, ARG 284 are basic in nature. The distance of interacting amino acid residues from the fullerene surface was 1.06, 1.59 and 1.50 Å respectively. A total three van der Waals interactions were formed with SER 241, ARG 273 and ARG 284 whereas with SWCNT, only two amino acid residues were involved in the interaction, ARG 273 and ARG 248 at a distance 0.95 and 1.02 Å. In cases of carbon-based nanoparticles, the progressive interactions were taken place between p53 protein and the hydrophobic surface of carbon-based nanoparticles. Fullerene and SWCNT are presumably adsorbed onto the complete active site cavity through van der Waals interaction.

DISCUSSION

The interaction between the metal oxide and carbon-based nanomaterials with p53 protein is basically based on the basic and polar amino acid residues. In the present docking studies, the most interacting residues were ARG 248 and ARG 273, and both play an important role in the DNA binding in p53 protein. Due to the geometrical arrangement of charged residues present within the binding cavity of p53 DNA binding domain, these sites would be a probable binding site on the metal and carbon-based nanoparticles. The DNA binding to p53 is mainly depended on the major, minor groove and DNA backbone. In the major groove, most important interaction is ARG 280, which provides the stability to α-helix of DNA by a salt bridge and in the minor groove, most important contact Arg248 from the loop L3 is packed against the DNA backbone because of the local compression of the minor groove as results it makes hydrogen bonds between Arg248 and G13. At last, the phosphate DNA backbone T11 bind to ARG273 and also form multiple interactions including a salt bridge. When nanoparticles interact with p53 DNA binding domain, then major, minor groove and DNA backbone were unable to form a most important major, minor groove and backbone interaction with ARG 248, ARG 273 and ARG 280 residues. From the above results, we have also explored the comparative bind affinity of metal oxide and carbon-based nanoparticles, TiO_2>ZnO>CuO>fullerene>SWCNT. TiO_2 has a higher affinity as compared to other nanoparticles because it formed more number of hydrogen bonds in the DNA binding domain and SWCNT has the lowest affinity towards the DNA binding domain due to van der Waals interaction with the residues as shown in Table 1. In the case of metal oxide and carbon based nanoparticles at DNA binding site ARG 248, ARG 273 and ARG 280 form hydrogen bond, Metal-Acceptor and van der waals interaction with TiO_2, ZnO, CuO, fullerene and SWCNT. Due to these interactions DNA is unable to interact with p53 DNA binding domain and this study clearly illustrates that due to the p53-contact docking of nanoparticles, the p53 DNA binding domain unable to bind with DNA. This bind loss might affect the p53- DNA interaction and leads to inhibition of the cancer suppression.

Conclusion

In the last decade, molecular docking is often used for the screening of the nanoparticles (NPs), which can bind to the target with experimental or modeled structures. The number of cases reported that NPs interact with biological macromolecules (Saptarshi *et al*., Kane and Stroock 2007). Recent studies have shown that NPs inhibit enzyme activity due to their interaction with the active site or binding directly with the substrate (Kain *et al*., 2012; Magdolenova *et al*., 2014). In addition, when DNA damage occurs, then activation of p53 will initiate and it will bind to the DNA for the activation of the transcriptional process but due to the nanoparticles already bind to the DNA binding domain, DNA will unable to bind with p53 DNA-binding domain as a result, it will unable to active transcriptional process, which is mainly responsible for the cell cycle arrest or DNA repair. Due that abnormal expression of p53 contributes to carcinogenesis.

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