Abstract

Background:

Incidents of cancer are increasing each year and lung cancer and head and neck cancers contribute to majority of deaths related with cancer. Environmental carcinogens are leading cause of lung cancer and head and neck cancer. BaP and NNK are the most dangerous environmental carcinogens which have been placed in group 1 category of carcinogens by IARC. Industrial and vehicle exhausts, tobacco smoke, pyrolysis of various organic matters are the major sources BaP. NNK is found in abundance in various types of tobacco related products like cigars, cigarettes, tobacco snuffs etc. It also gets formed endogenously in the saliva of people who come in contact of nicotine because of the reaction between salivary nitrate and nicotine.

In this study we have tried to identify the major biomolecular targets of BaP and NNK using various tools of systems biology. We have also tried to analyze the scavenging and protective potentials of carbon nanoparticles (Single walled carbon nanotubes, multiwalled carbon nanotubes and fullerenes) against these environmental carcinogens (BaP and NNK) with the help of molecular docking simulations and adsorption load analysis.

Objectives:

To fulfill the aims of our study, we have divided the study into four objectives

Objective 1: Identification of most probable biomolecular targets of environmental carcinogens (BaP & NNK) among the cell cycle regulatory proteome once they enter the biological system.

Objective 2: Construction of network system for functional coverage of most potent biomolecular targets of environmental carcinogens among the cell cycle regulatory proteome.

Objective 3: Designing of cell cycle regulatory bio-model along with its kinetics and determining the impact of environmental carcinogens on normal cell cycle regulation.

Objective 4: Determination of the binding efficiencies of environmental carcinogens with carbon-based nanoparticles, environmental carcinogens adsorption load over nanoparticles and comparison of binding efficiencies of carcinogens with their biomolecular targets and nanoparticles.

Methodology:

For finding the genes hampered by BaP, T3DB database was used and Pubmed was used for finding the genes that get hampered by NNK by using various keywords like NNK, humans, cancer, cell cycle etc. Once the genes were identified, protein-

protein interaction networks were generated with the help of STRING.db software. The networks were analyzed with the help of Cytoscape software. Modulation and enrichment analysis were done using MCODE and ClueGO apps of the cytoscape software. Seed proteins were identified from the clusters generated by MCODE and then network were generated using these seed proteins for BaP and NNK separately. The nodes present in both the BaP and NNK rewired PPINs were analyzed on the basis of their topological properties like degree, clustering coefficient, betweenness score and bottleneck scores. To further screen out the proteins, molecular docking simulations were performed on all the selected proteins for BaP and NNK. Once top bio-molecular targets were identified for BaP and NNK, cell cycle regulatory model was designed using cell designer software and then SBMLsqueezer was used to incorporate the bio-kinetics in the model. Time course analysis was performed using COPASI software and changes in concentrations and fluctuations in the oscillations were analyzed. Finally, we tried to analyse the scavenging capacity of carbon nanoparticles (SWCNT, MWCNT and Fullerenes) by comparing the binding efficiencies of carcinogens and carbon nanoparticles with that of carcinogens and their top bio-molecular targets and finding the adsorption load capacity of carbon nanoparticles for BaP and NNK.

Results:

4000 genes were found to be hampered by BaP where as 544 genes were extracted from Pubmed that were hampered by NNK. QSOX1, PTGS2, NOS2 were the

top three biomolecular targets for BaP. CDK7, CCNA1 and CDKN1B were the top biomolecular targets for NNK. On the analysis of the scavenging potentials of SWCNTs, MWCNTs and Fullerenes against BaP and NNK, it was found that MWCNT had the highest scavenging potential against BaP and showed highest adsorption capacity while for NNK, SWCNT showed the highest binding energy and MWCNT showed the highest adsorption load capacity.

Conclusion:

QSOX1, PTGS2 and NOS2 came out to most influencing key regulatory biomolecular targets which may govern whole BaP associated interactome while CDK7, CCNA1 and CDKN1B were the most influencing key regulatory biomolecular targets which may govern whole NNK associated interactome.

Out of all the three carbon based nano-particles used to scavenge BaP and NNK, MWCNT has the highest binding affinity as well as adsorption capacity against BaP while for NNK, SWCNT showed highest binding affinity and MWCNT showed highest adsorption capacity.