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Molecular Dynamic and Docking Study on to Interact Tetra Sodium Sulphunated Nickel (II) Phthalocyanine (NiPcTS) and Adenosine Deaminase

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All-atom molecular dynamics simulation of adenosine deaminase (ADA) was studied in the absence and presence of 0.014, 0.028 and 0.042 M of (NiPcTS) and different temperatures by Gromacs (4.5.4) molecular dynamics. One molecule of adenosine deaminase including 349 amino acid immerged in a box with 9.105×9.105×8.660 nm3. Then, different number of (NiPcTS) added to the cited. After preparing the input files, the system optimized at 275, 300, 325, 335, 350, 365, 375, 390, 425, and 450 K in the 20000 ps timescale. Accessible surface area (ASA), circular dichroism at 222nm (CD222nm), mid-point of transition temperature (Tm), number and distance of hydrogen bond, radial distribution function and other physical parameters were got from analysing trajectory of molecular dynamics. Results of calculated heat capacity at constant pressure (Cp) showed that transition temperature increases by increasing the (NiPcTS) concentration. Mid-point of temperature transition (Tm) got as 350 and 365 K in the absence and presence of 0.014 M of (NiPcTS), respectively. Thus two peaks will be viewed in the plot of Cp versus temperature. Radial distribution functions show that (NiPcTS) at low concentration behaves same as osmolytes that increases the beta form, increases the stability. Docking energy showed that binding energy of metalic is lower than nonmetalic phthalocyanine.

Keywords: Docking, Heat Capacity, Thermal Stability, Transition Temperature.

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RalA as a Therapeutic Target in Human Malignancies and their Cancer Stem Cells

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Ral (Ras like) leads an important proto-oncogenic signaling pathway,downs-stream of Ras, involved in multiple facets of neoplastictransformation. Since overactivation of Ras is a prevalent molecularabnormality in hepatocellular carcinoma (HCC), we decided to study therole of RalA activation in human cancers. For example, RalA was found tobe significantly overactivated in HCC cell lines as well as HCC tissues.Other elements of RalA pathway, such as Ral binding protein (RalBP1)and Ral guanine nucleotide dissociation stimulator (RalGDS), wereexpressed at higher levels in malignant samples. Aurora kinase, anupstream activator of RalA, was also found to be more phosphorylated(activated) in HCC as compared with non-malignant samples. However,protein phosphatase 2A (PP2A), a negative regulator of Ral activation,was expressed at comparable levels. Inhibition of RalA by gene- specificsilencing caused a robust decrease in the viability and invasiveness ofHCC cell lines. Additionally, the use of geranyl-geranyl transferaseinhibitor (GGTI, an inhibitor of Ral activation) and Aurora kinase inhibitor IIresulted in a significant decrease in the proliferation rate of HCC cells.Furthermore, we investigated the levels of RalA activation in HCC stemcells and concluded that active RalA, Ras and phospho-Aurora kinaselevels were increased in the fraction of cells which express CD133, awidely accepted marker for cancer stem cells. Investigation of the level ofRalA activation in transgenic mouse model for HCC (FXR-Knockout)revealed an elevated level of RalA-GTP in the liver tumors as compared toliver tissue from background animals. Finally, subcutaneous mouse modelfor HCC confirmed effectiveness of inhibition of Aurora kinase/Ral pathwayin reducing the tumorigenesis of HCC cells in vivo. In conclusion, RalAoveractivation is portrayed by our investigations to be an importantdeterminant of malignant phenotype in differentiated and stem cells ofHCC. Resembling data was obtained by our team studying othermalignancies such as cancers of lung, ovary and neurological system.Therefore, intervention with this signaling pathway has the potential tooffer a novel strategy for the treatment of a number of important human cancers.

Keywords: RalA, Malignancies, Cancer Stem Cells, CD133.
