Contribution ID: **16** Type: **not specified**

Molecular Modeling of the Interaction Between Cytokine EMAPII and Titanium Dioxide Nanoparticles

Protein-based therapeutics represent an important class of modern biopharmaceutical agents due to their high specificity and ability to regulate biological processes. One such molecule is the cytokine Endothelial Monocyte-Activating Polypeptide II (EMAPII), which exhibits antiangiogenic, proapoptotic, and immunomodulatory activity. However, its biomedical application is limited by aggregation in aqueous solutions, which reduces stability and efficiency. One possible strategy to overcome this limitation is the use of nanoparticles as stabilizing platforms and delivery carriers for protein molecules.

Titanium dioxide (TiO_2) nanoparticles are widely studied in nanomedicine due to their biocompatibility, chemical stability, and tunable surface properties. Their ability to interact with biomolecules makes them promising candidates for targeted delivery systems and nanocomposite therapeutic platforms.

In this study, the molecular interaction between EMAPII and a spherical TiO_2 nanoparticle (2 nm in diameter) was investigated using computational modeling. A two-step approach was applied: blind molecular docking was first performed to identify energetically favorable binding sites, followed by molecular dynamics simulations in an explicit aqueous environment.

Docking calculations revealed several possible binding modes on the EMAPII surface, with the most favorable conformations located within the hydrophobic pocket of the protein. The calculated binding energies ranged from −12.15 to −11.24 kcal/mol, indicating strong affinity between the nanoparticle and the protein. The interaction is primarily driven by electrostatic attraction between negatively charged oxygen atoms of the TiO_2 surface and positively charged residues such as Arg73, Lys123, and Lys166, while hydrogen bonds and hydrophobic contacts further stabilize the complex.

Molecular dynamics simulations (100 ns, GROMACS, CHARMM27 force field) demonstrated that the EMAPII–TiO_2 complex remains stable in aqueous solution. Structural deviations of the protein were minimal (RMSD < 0.2 nm), indicating that the nanoparticle does not significantly perturb the native structure of the cytokine. Stable contacts were observed with several residues, including Asp26, Arg73, Lys123, Lys166, Trp125, and Glu126. Analysis of interaction energies showed that electrostatic forces dominate the binding process, whereas van der Waals interactions provide a smaller contribution.

Overall, the results demonstrate that TiO_2 nanoparticles can form stable complexes with EMAPII without disrupting its structural integrity. These findings highlight the potential of TiO_2 nanostructures as carriers and stabilizing platforms for cytokine-based therapeutics.

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