Computational investigations for the design of a Multimodal Innovative Theranostic Nanosystem (MITHOS)

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Drug delivery systems based on stimuli-responsive metal oxide nanoparticles (MeOx NPs) for cancer treatment gained interest in the past few years. Due to their enhanced targeting ability, they can limit the drugs toxic effects and allow for better tuning of the dose/response behavior [1, 2]. Biomedical MeOx NPs rely on NP surface functionalization with different agents, which allows their solubility, drug loading and specific targeting. Within the PRIN project MITHoS, functionalized NP are covered by a lipid membrane and used as an ultrasound-responsive carrier of the anti-cancer drug carfilzomib (CFZ) against multiple myeloma. Here, we used Molecular Dynamics (MD) simulations to investigate the structure and dynamics of these functionalized MeOx NPs and guide the design of better-performing theranostic agents. Our target NP is a ZnO NP functionalized with oleic acid (OLA) and 3-(aminopropyl)trimethoxysilane (APTMES) or N-(2-Aminoethyl)-3-aminopropyltrimethoxysilane (L-APTMES). We designed molecular models with a coarse-grained (CG) resolution of ZnO NPs, ligands, and CFZ drug. We performed metadynamics simulations to characterize CFZ adsorption on a ZnO surface functionalized with APTMES and L-APTMES with or without OLA in water and in ethanol. The free energies of adsorption profiles showed that using L-APTMES instead of APTMES can lead to a more efficient CFZ adsorption. The addition of OLA as a NP stabilizing agent in ethanol enlarged the range of attractive interaction between CFZ and the functionalized surface. When a lipid bilayer is added on top of the functionalized (OLA+L-APTMES) surface, we observe that its leaflets exhibit an asymmetric lipid distribution, due to their interactions with the ligand layer. Regarding CFZ, most of the molecules are most favorably adsorbed in the region delimited by the ligand layer and the lower lipid bilayer leaflet. In the next steps, we aim to investigate the possible mechanisms and the energetics of drug release.

[1] Dhas Namdev, et al., J Control Rel 333, 188 (2021).
[2] Anjum Sumaira, et al., Cancers 13.18, 4570 (2021).

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