ESF – Short Visit Grant – Applicant: Daniele Dell'Orco

Scientific Report

Project: Discussion and setting-up of novel biophysical strategies to study the interaction of peptide-covered nanoparticles with cellular targets

Background and motivation

Proteins, lipids, and carbohydrates found in any biologic fluid interact with nanoparticles, thus creating a complex corona around the particle surface. The composition and characteristics of this corona is determined by the particle surface and the chemical nature of the surroundings. The corona is dynamic in its nature and the proteins undergo continuous association/dissociation processes at characteristic rates, until equilibrium is reached [1]. Experimental evidence showed that very abundant biomolecules bind at first, but they are subsequently replaced by less abundant biomolecules with higher affinity [1-3]. Such behavior has been recently rationalized and quantified by mathematical modeling [4]. The detailed study of the nanoparticle-protein corona has opened new challenges and question as on the next investigations to be performed, especially toward the characterization of nanotoxicity of such systems.

Project outline

In the community, there is increasing interest in the potential applications of nanoparticles for biomedical purposes. In particular, a relevant and promising field is the influence of peptide-covered nanoparticles over certain biochemical pathways, which are normally triggered by the interaction of peptides with cellular receptors and targets. Clearly, the knowledge accumulated on the formation and the behavior of the nanoparticle protein corona will be useful to quanititatively understand how the interaction between peptides and targets is influenced by the nanoparticle and its dynamic nature.

We plan to perform a detailed biophysical investigation of the interaction of some peptide-target interactions, initially focusing on some suitable model system, e.g. the calmodulin-target peptide complex. The study will concern initially nanoparticles in which the target peptide has been covalently linked to the nanoparticle surface, and the biophysical chemistry of the interaction with the receptor will be compared to that in which the peptides are present in solution. In a subsequent step, the peptide-covered nanoparticles will be placed in contact with a biological fluid such as human plasma, and the perturbation on the same interactions will be assessed and quantified.

In this short visit, a deep discussion as on the biophysical techniques that better suit the purpose took place at the Host Institution. The relevant issues concerning experimental details were analyzed and some preliminary settings of parameters for numerical simulation of the same interactions were done.

The project is meant for future collaboration between the applicant and the Host Institution.

Outcome of the meeting

During the discussion, the available data as on typical diffusion of nanoparticle of various size in water were analyzed together with the theoretical implications for the association rates of peptides covalently bound to such nanoparticles to some generic cellular target, i.e. cell receptors. After careful analysis of the literature and the formerly developed mathematical model [4], the working

group came to the conclusion that the first important step to address the issue of the effects of nanoparticle corona on nanoparticle delivery through specific receptor-targeting epitopes is to simulate by dynamic modeling the perturbation of the target-receptor binding, when the peptide has to compete with other proteins forming the nanoparticle corona. In this respect, the data were analyzed as on typical peptide-coverage levels of nanoparticles and on hypothethical perturbation of the affinities for cell receptors compared to the case when peptides are free in solution.
The final goal of the modeling would be to estimate the delivery success rate of the peptide toward its receptor as a function of some measurable parameter, such as the receptor size, the association rate constant (related to the diffusion of the nanoparticle-bound peptide) and the affinity for the receptor. This computational investigation will hopefully provide a range of conditions that are experimentally testable and would help to optimize the delivery of the nanoparticle-bound peptides in the presence of corona-forming proteins.
The second step would be to possibly test the predictions on some model system, e.g. calmodulin and its target peptide. A further meeting will follow in which the results of computations will be analyzed and suitable biophysical experiments will be designed to directly test the outcome of simulations on real systems.

References

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