Optimization of Targeting for Gene Delivery: Computer Modeling

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Introduction

Targeted gene and drug delivery holds a great potential for the successful treatment of many deadly diseases. [1] Approaching the tumor via blood circulation should allow several advantages over the local intratumoral injection such as reaching multiple distant metastases. One of the considerable problems preventing the creation of such a gene delivery carrier is inefficient site-specific targeting. Modification of nanoparticles with poly(ethylene glycol) (PEG) chains offers a reduction of non-specific binding to cell surfaces and improves the circulation time of the gene/drug delivery vehicles in blood. There is a large variation in the experimentally reported results of PEGylation on efficacy of site-specific binding. Several reports show a reduction of transfection efficiency of DNA-based complexes, most likely due to shielding targeting functional groups. [2] There are many factors (including conformation, structure, grafting density, chain length of PEG as well as concentration of functional groups), which may influence the efficacy of targeting. We have applied computer simulations to study the influence of some of these factors.

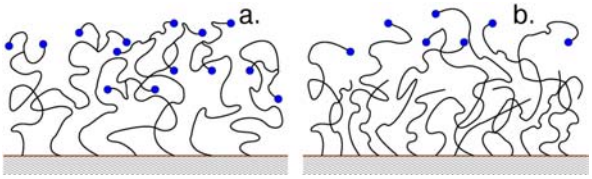

Figure 1. Schematic presentation of a layer of branched (bi-functional) polymers (a) and a mixed polymer layer (b).

Computational

We have applied Monte Carlo (MC) simulations to analyze the distribution of functional groups inside the PEG layer and to study the interaction between these groups and an attractive surface. In our MC simulations we considered a planar surface (z=0) to which polymers were homogeneously tethered by one end. The simulation box was periodic in the x and y directions (with the sizes L_x=L_y=64) and closed in the z direction (with L_z=256). We have applied the bond-fluctuation model, [3] which accounts for the volume interactions between polymer and solvent corresponding to the good solvent condition, which is typical for PEG in water under physiological conditions. Using Monte Carlo simulations we have studied the effects of chain architecture (branching, as shown in **Figure 1a**) on the distribution of functional groups inside the polymer layer. We have also tested the idea of using a mixed polymer layer, (composed of short and long chains, as shown in **Figure 1b**), to improve accessibility of functional groups attached to ends of the long chains.

Results and discussion

End-group distribution. Varying the degree of branching and position of branches along the chains we found that the fraction of end-groups in the periphery of the brush formed by a linear chain, a chain with two end-branches and four end-branches is essentially the same within the error of estimation. The brush with six side-chains provided the best result in the series, although the differences between the various cases are not so large. The main test of efficiency of multivalent interactions can be ascertained in binding studies, described below. We have also studied the end-group distribution, as shown in **Figure 2**, in mixed planar polymer brushes (containing 64 chains in total), among which 7/8 (triangles), 1/2 (circles) and 0 (squares) were short. The number of monomer units in the long and short chains was kept constant (N_L=64 and N_S=40, respectively). We found that an increase in the fraction of short chains considerably enhances the distribution of end-groups of long chains at the periphery of the brush (see **Figure 2**). Besides of varying the grafting density, we have also studied the chain length effect to find the optimal ratio between the length of short and long chains to provide the maximal fraction of long-chain end-groups in the periphery of the brush.

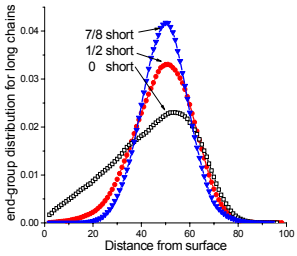

Figure 2. Distribution of end-functional groups (attached to the long chains) in mixed brushes with different content of short chains.

Binding study. The ultimate efficiency of targeting is determined by the interaction of the functional groups with the receptors. [4] For the cases of both branched and mixed polymer brushes we have studied the end-functional groups binding to an attractive surface as a function of the distance between the surfaces (see **Figure 3**). We have analyzed the fraction of functional groups adsorbed onto the attractive surface at equilibrium as a function of the distance between the adsorbing surface and the polymer brush. As the distance approaches the average height of the polymer brush, the fraction of functional groups adsorbed on the surface reaches nearly 70% for the mixed symmetric brush, whereas it is less than 50% for the homogeneous brush (containing long chains only). This demonstrates that the mixed polymer brush shows considerable improvement in binding efficiency.

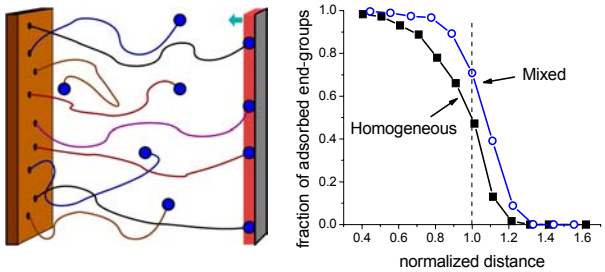

Figure 3. Schematic presentation of binding study (left) and its results for fraction of the adsorbed end-groups for a homogeneous and mixed brush as a function of the distance between surfaces (right).

Conclusion

We have found that both chain branching and composition of protective polymer layer have considerable influence on end-functional group distribution and binding capability. We found that there is an optimal ratio between the length of short and long chains in mixed brush, which provides the maximal fraction of long-chain end-groups in the periphery of the brush. Both the end-group distribution simulation study and the binding study confirm that using mixed brush of short and long chains considerably improves the targeting capability of the polymer brush.

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References

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