

Procoagulant properties of bare or highly-PEGylated vinyl-modified silica nanoparticles: comparison with Synthetic Amorphous Silica, PLGA and liposomal nanoparticles

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Abstract

Nanoparticle-based imaging and drug delivery have been increasingly proposed in recent years. The administration through nanosystems of various types of drugs is believed to increase their therapeutic efficacy and selectivity to cancer cells. Nonetheless, the potential toxicity of nanostructures still remains a major concern and must be carefully tested to evaluate their bio-compatibility. An immediate risk hampering the medical use of nanoparticles to be injected in the bloodstream is the activation of coagulation either by direct interaction with clotting factors or through the activation of hemostatically active cells such as platelets, monocytes and endothelial cells. Coagulation is a major drawback for the use of medical devices in contact with the blood, both at the macroscopic and at the nano-scale level. Available evidence suggests that NPs of different nature are able to alter the coagulation balance. External coating with hydrophilic polymers, like PEG, is a current strategy to prevent such a complication. Organically Modified Silica (ORMOSIL) is a promising constructing material to design nanoparticles (NPs) for selective drug targeting and possibly other innovative therapies. Therefore we quantified the procoagulant activity (PCA) of naked and highly-PEGylated ORMOSIL NPs, synthesized by polymerization of vinyltriethoxysilane with a one-pot procedure recently described by us. ORMOSIL-NPs effects were compared with those determined by commercially available Amorphous Silica (AS) NPs, fully inorganic structures largely used in industry, and of poly(lactic-

co-glycolic acid) (PLGA) and liposomal NPs, two formulations already approved for the use in humans. While AS-NPs strongly activated the intrinsic (contact) coagulation cascade, ORMOSIL-NPs had a much reduced activity, which was totally abolished by surface PEGylation. Although, after a prolonged incubation, bare ORMOSIL-NPs induced Tissue Factor (the initiator of the extrinsic coagulation pathway) and a procoagulant phenotype in monocytes, this effect was strongly reduced by PEGylation. No tested NPs activated platelets and endothelial cells. PEGylated ORMOSIL NPs showed a very little PCA comparable to those induced by PEGylated PLGA and liposomal NPs. However, while PEGylated PLGA and liposomal NPs bind to monocytes, endothelial cells and platelets to the same extent as their naked version, PEGylation resulted in a clear-cut reduction of ORMOSIL NPs association to these cells. In conclusion, the dense PEG-coating achievable with our synthetic procedure renders the ORMOSIL-NPs a promising constructing material to design stealth nanoparticles for selective drug targeting, such as Photo Dynamic Therapy or other innovative therapies, devoid of procoagulating effects, a major drawback of any medical devices in contact with the blood.

We are at present testing in cellular and animal models the possibility of generating PEGylated ORMOSIL-NPs containing photosensitizers covalently linked to the silica matrix. We will subsequently improve these nanoparticles by their superficially derivatization with cancer specific ligands for a more efficient therapy approach.

Acknowledgement: This project received research funding from EU's Seventh Framework Programme, Grant 201031 NANOPHOTO