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Surface modified magnetic nanoparticles for immuno-gene therapy of murine mammary adenocarcinoma

Sara Prijic [a,1], Lara Prosen [a,1], Maja Cemazar [b,g], Janez Scancar [c], Rok Romih [d], Jaka Lavrencak [e], Vladimir B. Bregar [f], Andrej Coer [g], Mojca Krzan [h], Andrej Znidarsic [a], Gregor Sersa [b,*]

[a] Kolektor Group, Nanotesla Institute, Ljubljana, Slovenia
[b] Institute of Oncology Ljubljana, Department of Experimental Oncology, Ljubljana, Slovenia
[c] Josef Stefan Institute, Department of Environmental Sciences, Ljubljana, Slovenia
[d] University of Ljubljana, Faculty of Medicine, Institute of Cell Biology, Ljubljana, Slovenia
[e] Institute of Oncology Ljubljana, Department of Cytopathology, Ljubljana, Slovenia
[f] Kolektor Group, Kolektor Magma, Ljubljana, Slovenia
[g] University of Primorska, Faculty of Health Sciences, Izola, Slovenia
[h] University of Ljubljana, Faculty of Medicine, Institute of Pharmacology and Experimental Toxicology, Ljubljana, Slovenia

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ABSTRACT

Cancer immuno-gene therapy is an introduction of nucleic acids encoding immunostimulatory proteins, such as cytokine interleukin 12 (IL-12), into somatic cells to stimulate an immune response against a tumor. Various methods can be used for the introduction of nucleic acids into cells; magnetofection involves binding of nucleic acids to magnetic nanoparticles with subsequent exposure to an external magnetic field. Here we show that surface modified superparamagnetic iron oxide nanoparticles (SPIONs) with a combination of polyacrylic acid (PAA) and polyethylenimine (PEI) (SPIONs-PAA-PEI) proved to be safe and effective for magnetofection of cells and tumors in mice. Magnetofection of cells with plasmid DNA encoding reporter gene using SPIONs-PAA-PEI was superior in transfection efficiency to commercially available SPIONs. Magnetofection of murine mammary adenocarcinoma with plasmid DNA encoding IL-12 using SPIONs-PAA-PEI resulted in significant antitumor effect and could be further refined for cancer immuno-gene therapy.

1. Introduction

The translation of nanotechnology has already widespread into biomedicine for diagnostic, therapeutic and theranostic purposes [1]. Superparamagnetic iron oxide nanoparticles (SPIONs) can be guided by an external magnetic field, yet due to quantum effects at the nanometer scale they do not retain residual magnetism in the absence of an external magnetic field [2], which makes them especially suitable for diverse biomedical applications [3]. In the field of oncology, SPIONs have been exploited for diagnostic purposes as contrast enhancers for magnetic resonance imaging and as vehicles for biomarkers detection [4]. For therapeutic purposes SPIONs have been used for isolation and transfection of hematopoietic stem cells for gene therapy – magselectofection [5], in magnetic hyperthermia [6] and as delivery systems for different therapeutics [7].

Magnetofection is a non-viral transfection method that uses an external magnetic field to target cells with nucleic acids that are bound to magnetic nanoparticles [8]. Magnetofection has recently celebrated its 10th anniversary, and its progress and prospects are described in the thorough review paper [9]. Many studies regarding magnetofection have used commercially available SPIONs [8,10–18]. The majority were coated and/or functionalized with positively charged PEI due to its electrostatic interaction with negatively charged sugar phosphate backbone of nucleic acid and proton sponge effect, which enables release of SPIONs-PEI-nucleic acid complexes from endolysosomes into cytoplasm. Although PEI is a transfection agent *per se* [19], it has been shown that when coupled with SPIONs, magnetofection efficiency increased in comparison to the transfection efficacy of PEI only [11,20]. Despite of its extended usage for gene delivery, PEI compromises cell membrane integrity and induces formation of channels in the outer mitochondrial membrane [21], which could lead to cell death.

* Corresponding author.
E-mail address: gsersa@onko-i.si (G. Sersa).
[1] Authors contributed equally to this work.

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