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Penetration of PLGA Nanoparticles into the Intracranial Rat C6 Glioma: INFLUENCE OF SURFACTANT COATING

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Introduction

Our previous results have shown that PLGA nanoparticles (PLGA NPs) coated with poloxamer 188 (P188) enable the delivery of drugs across the blood–brain barrier (BBB) after intravenous injection. Doxorubicin loaded PLGA NPs (Dox-PLGA) coated with P188 produced a considerable anti-tumour effect against the intracranial glioblastoma in rats [1]. The objective of the present study was to evaluate the internalization of the P188-coated PLGA NP in the intracranial C6 glioma in rats.

Experimental Methods

For visualization using scanning laser confocal microscopy (SLCM) (Nikon A1 MP) and the intravital fluorescence imaging system Ivis®Spectrum CT (Perkin-Elmer) the NP were labeled with Dil (Dil-PLGA NP).

Preparation of drug-loaded PLGA nanoparticles.

The Dil-PLGA NP were prepared by an emulsion-solvent evaporation technique. The Dil:PLGA ratio was 1:750. The solution of PLGA and Dil in dichloromethane was added to 1% aqueous solution of PVA (9-10 kDa) and passed through a high-pressure homogenizer (Panda Plus2000) at 1000 bar. The organic solvent was evaporated under vacuum followed by addition of 2.5% mannitol and lyophilization. Free Dil was removed from the nanosuspension by gel filtration chromatography using a Sephadex G-25 column.

Nanoparticle characterization.

The average particle size and zeta-potential were measured using a Zetasizer Nano ZS (Malvern, GB) and were found to be 42.8 ± 2.2 nm and -11.4 ± 0.4 mV respectively.

Nanoparticle administration.

The freeze-dried NP were reuspended either in P188 or in water for injections, incubated for 30 min and administered i.v. into rats with intracranial C6 glioma on day 15 after tumour inoculation. The presence of mass lesion was verified by previous MRI. Two hours after administration of the NP, the rats were perfused transcardially with 4% paraformaldehyde solution, organs were recovered, and the fluorescence intensity was assessed using an Ivis® Spectrum CT system.

Histological analysis.

Brains were removed and fixed with 4% paraformol solution for at least 24h, afterwards 50 micron-thick sections were prepared using vibrotome. To assess NP localization in brain sections immunohistochemical staining with antibodies against GFAP (astroglial marker), beta-III Tubulin (neuronal marker), was performed. Goat anti-mouse Alexa Fluor 633 and Goat anti-rabbit Alexa Fluor 488 (Invitrogen) were used as the second antibodies.

Results

Brain fluorescence (Ivis® Spectrum CT) in rats with glioma C6 after transcardial perfusion. A. Dil-PLGA/P188 NP; B. Uncoated Dil-PLGA NP.

Quantitative fluorescence analysis (SLCM) on rat brain sections with C6 glioma 2 h after i.v. administration of Dil-PLGA NPs. A–B. Panoramic images – Dil-PLGA/P188 NP (A) and uncoated NP (B). Bar=1000 μm. C–D. 3-D fluorescence intensity histograms of the same sections.

Accumulation of Dil-PLGA/P188 NP in some populations of neurons of contralateral hemisphere. A. Merged image. B. Fluorescence of cell nuclei (Hoechst staining). C.Beta-III-tubulin positive neurons of the cerebral cortex. D. Dil fluorescence . Bar scale 50 μm. SLCM.

The fluorescence intensity of the hemisphere with the implanted glioma was 4-fold higher for the P188-coated NP (Dil-PLGA/P188 NP), as compared to the uncoated NP (45.1×10⁶ vs 9.5×10⁵ photons/sec/cm²), respectively according to intravital fluorescence imaging data.

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References


Conclusion

Together with the data obtained previously, the results of the present study demonstrate that coating of the PLGA NP with poloxamer 188 considerably enhances NP delivery to the brain tumor.