



Effective transvascular delivery of nanoparticles across the blood-brain tumor barrier into malignant glioma cells

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Background

Effective transvascular delivery of nanoparticle-based chemotherapeutics across the blood-brain tumor barrier of malignant gliomas remains a challenge. This is due to our limited understanding of nanoparticle properties in relation to the physiologic size of pores within the blood-brain tumor barrier. Polyamidoamine dendrimers are particularly small multigenerational nanoparticles with uniform sizes within each generation. Dendrimer sizes increase by only 1 to 2 nm with each successive generation. Using functionalized polyamidoamine dendrimer generations 1 through 8, we investigated how nanoparticle size influences particle accumulation within malignant glioma cells.

Methods

Magnetic resonance and fluorescence imaging probes were conjugated to the dendrimer terminal amines. Functionalized dendrimers were administered intravenously to rodents with orthotopically grown malignant gliomas. Transvascular transport and accumulation of the nanoparticles in brain tumor tissue was measured in vivo with dynamic contrast-enhanced magnetic resonance imaging. Localization of the nanoparticles within glioma cells was confirmed ex vivo with fluorescence imaging.

Results

We found that the intravenously administered functionalized dendrimers less than approximately 11.7 to 11.9 nm in diameter were able to traverse pores of the blood-brain tumor barrier of RG-2 malignant gliomas, while larger ones could not. Of the permeable functionalized dendrimer generations, those that possessed long blood half-lives could accumulate within glioma cells.

Conclusion

The therapeutically relevant upper limit of blood-brain tumor barrier pore size is approximately 11.7 to 11.9 nm. Therefore, effective transvascular drug delivery into malignant glioma cells can be accomplished by using nanoparticles that are smaller than 11.7 to 11.9 nm in diameter and possess long blood half-lives.

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