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Submission Category:
Radiotherapy and Radiotheragnostics

Title:

Radiolabeled Gold Nanoseeds containing Substance P Peptides: Synthesis, Characterization and Evaluation in Glioblastoma Cells

Abstract:

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Objectives

Current therapeutic strategies for glioblastoma multiforme (GBM), the most frequent brain tumor, rely on open surgery, chemotherapy and radiotherapy. Despite some progress, the overall survival of patients with GBM remains extremely poor. In this context, there is a pressing need to develop innovative therapy strategies for GBM, namely based on nanomedicine approaches. The aim of this study was to promote increased accumulation of gold nanoparticles having a small-sized gold core (ca. 4 nm) and carrying DOTA chelators (AuNP-TDOTA)[1] in human GBM cells by functionalizing AuNP-TDOTA with substance P (SP) derivatives that bind to the neurokinin-1 receptor (NKR1)

expressed on the glioma cell surface.

Methods

The new SP-containing AuNPs (**AuNP-SP** and **AuNP-SPTyr8**) were synthesized and characterized by a variety of analytical techniques, including TEM and DLS measurements. Their labeling with diagnostic and therapeutic radionuclides was efficiently done by DOTA complexation of the trivalent radiometals ^{67}Ga and ^{177}Lu or by electrophilic radioiodination with ^{125}I of the tyrosyl residue in **AuNP-SPTyr8.** The resulting radiolabeled AuNPs were biologically evaluated through cellular uptake studies in human GBM cells (U87, T98G or U373). To have a first insight on the influence of the target-specific approach in terms of therapeutic efficacy of the designed nanoseeds, the radiobiological effects induced by **^{177}Lu-AuNP-SPTyr8** and **^{177}Lu-AuNP-TDOTA** (without SP derivative) in U373 cells were compared.

Results

The AuNP-TDOTA nanoparticles were successfully used to prepare the SP-containing AuNPs and their respective radiolabeled nanoseeds with good radiochemical yields, high radiochemical purity and high stability. Cellular studies with radiolabeled AuNPs in NKR1-positive GBM cells (U87, T98G and U373) have shown that the presence of the SP peptides has a crucial and positive impact on their internalization by the tumor cells. Consistently, **^{177}Lu-AuNP-SPTyr8** showed more pronounced radiobiological effects in U373 cells when compared with the non-targeted congener **^{177}Lu-AuNP-TDOTA,** as assessed by the MTT and clonogenic assays.

Conclusions

177Lu-AuNP-SPTyr8 has emerged in this study as a very promising radiolabeled nanoseed for the treatment of localized GBM upon intratumoral administration and deserves a further preclinical evaluation, including radiotherapeutic assays in GBM xenografts.

Acknowledgments

This work was supported by Fundação para a Ciência e Tecnologia (FCT) (projects UID/Multi/04349/2019 and PTDC/MEDQUI/29649/2017) and by FCT and Agência Nacional de Inovação (ANI) (project LISBOA-01-0247-FEDER-045904).

References

[1] Silva, F. et al., *Bioconjugate Chem* **27**, 1153 (2016); Silva, F. et al., *Materials* **13**, 17 (2020).

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