Materials Proceedings

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Abstract

The Influence of Surface Protein Adsorption on Gold Nanoparticle Intratumoral Distribution and Retention †

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† Presented at the 2nd International Online-Conference on Nanomaterials, 15–30 November 2020; Available online: https://iocn2020.sciforum.net/.

Abstract: Nanomedicines' inability to penetrate throughout the entire volume of a tumor due to heterogeneous distribution within the tumor mass remains a crucial limiting factor for a vast range of theranostic applications, including image-guided radiation therapy. Despite many studies conducted on the topic having shown the efficacy and biocompatibility of colloidal gold nanoparticles (GNPs), the biological effects of GNPs in the tumor microenvironment, including the particle–protein interaction and the consequent impact on cellular pathways and contrast enhancement remain unclear. In this regard, further investigations on how GNP surface passivation affects X-ray attenuation as well as in vivo biodistribution will clarify several aspects still under discussion in the scientific community, which so far have limited the clinical translation of their cancer-related applications. We aim to evaluate the influence of protein surface adsorption on the GNP biodistribution in Lewis lung carcinoma (LLC) tumor-bearing mice using high-resolution computed tomography (CT) pre-clinical imaging. We hypothesize that, by controlling the adsorption of proteins on the GNP surface, we can influence the intratumoral distribution and retention of the particles. GNPs approximately 34 nm in diameter were synthesized with a surface plasmon peak at ~530 nm, surface passivated with bovine serum albumin (BSA) to reduce opsonization and improve colloidal stability, and characterized with standard methods. Modulation of BSA adsorption on the GNPs was observed by tuning the pH of the immobilization medium from acidic to alkaline, which we quantified using Langmuir isotherms. CT phantom imaging was used to determine X-ray attenuation as a function of GNP concentration and surface functionalization. The in vitro study for evaluating the uptake of GNPs by LLC cells highlighted a difference in the internalization depending on the surface functionalization. In both cases, macropinocytosis was the trafficking mechanism, but while endosomes with citrate-GNPs can be found in different stages of maturation, cells treated with BSA-GNPs presented larger vesicles up to 1 μm in diameter. The in vivo study was performed by injecting intratumorally, concentrating GNPs into LLC solid tumors grown on the right flank of 6-week-old female C57BL/6 mice. Ten days post-injection, follow-up assessments with CT imaging showed the distribution and retention of the particles in the tumor. CT attenuation quantification based on bioimaging analysis for each time point was conducted. In vivo results showed significant heterogeneity in the intratumoral biodistribution of GNPs dependent on surface passivation. BSA-GNPs perfused predominately along the tumor periphery with few depositions throughout the entire tumor volume. This response can be explained by the abnormal and heterogeneous vascular structure of the LLC tumor, suggesting perfusion rather than permeability as the limiting factor for tumor accumulation of the GNPs. Despite the perivascular cluster accumulation, the BSA-GNP distribution diverged from that obtained after unpassivated, citrate-GNP intratumoral injections. In conclusion, our investigations have shown that surface passivation of GNPs is able to influence the

Citation: Terracciano, R.; Butler, E.B.; Demarchi, D.; Grattoni, A.; Filgueira, C.S. The Influence of Surface Protein Adsorption on Gold Nanoparticle Intratumoral Distribution and Retention. *Mater. Proc.* **2021**, *4*, 46. https://doi.org/10.3390/IOCN2020-07965

Academic Editors: Ana María Díez-Pascual, Antonio Di Bartolomeo and Guanying Chen

Published: 12 November 2020

mechanism of cellular uptake in vitro and their in vivo intratumoral diffusion, highlighting the spatial heterogeneity of the solid tumor.

Keywords: lung cancer; gold nanoparticles; surface passivation; computed tomography

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/IOCN2020-07965/s1.