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Tridimensional cellular models of prostate cancer for the evaluation of copper-64 chloride as a theranostic agent

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Prostate cancer (PCa) is one of the most common cancer types in men, and, despite the advances that led to a decline in mortality, it is still considered incurable in advance stages. Thus, it is exceedingly important to ensure an early diagnosis and develop new approaches to overcome PCa chemoresistance. Radiopharmaceuticals emerge as possible solutions for this challenge, as they have the potential to be used in diagnosis, therapy or even simultaneously for both purposes (theranostics). In particular for PCa, it was already demonstrated by the Radiopharmaceutical Sciences group that copper-64 chloride (64CuCl2) has the potential to induce damage in monolayer cultured PCa cell lines, while bearing minimal side effects in non-tumoral cells, being a promising theranostic agent for PCa [1]. Nevertheless, the monolayer culture model has a limited predictive value, and results obtained might not be translatable in vivo. Multicellular tumor spheroids are a 3D culture model that overcome some of the limitations of the monolayer model, replicating the metabolic and proliferative gradients of in vivo solid tumors. Furthermore, unlike the monolayer model, the spheroids have an increased population of cancer stem cells (CSCs), involved in increased tumor resistance and recurrence [2]. In this work, we further assessed the theranostic potential of 64CuCl2 using PCa spheroids to better replicate the in vivo tumor environment [3]. After the initial establishment and characterization of the morphology and CSCs populations of spheroids derived from three PCa cell lines (22RV1, DU145 and LNCaP), we assessed the cellular uptake of 64CuCl2. We also evaluated changes in the growth profile and viability of the spheroids exposed to 64CuCl2, along with the clonogenic capacity of spheroid-derived cells. The results obtained revealed that 64CuCl2 is able to significantly reduce the spheroids' growth and viability, as well as their reproductive capacity. Interestingly, the spheroids with the highest initial percentage of stem-like cells, derived from the DU145 cell line, were found to be the most resistant to 64CuCl2.

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