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Metal Nanoparticle Radiosensitization for Improving Radiotherapy

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Metal nanoparticles have gained market approval for enhancing the effects of ionizing radiation in radiotherapy treatment of cancer. However the mechanism of action of metal nanoparticles exerting their effect remain controversial and poorly elucidated. We have developed a methodology inspired by Quality-by-Design principals to investigate the structure-function relationship of nanoparticle parameters with radiobiological effect. A cross-correlative methodology was developed to measure biological parameters such as the number of DNA breaks in single cells after irradiation with clinical X-ray sources coupled with quantitative analysis of the number nanoparticles in the same individual cells with XRF. A major challenge in identifying mechanisms is the massive degree of heterogeneity between cells.1
Sub-cellular populations were identified and radiobiological response was determined for individual cells as a function of the number of nanoparticles in the same cells. The data is continuing to reveal many insightful aspects of nanoparticle-cell interactions and the consequence these have on radiobiological response of cancer cells. Importantly, a number of biological mechanisms exist that not only sensitize cells but can actually de-sensitize cells. These mechanisms contravene the physical concepts of radiosensitization. Nanoparticle uptake is highly heterogeneous and the observations made in our research cannot be deduced by conventional bulk assays. Biological mechanisms, such as down regulating proteins involved in DNA damage repair, lead to preferential sensitization of the most radio-resistant S-phase cells which act as a negative prognostic factor for many indications.2 Despite metal nanoparticles entering clinical use, we highlight many questions that remain in how they exert their function. Our research is revealing these mechanisms and will enable optimization of radiosensitizer formulations.

References

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