X-ray-Activatable Photodynamic Nanoconstructs

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X-ray induced photodynamic therapy enables chemotherapy-free treatment of deep-tissue cancer with a low dose of X-ray radiation.

Photodynamic therapy (PDT) is a rapidly evolving cancer treatment modality, wherein a light-activatable molecule (photosensitizer) is used in conjunction with light to locally produce reactive oxygen species (ROS). While PDT provides high spatiotemporal precision at the location to which the ROS-induced damage is inflicted, poor light tissue penetration (<1 cm) has been a major hurdle for PDT clinical implementation in the context of deep-seated tumors. A significant amount of effort has been devoted toward the development of photosensitizing materials that would be able to overcome the challenges imposed by such limited light penetration. These include the development of chemi- and bioluminescent probes as well as multi-photon and upconverting materials. On the other hand, external ionizing radiation (such as X-rays) penetrates deep into the human body and is widely used as a neoadjuvant treatment for shrinking nonresectable tumors. In the current study reported by Deng and co-authors, combining PLGA-TPP together with subtherapeutic (4 Gy) radiation inhibited tumor growth equivalent to a therapeutic (12 Gy) radiation dose (Figure 1C). Such a reduction in dose helped alleviate radiation-associated weight loss, which makes this study one of a handful that demonstrate the therapeutic potential of X-PDT in vivo.

Biologically, PDT and X-rays can trigger separate but complementary cytotoxic pathways. In practice, however, the application of X-PDT relies on a complex set of principal components, in which the photosensitizer class, subcellular localization, as well as radiation dosimetry, can result in either synergistic, additive, or antagonizing effects. It is generally accepted that mitochondrial photosensitizer localization results in more effective cell killing than lysosomal localization. In this study, a mitochondrial-targeting moiety triphenylphosphonium (TPP) was introduced to impart mitochondrial localization resulting in additional cytotoxicity compared to its nontargeted counterpart (Figure 1A). The authors validated the targeted effects of PLGA-TPP by demonstrating a decrease in the structural integrity of the mitochondrial membrane.

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From a biocompatibility point of view, many X-PDT agents contain cytotoxic components that increase their long-term off-target toxicity and reduce their potential for clinical translation.7,8 Deng et al., on the other hand, utilized widely available and extensively characterized components, such as biodegradable polymer poly(lactic-co-glycolic acid), 2−5 nm gold nanoparticles, and a commonly used photosensitizer verteporfin (Figure 1B). All of these nanoparticle components are approved by the U.S. Food and Drug Administration, which opens the door for further clinical translation.

While the PLGA-TPP particles reported by Deng and colleagues have demonstrated promising therapeutic efficacy in the preclinical investigation, many questions regarding the mechanism of X-ray-induced photodynamic activation for these nanoconstructs remain open. For example, it is unclear why there was no correlation between the different gold and verteporfin molar ratios in relation to the X-ray-induced ROS generation, given that both gold nanoparticles and verteporfin are known radiosensitizers.9,10 Further studies are necessary to distinguish purely radiosensitizing effects from cathodoluminescence-induced verteporfin activation.

Specifically, it is essential to establish a correlation between the nanoscintillator and photosensitizer stoichiometry, X-ray exposure, and ROS generation, as well as to characterize the role of the scintillator-photosensitizer nanostructure in the context of energy transfer. Ultimately, a set of rational guidelines will aid the field in the development of the next-generation X-PDT agents.

The use of ionizing radiation as a means for photosensitizer activation holds immense clinical promise, and the current study opens multiple avenues for the subsequent mechanistic and translational pursuits. From a clinical perspective, decreasing high radiation doses required to shrink tumors prior to surgery will provide a clear benefit to patients by alleviating radiation-induced adverse effects. To accelerate clinical translation of X-PDT nanoconstructs, there is a strong rationale for further exploration of various biocompatible materials, focusing not only on maximizing X-ray-induced photodynamic capabilities, but optimizing pharmacokinetics and biodistribution profiles.

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