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Photoinduced Plasmon Electron Transfer-based Bioorthogonal Cleavage Reaction for Precision Tumor Therapy

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Photocatalytic reactions have been harnessed to develop advanced medical solutions for transformative cancer therapy. However, their limited catalytic activities within biological environments must be enhanced to maximize their potential in practical applications. Here, a spatiotemporally controllable photocatalytic cancer therapy is reported through the photoinduced plasmon electron transfer (PiPET)-based biorthogonal cleavage reaction of a pro-photosensitizer, allyl carbamate-conjugated methylene blue (MB). The electron transfer in Pd-conjugated Au nanobipyramids is examined to improve catalytic activity by simulating the energy differences between the desorbed and adsorbed states, bond distances, and charge densities with and without excess electrons. A significantly enhanced release of allyl carbamate-conjugated methylene blue is achieved by ninefold and demonstrated precise spatiotemporal control of the bioorthogonal reaction in vivo. Both in vitro and in vivo studies reveal the remarkable tumor-suppressing capability of the bioorthogonal system, which is attributed to the photothermal and PiPET effects, coupled with the prevention of leuko-MB formation. The PiPET-based bioorthogonal cleavage reaction can offer an innovative solution for precise tumor therapy using spatiotemporal phototherapeutic strategies.

1. Introduction

Leveraging the endogenous properties of cells facilitates the localization of drugs to targeted areas, potentially reducing the required dosage and mitigating the adverse effects on healthy tissues due to non-specific drug interactions.[1–3] Nevertheless, the practical application of this strategy has been constrained due to the unpredictable heterogeneity within the tumor microenvironment and the dependency on intrinsic cellular substrates.[4–6] Recently, encapsulating anticancer drugs with appropriate functional groups has offered the potential to deactivate these drugs temporarily, restoring their activity upon selective removal of the caging groups at the desired location and time.[7–9] Bioorthogonal uncaging reactions are crucial for activating drugs within a living organism, as they enable chemical transformations beyond the capabilities of natural biological processes, apart from

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