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Intelligent nanoparticles for combination photoimmunotherapy of cancer

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Photoimmunotherapy (PIT) has emerged as a promising clinical modality for cancer therapy due to its ability to initiate an antitumor immune response. However, PIT is severely impaired by tumor cell immunosuppression of host T-cell antitumor activity through the programmed cell death 1 ligand (PD-L1) and programmed cell death receptor 1 (PD-1) (PD-L1/PD-1) immune checkpoint pathway. In this study, we demonstrate that PIT can be augmented by PD-L1 knockdown (KD) in tumor cells. We rationally designed a versatile micelleplex by integrating an acid-activatable cationic micelle, photosensitizer (PS), and small interfering RNA (siRNA). The micelleplex was inert at physiological pH conditions and activated only upon internalization in the acidic endocytic vesicles of tumor cells for fluorescence imaging and PIT. The combination of PIT and PD-L1 KD showed significantly enhanced efficacy to inhibit tumor growth and distant metastasis in a B16-F10 melanoma xenograft tumor model. These results suggest that acid-activatable micelleplexes utilizing PDT-induced cancer immunotherapy are more effective when combined with siRNA-mediated PD-L1 blockade.

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