

Immunogenic and systemic antitumor responses induced by photodynamic therapy: a systematic review of the abscopal effect

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Abstract

Photodynamic therapy (PDT) is a light-activated treatment that induces tumor cell death through the production of reactive oxygen species (ROS). There is emerging evidence that PDT can also elicit systemic antitumor immunity (abscopal effect) through the mechanisms of immunogenic cell death and immune reprogramming. The aim of this review was to systematically evaluate preclinical evidence of the abscopal and systemic immune responses induced by PDT. Following preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guidelines, PubMed, Scopus, Web of Science, and Embase were searched up to September 2025. Eligible studies included animal models assessing distant tumor regression or systemic immune activation following PDT, with or without combination therapies. Twenty-four preclinical studies met the inclusion criteria. PDT consistently induced local tumor regression and immune activation, evidenced by damage-associated molecular pattern release, calreticulin exposure, and cytotoxic CD8-positive T lymphocyte infiltration. Several studies demonstrated clear abscopal effects, particularly when PDT was combined with programmed cell death protein-1/programmed death ligand 1 blockade or adjuvants. Reported cytokine upregulation, including interleukin-6, interferon-gamma, and tumor necrosis factor-alpha, confirmed robust systemic immune activation. Preclinical and early clinical studies suggested that PDT could be used to induce systemic, immune-mediated tumor control, similar to the abscopal effect. Optimizing treatment parameters and combination with immunotherapies may allow PDT to develop from a local, cytotoxic treatment to a systemic cancer immunotherapy.

Keywords Metastatic cancer · Phototherapy · Immunogenic cell death · Tumor microenvironment · Immune checkpoint blockade

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and blocks the creation of lasting responses [52]. The effectiveness of treatment strategies that combine PDT with immunomodulatory therapies like checkpoint inhibitors and TLR agonists shows the need for optimized protocols to boost DCs activation and T-cell priming. Additionally, the total prevalence of the abscopal effect as reported in this review can be biased by publication bias since articles reporting negative or null results are less likely to be published. Thus, the actual rate of PDT-induced abscopal effect in preclinical models might be less than the positive reports published so far. Future research should establish standardized preclinical models and immune readouts while applying real-time imaging and dosimetry for treatment guidance and initiating early-phase clinical trials to endorse these preclinical results. To fully harness the potential of PDT as a systemic immunotherapeutic modality, essential research on the interactions between PDT parameters, immune responses, and the TME should be conducted.

Conclusion

This systematic review has compiled strong evidence from experimental models and preclinical studies, demonstrating that PDT under appropriate experimental conditions can induce a systemic antitumor immune response and abscopal effects. The abscopal effect has been reported in 24 preclinical studies. PDT was found to induce ICD and trigger the release of DAMPs, including CRT and HMGB1. The activation of cytotoxic T lymphocytes was shown to lead to the regression of distant tumors. Combination with immune checkpoint blockade or immunoadjuvants has emerged as a robust approach to consistently achieve a stronger and more reproducible abscopal response in both murine and human systems. Mechanistic studies align with the hypothesis that PDT can serve as an in situ tumor vaccination strategy. Future directions in this field should include a more detailed mechanistic understanding, further optimization of PDT parameters, and clinical translation through well-designed combination studies.

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Data availability All data used in this study are derived from previously published studies and publicly available sources.

Declarations

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