EBioMedicine 67 (2021) 103351

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Reducing the immunosuppressive tumor microenvironment enhances photoimmunotherapy efficacy

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ARTICLE INFO

Article History:
Received 7 April 2021
Accepted 7 April 2021

Photodynamic therapy (PDT) is a treatment that utilizes photosensitizers and light of a specific wavelength to kill cancer cells [1]. Additionally, the therapy may offer long term protection through activation of antitumor immune responses. Although PDT is an attractive therapeutic option for several types of cancer, there are several limitations that prevent its implementation as a universal cancer treatment. First, most of the currently used photosensitizers do not target tumors efficiently or avoid normal cells. Second, typical photosensitizers are most effectively excited by light with an approximate wavelength of 400 nm and less efficiently by light in the 600 to 800 nm range, limiting the treatment of deep tumors. Third, the generated immune responses are not robust enough to eliminate tumors due to the immunosuppressive tumor microenvironment [2]. Hence, the development of active compounds and/or therapeutic strategies that can overcome these shortcomings are of utmost importance for cancer treatment.

Kobayashi's group has described a target-selected PDT strategy, named photoimmunotherapy (PIT) that uses antibodies conjugated to the photosensitizer IR700 [3]. Unlike conventional photosensitizers, the new highly hydrophilic IR700 induces cell death only when bound to the target cells and presents no cytotoxicity in the absence of light exposure. Moreover, its absorption peak in the near-infrared (NIR) spectrum constitutes a significant advantage of this agent as it permits increased light penetration across tissues. IR700 is versatile enough to be conjugated to any targeting moieties (e.g. antibodies, peptides, small molecules). A clinical trial using cetuximab-targeted IR700 is being conducted in patients with recurrent or metastatic head and neck cancer (NCT03769506). Cetuximab targets the epidermal growth factor receptor (EGFR), which is overexpressed in multiple tumor types [4].

In spite of these technical advances, there remains a need for improving patient outcomes after NIR-PIT. Bas Based on several studies, the tumor microenvironment becomes so immunosuppressive that PIT-targeting only tumor cells may not be enough to prevent tumor growth [5,6]. While the cause of this immune suppression is clearly multifactorial, regulatory T cells (Tregs) are perhaps most frequently implicated in this process and are present at increased numbers in both the tumors and peripheral blood of cancer patients [2]. In this issue of the journal, Okada et al. took the NIR-PIT technology a step further by targeting EGFR along with the CD25 receptor expressed by Tregs, which would allow for more effective killing of cancer cells. The authors showed that the combined NIR-PIT approach (Panitumumab-IR700 + anti-CD25-IR700) is more effective than individual therapy in an immune-competent, syngeneic murine model [7]. The observed synergistic effect of the combined treatment was due to the enhanced induction of anti-tumor CD8+ T cells as CD8-depleting antibodies resulted in complete abrogation of the survival benefit. Interestingly, PIT-treatment neither affected the frequency of circulating splenic Tregs nor affected the level of effector T cells. Therefore, there was no collateral depletion of CD25+ T cells as seen with other approaches aiming to deplete Tregs. Importantly, the strategy induced memory T cells that fully protected treated mice from tumor cell rechallenge. Collectively, the data provide strong preclinical evidence that combinatory targeting of Tregs and tumor cells is a strategy that has high potential value for future clinical trials in patients with cancer. However, whether this NIR-PIT combination will be equally effective in humans has yet to be explored as it is difficult to model experimentally human tumor microenvironment using murine models. Also, the outcome of the treatment will depend on the immunogenicity of tumor cells that was not addressed by the present study.

For NIR-PIT to be effective against human tumors, the photosensitizers must be taken up by all malignant cells. This is unlikely to happen, in part, due to the limited penetration potential of monoclonal antibodies into solid tumors. The proportion of unaffected tumor cells is expected to increase with tumor sizes. An approach that locally eradicates most tumor cells and induces a robust anti-CD8+ T cells to kill those cells that escaped the treatment including distant tumors that cannot be reached by light, will definitely benefit patients with cancer. Notably, distant/occult metastases are responsible for most cancer-related deaths. When it comes to enhancing antitumor immunity, immune checkpoint blockade using anti-CTLA-4 and anti-PD-1 antibodies enable immune responses to tumor cells [8]. Antibody

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.103345.
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https://doi.org/10.1016/j.ebiom.2021.103351

blockade of CTLA-4 or PD-1 signaling on Tregs can also synergize with NIR-PIT [9,10]. Furthermore, a global clinical trial using cetuximab-IR700 conjugate combined with the anti-PD1 antibody pembrolizumab is now underway (NCT04305795). Hence, it will be interesting to benchmark the strategy described by Okada et al. [7] against other agents targeting Tregs in order to allow clinicians to choose the best combination therapy for their patients.

Because treatment options for certain cancers are mainly limited to surgery and chemotherapy, utilization of NIR-PIT to revert the suppressive microenvironment into a milieu that facilitates the generation of cytotoxic CD8+ T cells, as demonstrated by the authors, is of particular interest and should motivate basic and translational research.

Contributors

The author did the literature search and wrote the commentary.

Declaration of Competing Interests

The author declares no conflict of interest.

Acknowledgements

This work was supported by a research grant from the Norwegian Cancer Society (182593), the Regional Health Authority (2020030) and the RadForsk Research Foundation (35423).

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