

Commentary on “A Vaccine for Photodynamic Immunogenic Cell Death: Tumor Cell Caged by Cellular Disulfide–Thiol Exchange for Immunotherapy”

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Commentary

Tumor immunotherapy, including monoclonal antibody of immune checkpoint blockade, therapeutic antibody, cancer vaccine and cell therapy, etc., is to restart and maintain the tumor immune cycle, restore the normal anti-tumor immune response of the body, so as to control and eliminate the tumor [1,2]. Among them, tumor vaccine, which can elicit robust immune response and produce sustained immune memory effect, is particularly favored in the treatment and prevention of tumor recurrence [3,4]. Notably, compared with specific antigen vaccine, whole cell vaccine does not need complex antigen screening and purification process, and can provide all antigens of specific tumor, so it has great prospects [5,6]. Nevertheless, the immune effect of whole cell vaccine is not satisfactory because of its low immunogenicity and limitation efficiency of antigen presentation [7,8].

To solve above issues, Li et al. developed a strategy of caged live cell vaccine (CLCV) based on disulfide-mediated assembly onto the tumor cell surface for photodynamic immunogenic cell death [9], which not only could convert “cold” tumor cells into a versatile “hot” cell vaccine, but could also exert durable antigen exposure and multi-durable immunostimulatory properties. To construct such CLCV system, the authors used thiol-activated bovine serum albumin (BSA) nanoparticles, anchored onto B16F10 tumor cells surface through fast disulfide thiol exchange with thiol groups on the cell surface, as the cage material. Then, Chlorin e6 (Ce6) was chose as an immunogenic cell death (ICD) inducer to integrate with the exposed protein of the cage through hydrophobic

interaction, and CpG oligonucleotide was employed as an adjuvant, a TLR9 agonist, to attach on the caged cells surface *via* electrostatic interactions with cationic BSA (ethylenediamine-modified BSA). Confocal laser scanning microscope images and transmission electron microscopy images directly verified the formation of cage on the cell surface. The authors then examined the necessity of the cell cage *in vitro* and *in vivo*. Interestingly, the cell cage at high concentration could completely restrict the division and proliferation of B16F10 and still maintain metabolic activity compared with native B16F10. Similarly, the authors also confirmed that caged cells at therapeutic doses could not form tumor by subcutaneous inoculation, indicating the biosafety of caged cells.

Then, the caged cells integrated Ce6 and CpG to form CLCV. At the cellular level, the authors screened that when the concentration of Ce6 was $1.0 \mu\text{g}\cdot\text{mL}^{-1}$ and the laser power was $7.85 \text{ mW}\cdot(\text{cm}^2)^{-1}$ at 650 nm for 3 min, CLCV showed the same slow apoptosis characteristics as naked B16F10 cells, and it was accompanied by increased expression of HSP70 on the cells surface, compared with native cells. The author confirmed that the formation of cell cages greatly improved the phagocytosis of BMDC to live cells vaccines through flow analysis. Besides, under the combined action of CpG in the cage and photodynamics, CLCV significantly induced the maturation of bone marrow-derived dendritic cells (BMDC) with the expression of co-stimulatory signals (such as CD40 CD80 CD86 and MHC-II) and the secretion of inflammatory cytokines (TNF- α and IL-12). Notably, photoactivated CLCV could sustain exposure of immunogenic tumor antigens and promote migration to lymph nodes, thereby enhancing the mutation of DC and

stimulating T cell responses *in vivo*. Most strikingly, this CLCV plus laser irradiation protected 75% of the mice against tumor initiation and significantly increased the population of CD3⁺CD8⁺ T cell in tumor. Together, all evidence highlights the promising of the strategy of CLCV in developing novel vaccine platform.

It has been reported that ICD is a distinctive form of cell death, which could release tumor-associated antigens (TAAs) and danger-associated molecular patterns (DAMPs) *in situ*, thereby converting dying cancer cells into regional vaccines to evoke systemic anti-tumor immunity [10,11]. However, *in situ* regional vaccines are often affected by the tumor-suppressive microenvironment, which prevents the effective presentation of antigens to immune cells. Li et al. proposed novelty strategy of *in vitro* cage tumor cell framework with ICD-inducing modality that does not rely on *in situ* tumor cells and can effectively avoid the negative influence of tumor-suppressive microenvironment to vaccine. Compared with hydrogels [12,13] and microneedle patch [14,15] that have been used to co-deliver whole tumor cells or lysates with other adjuvants, tumor cell caged strategy is a novel concept in vaccine construction. It would be interesting to see whether this strategy has a broad effect to evoke effective T effector response in preventive and established various tumor models.

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