AUTHOR'S VIEW

Spotlight—author's view for "Metabolic glycan labeling immobilizes dendritic cell membrane and enhances antitumorefficacy of dendritic cell vaccine"

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HIGH DEMAND ON EFFECTIVE THERAPEUTIC CANCER VACCINE

Dendritic cell (DC), as the prominent type of antigen presenting cells in the body, has been the main target of intervention for developing therapeutic cancer vaccines. Indeed, Sipuleucel-T, a type of DC vaccine, was among the first FDA-approved cancer immunotherapy (approved for prostate cancer treatment in 2010) [1]. However, the therapeutic benefit of Sipuleucel-T is modest, with a 4.1-month improvement in median survival. The past decade has witnessed extensive attempts to improve the therapeutic efficacy of DC vaccines while maintaining the favorable safety profile. Various other types of therapeutic vaccines, including nanovaccines, tumor exosome vaccine, mRNA vaccines, DNA vaccines, and biomaterial scaffold vaccines have also been developed [2, 3]. However, despite the significant progress in preclinical settings, Sipuleucel-T remains the only FDA-approved therapeutic cancer vaccine to date.

A FACILE APPROACH TO IMPROVING DENDRITIC CELL VACCINE

DC vaccine functions by isolating monocytes from the blood of patients, differentiating them into DCs with exogenous cytokines such as granulocyte macrophage colony-stimulating factor (GM-CSF), loading the DCs with tumor antigens, and infusing the engineered DCs back to the patient [4]. To improve the potency of DC vaccines, extensive efforts have been made to optimize the source, differentiation process, and the activation and antigen presentation processes of DCs, and decipher the correlation of each subset of DCs to the overall therapeutic efficacy. However, strategies to modulate the adoptively transferred DCs in vivo are lacking. Recently, Han et al. reported a metabolic glycan labeling approach to tagging DCs with unique chemical tags (e.g., azido groups) during the ex vivo DC manufacturing step (Fig. 1) [5]. This can be achieved by simply adding a type of azido-sugar, tetraacetyl-*N*-azidoacetylmannosamine (Ac_4ManNAz), into the culture medium of DCs. Upon cellular internalization, Ac_4ManNAz can undergo the metabolic glycoengineering process and eventually become expressed on the DC membrane in the form of glycoproteins and glycolipids. The cell-surface azido groups then enable targeted conjugation of dibenzocyclooctyne (DBCO)-bearing immunomodulatory agents via efficient and biooorthogonal click chemistry.

Surprisingly, the authors found that metabolic glycan labeling itself is able to activate DCs, as evidenced by the upregulated expression of surface activation markers including CD86, MHCII, CD40, and CCR7 [5]. The gene expression profile and cytokine secretion profile of Ac_4ManNAz-treated DCs also exhibit radical changes in comparison with untreated DCs. One plausible mechanism the authors suggested is the alteration of membrane physics caused by the installation of unnatural sugars on the cell membrane. By transfecting DCs with two types of fluorescently tagged membrane proteins, ICAM1-GFP and YFP-Mem, and performing the fluorescence recovery after photobleaching (FRAP) assay, it was shown that Ac_4ManNAz-treated DCs exhibited a reduced membrane mobility than untreated DCs. The reduced membrane mobility could lead to changes in receptor clustering and downstream activation pathways, as a potential mechanism underlying the activation of DCs. Following tumor studies demonstrated the enhanced $CD8^+$ T cell response and therapeutic efficacy of azido-labeled DC vaccines.

In addition to the direct activation effect on DCs, the azido tags installed on the membrane of DCs enable targeted modulation of adoptively transferred DCs via click chemistry. For example, at hours or days after the adoptive transfer of antigen presenting DCs, DBCO-functionalized IL-15, one representative proinflammatory cytokine, can find and conjugate to the azido-labeled DCs. This was shown to improve subsequent T cell priming and further enhance the tumor-specific $CD8^+$ T cell response and therapeutic efficacy [5].

Overall, the metabolic glycan labeling provides a facile and universal approach to improving the $CD8^+$ T cell response and therapeutic efficacy of DC vaccines, and also provides a platform to manipulate the interactions between DCs and T cells. This

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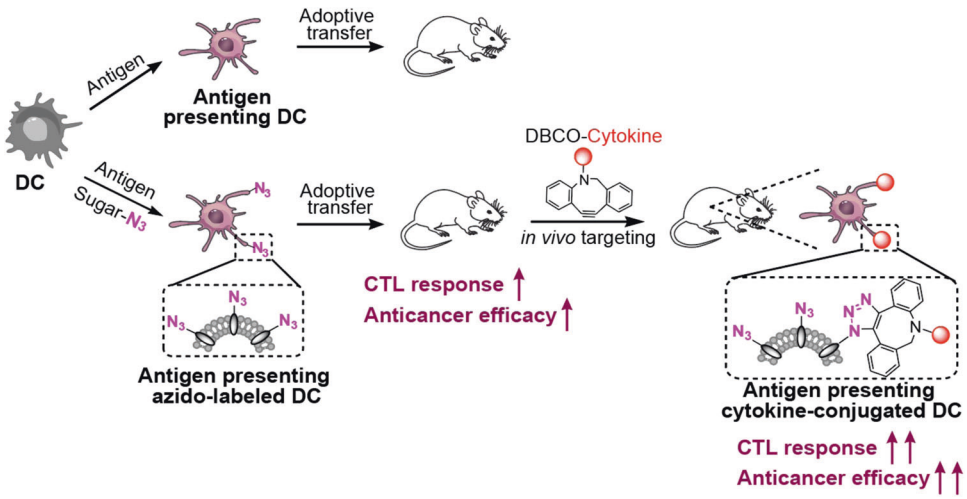

Fig. 1 Azido-sugars can be metabolized by DCs and become expressed on the cell membrane in the form of glycoproteins and glycolipids, which itself improves the activation status and antigen presentation ability of DCs. The azido-labeled DCs also enable conjugation of DBCO-cytokines (e.g., IL-15) post adoptive transfer, for further improved CTL response and antitumor efficacy [5].

approach can be executed by simply adding a sugar compound to the culture medium of DCs and does not interfere with the clinical manufacturing process of DC vaccines, conferring high translation potential.

FUTURE OF DC VACCINES

Looking forward, there is still significant room for improving the potency of DC vaccines. Existing research efforts that optimize the ex vivo manufacturing processes of DC vaccines are undoubtedly critical and have laid the foundation for the clinical translation of DC vaccines, but strategies to monitor the behaviors and functions of those engineered DCs after adoptive transfer are also important, in order to better understand the hurdles barring from achieving satisfactory therapeutic benefits. Further, strategies to modulate the function of adoptively transferred DCs in vivo are needed, considering that DCs may lose function rapidly after injection and the fraction of DCs that eventually encounter T cells in lymphatic tissues is minimal. Metabolic glycan labeling provides one viable approach to tracking and targeting DCs in vivo, but the long-term targeted modulation of DCs remains a challenge. In the years to come, we expect to see the development of new exciting technologies enabling long-term tracking and targeted modulation of DCs in vivo. After all, the DC vaccine is still one of the most promising types of therapeutic cancer vaccines with well-documented safety profiles, and facile and effective strategies to improve the potency of existing cancer vaccines could have a clear path to clinical translation.

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JZ wrote the initial draft of the manuscript. HW revised the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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