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FIRST REACTIONS

A Magnetic Nanovaccine Enhances Cancer Immunotherapy

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Magnetic nanoparticles retain cancer vaccine in the lymph node for a much longer time and enhance the vaccination performance against cancer.

Since the first attempt to treat cancer using bacteria by William B. Coley, later known as the Coley's Toxins, cancer vaccines have been pursued for immunotherapies for more than 100 years. However, the clinical efficacy remains modest to date for therapeutic cancer vaccines. Major challenges faced in the development of an effective and safe cancer vaccine include the lack of specific and immunogenic tumor antigens, inefficient delivery and retention in lymph nodes or other lymphoid organs, uncontrolled antigen presentation pathways, and so on. Among those challenges, enhancing the retention of tumor antigens in tandem with adjuvants in secondary lymphoid organs has been rarely addressed. In this issue of *ACS Central Science*, Hai-Yan Xie, Wei Wei, and colleagues report a magnetic cancer nanovaccine showing drastically improved lymph node retention under the control of a magnetic field and, therefore, enhanced vaccination performance against cancer.[1]

Xie's team previously synthesized the Fe_3O_4 magnetic nanocluster imparted with both superior magnetization and superparamagnetism (a desired property for magnetic resonance imaging) concurrently in one particle and applied this novel nanoparticle for the construction of artificial antigen-presenting cells to expand cytotoxic T cells ex vivo and control their trafficking in vivo, with the guidance of a magnetic field.[2] In the current study, Li et al. extended this approach to magnetically controlling the homing and retention of cancer vaccines in lymph nodes (Figure 1). They fabricated a "magnetosome" with the Fe_3O_4 nanocluster as the magnetic core, which was further coated via electrostatic interactions with CpG oligodeoxynucleotide, a Toll-like receptor 9 agonist, and cancer cell membrane as a tumor antigen reservoir. CpG as a vaccine adjuvant was used to promote dendritic cell (DC) maturation. As a natural pool of tumor antigens, the whole tumor cell lysate has been often used in cancer vaccines. Recently, it has been reported that tumor cell membranes exhibit an antigenic profile closely resembling that of the source cancer cells.[3] Thus, it is reasonable to use cell membranes with associated surface antigens as an alternative to the tumor cell lysate.

Nanosized carrier (~5−100 nm) has been widely used to enhance the lymph node targeting of soluble antigens and adjuvants.[4] Consistent with previous observations, the magnetosome vaccine alone showed much increased lymph node targeting efficiency as compared to soluble cancer cell membrane fragments. However, the signal from the labeled magnetosome in the lymph node quickly attenuated and eventually disappeared on day 9, likely due to the efferent lymphatic vessels. In contrast, upon continuous application of a magnetic field (by fixing a magnet close to the draining lymph node of the immunized mouse), not only did the amount of antigens accumulated in the lymph node substantially increase but also the retention time of the membrane-associated antigens was extended remarkably to more than 21 days. Interestingly, less success has been reported in magnetic field navigated drug delivery upon intravenous administration. It may indicate that magnetic navigation may be far more feasible to control the distribution of subcutaneously injected nanoparticles. As magnetic fields are a commonly used noninvasive tool in the clinic, such magnetic-field-guided vaccinations have a high potential for future clinical applications.

Eliciting potent cytotoxic $CD8^+$ T cell responses is the key to an effective therapeutic cancer vaccine. Soluble subunit antigens acquired by antigen-presenting cells are typically loaded onto major histocompatibility complex (MHC) class II molecules for presentation to $CD4^+$ helper T cells. Promoting the presentation of antigens by MHC class I molecules to $CD8^+$ killer T cells, a process termed cross-presentation, is thus critical for enhanced immunity against cancer. Li et al. modified the surface of the magnetosome

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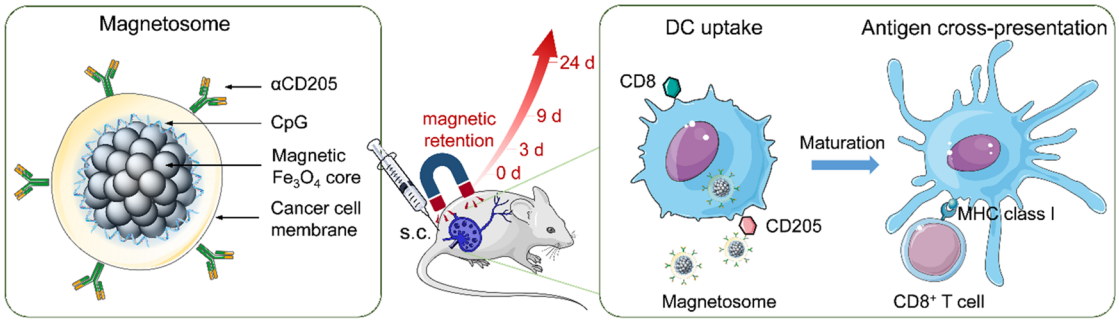

Figure 1. Schematic illustration of the magnetosome cancer vaccine for enhanced lymph node retention and antigen cross-presentation. (Left) Schematic composition and structure of magnetosome. (Middle) Increased retention of magnetosome vaccine in lymph nodes upon subcutaneous (s.c.) injection under the control of a magnetic field. (Right) targeted delivery of magnetosomes modified with anti-CD205 antibody (αCD205) toward $CD8^+$ dendritic cells (DCs) for enhanced antigen cross-presentation.

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with anti-CD205 antibody through click chemistry enabled bioconjugation to target the magnetosome to the $CD8^+$ DCs, a subset of DCs with superior capability for cross-presentation of acquired antigens. Upon the application of a magnetic field, internalization of anti-CD205-decorated magnetosomes by $CD8^+$ DCs in lymph nodes was markedly increased. Accordingly, significantly enhanced $CD8^+$ T cell proliferation, activation, and the increased clonal diversity were, therefore, achieved in the lymph nodes of the vaccinated mice.

With the robust immune response elicited by the magnetosome vaccine in mice, Li et al. next assessed its anticancer efficacy against a primary tumor, metastases, as well as post-operative recurrence using 4T1 murine breast cancer model. This model is a triple negative breast cancer, which has been reported to be difficult to treat with immunotherapies.[5] Impressively, two doses of magnetosome vaccinations in combination with PD-1 blockade significantly inhibited the growth of the primary tumor inoculated orthotopically as well as the metastases and protected the mice with 100% survival up to 80 days. In other models, mice with primary tumors resected were rechallenged with 4T1 tumor cells; the same combination therapy completely rejected the tumor cells and protected all the mice from tumor recurrence suggesting possible long-term immune memory effects. In addition, in all the mouse studies, the magnetosome vaccine showed good safety profile without any overt toxicities.

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Personalized cancer vaccines with the possibility to target antigens derived from random somatic mutations found only in tumor cells, termed neoantigens, have recently shown great promise in the treatment of various malignancies, including late-stage melanoma. Compared to self-antigens, neoantigens could be recognized as nonself by the host immune system and are thus attractive targets for immunotherapies with potentially increased specificity, efficacy, and safety.[6] Vaccine derived from the patient's own cancer cell membrane is intrinsically a personalized vaccine for which the magnetosome described in this paper could serve as an excellent delivery platform. However, future work is necessary to well define certain key antigens responsible for the enhanced anticancer immunity from the entire reservoir of cell membrane associated antigens. Enriching neoantigens from the rest is also an attractive strategy to further enhance the efficacy and safety as well as limit the possible tolerogenic effect of self-antigens. In addition, the $CD4^+$ T cell responses elicited by the magnetosomes must be better characterized to understand the possible synergistic effect together with $CD8^+$ T cell, which is known to be crucial for eradicating tumors.

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Moving forward, the dose and retention time of the magnetosome nanovaccines in lymph nodes may also need to be optimized to avoid any possible negative effects, such as activation-induced cell death of DCs upon long-term stimulation, sequestration and deletion of T cells at vaccination sites, or even tolerance upon continuous antigen exposure.[7]

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Notes

The authors declare no competing financial interest.

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