Resident Memory T Cells as Surrogate Markers of the Efficacy of Cancer Vaccines

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Cancer vaccine boost via the cervicovaginal rather than the intramuscular route of immunization appears to be crucial to induce genital CD8+ T cells and tumor regression. This clinical activity is correlated with the ability of the mucosal boost to elicit resident memory T cells in the genital tract.

In this issue of Clinical Cancer Research, Sun and colleagues provide various clues to improve cancer vaccine (1). Possible control of tumor growth by the immune system is now widely accepted with the clinical breakthrough provided by the blockade of inhibitory pathways (i.e., PD-L1/PD-1, CTLA-4-CD80/CD86). Although cancer vaccines have been tested for more than 20 years, clinical success rates remain modest. Provenge was the only cancer vaccine approved on the basis of its ability to prolong survival of hormone-refractory prostate cancer patients by an average of 4 months (2). Various recent phase III therapeutic cancer vaccine trials (Magrit, telomerase vaccine GV1001, Stimuvax, Immatics, etc.) failed to achieve their primary objectives (3, 4). Improvement of cancer vaccine design is therefore mandatory for their clinical implementation. Sun and colleagues demonstrate that heterologous prime-boost vaccination elicited stronger specific CD8+ T-cell response than homologous prime-boost immunization using DNA vaccine or recombinant vaccinia-based boost (TA-HPV) encoding HPV16 E6 and E7 proteins (1). Although the mechanisms explaining the efficacy of this heterologous prime-boost regimen have not been fully elucidated, heterologous prime-boost is known to recruit various arms of the immune response and focus the response on the antigens shared by Sun and colleagues is in line with various infection models, in which mucosal vaccines induce a better local immune response to pathogens than the systemic route of administration. This better local immune response results in better control of the mucosal pathogens (7). Recently, our group also reported, in an orthotopic head and neck cancer model, a greater infiltration of antitumor CD8+ T cells after tumor graft in mice that had been previously intranasally immunized with a cancer vaccine than in mice vaccinated via the intramuscular route with the same vaccine (8). Interestingly, in the study by Sun and colleagues, cervicovaginal vaccine-induced specific CD8+ T cells expressed the CD103 integrin, which qualified them as memory resident T cells (TRM; ref. 1). These cells have been shown to stably reside in peripheral tissues and do not enter the circulation for prolonged periods of time. TRM rapidly acquire effector functions following secondary antigenic stimulation and are highly protective against subsequent local infections (9). Intravaginal immunization with human papillomavirus vectors (HPV pseudoviruses) that transiently expressed a model antigen in cervicovaginal keratinocytes also induced a greater number of tissue resident CD8+ T-cell responses than the intramuscular route of immunization (10). In human cancer, various recent studies have shown that infiltration of tumors by CD103+CD8+ T cells was correlated with better clinical outcome in patients with lung cancer, ovarian cancer, and bladder cancer (11).
CD8+ T-cell responses (TRM) may therefore be the key to the development of cancer vaccines. Various approaches have been successfully developed to harness this local tumor immunity and the generation of TRM. We and other authors have shown that the mucosal route of immunization imprints T cells with a mucosal homing program defined by a profile of integrin and chemokine receptors promoting their homing to the site of initial activation. Tumors located at mucosal sites (lung, colorectal, genital, head and neck) are exposed to mucosal immunity, organized within a connecting network called MALT (mucosal-associated lymphoid tissues), which may explain why the intranasal route of immunization may induce a genital immune response via the recirculation of mucosal dendritic cells (12).

In the study by Sun and colleagues, α4β7 and CCR9 induced on T cells are necessary for the homing of antitumor-specific T cells to the cervicovaginal tract (1). The same set of molecules are also required for the homing to the digestive tract, whereas expression of CCR10 and P- and E-selectin ligands on T cells direct the homing of T cells to the skin (7). Sun and colleagues showed that the ability of dendritic cells in the cervicovaginal tract to produce retinoic acid may explain in part the specific integrin program induced after cervicovaginal immunization (1). It extends previous results about the key role of local dendritic cells to imprint a specific program on T cells to favour their homing to the site of their initial activation (8, 13).

After systemic vaccination, a combined mucosal signal delivered via the local administration of TLR ligands or chemokines was also efficient to promote migration of T cells to the mucosal site, resulting in clearance of pathogens or tumor regression (14).

However, other studies have claimed that systemic immunization without mucosal signal delivery can overcome immune compartmentalization. A DNA vaccine targeting HPV proteins...
administered via the intramuscular route induced regression of cervical intraepithelial neoplasia by two third in 48.2% of cases compared with a spontaneous regression rate of 30% in the placebo group. This 18.2% difference between the two groups is the first demonstration of the efficacy of a vaccine directed against mucosal tumors (15). However, in this case and in other cases, the respective efficiency of mucosal and systemic immunization regimen has never been compared and the mucosal route of immunization could enhance the modest efficacy already observed.

Overall, two important translational clinical considerations can be drawn from Wu and colleagues’ study: (i) monitoring of cancer vaccines in clinical practice is based on analysis of the immune response in the blood, which does not always reflect the intensity of intratumor immune response (1, 8). This point may explain some of the controversies concerning the clinical value of vaccine-induced immune response to predict cancer vaccine efficacy; (ii) induction of local antitumor immunity and especially resident memory T cells should constitute a new criterion for the successful clinical development of therapeutic cancer vaccines.

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No potential conflicts of interest were disclosed.

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