Chemokine-enhanced DNA vaccination in cancer immunotherapy.

Olga Igoucheva
Thomas Jefferson University

Rebecca Jonas
Thomas Jefferson University

Vitali Alexeev
Thomas Jefferson University

Follow this and additional works at: https://jdc.jefferson.edu/dcbfp

Part of the Medicine and Health Sciences Commons

Let us know how access to this document benefits you

Recommended Citation
Igoucheva, Olga; Jonas, Rebecca; and Alexeev, Vitali, "Chemokine-enhanced DNA vaccination in cancer immunotherapy." (2013). Department of Dermatology and Cutaneous Biology Faculty Papers. Paper 32.
https://jdc.jefferson.edu/dcbfp/32

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's Center for Teaching and Learning (CTL). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Dermatology and Cutaneous Biology Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.
Chemokine-enhanced DNA vaccination in cancer immunotherapy

Olga Igoucheva, Rebecca Jonas, and Vitali Alexeev*

Department of Dermatology and Cutaneous Biology; Jefferson Medical College; Thomas Jefferson University; Philadelphia, PA USA

Keywords: chemokines, intratumoral vaccination, DNA vaccine, intradermal vaccination, leukocyte recruitment, therapeutic vaccine

During the past decade, immunotherapy has emerged as a powerful modality to treat aggressive neoplasms for which a few (if any) curative treatment modalities are currently available. Cell-based immunotherapies, including the adoptive transfer of tumor-infiltrating lymphocytes, dendritic cell (DC)-based vaccines and T cells expressing recombinant tumor-specific T-cell receptors (TCRs) or chimeric antigen receptors (CARs), showed promising results in both pre-clinical and clinical settings. Nevertheless, the widespread application of these strategies to treat cancer is hindered by several factors. Along similar lines, the administration of cytotoxic T lymphocyte-associated protein 4 (CTLA4)-targeting antibodies (such as Ipilimumab) to patients with advanced melanoma appears to be particularly effective in the elicitation of tumor-specific immune responses. However, severe adverse events related to the unspecific activation of T cells at the systemic level (and hence to the elicitation of autoimmune reactions) remain a barrier to the widespread application of this immunotherapeutic regimen. Active vaccination protocols based on tumor-associated antigens, including peptide- and DNA-based vaccines, have been also tested in different pre-clinical and clinical settings. Although these approaches offer multiple advantages and have been associated with antineoplastic activity in pre-clinical settings, the lack of efficacy in clinical scenarios offsets the advantages of peptide- and DNA-based anticancer vaccines. Hence, there is an unmet need to improve these approaches to achieve adequate activation of tumor-specific immunity and clinically significant outcomes.

Multiple studies demonstrated that recruitment of different subsets of leukocytes to neoplastic lesions facilitates recognition and elimination of malignant lesions. As we had previously observed that elevated intratumoral levels of a secondary lymphoid chemokine, CCL21, effectively recruit T cells to the deep recesses of melanoma mass, hence boosting tumor elimination, we hypothesized that altering chemotactic gradients within established tumors would improve the therapeutic efficacy of anticancer vaccines. Consistently, we recently reported a significantly greater tumor growth inhibition in CCL21-primed tumors following DNA vaccination (Fig. 1A). This vaccination protocol resulted in the regression of the pre-established melanomas associated with generation and expansion of the intratumoral antigen (Ag)-specific cytotoxic T cells (CTL) (Fig. 1A).

Two distinct components of this immunotherapeutic regimen favorably influenced its outcome: the composition of the DNA-based vaccine and the priming of neoplastic lesions with chemokines. In our hands, administration of a fusion protein containing the pan DR epitope (PADRE), which enhances activation of helper, effector, and memory CD8+ T cells in mice and humans, was critical for the activation of tumor-specific immune response. On the other hand, priming of neoplastic lesions with selected chemokines, namely, CCL20 and CCL21 (alone or in combination), led to somehow contrasting results. Indeed, while the expression of CCL20 was expected to recruit immature DCs and promote both antigen uptake and activation of tumor-specific T cells, elevated levels of this chemokine led to the recruitment of regulatory T cells, which inhibited vaccine-elicited immune response. On the contrary, priming of melanoma lesions with CCL21 alone resulted in the activation of superior melanoma-specific immune response. Although we and others have previously demonstrated that a permanent intratumoral gradient of CCL21 facilitates recognition of malignant cells by the immune system, our recent findings demonstrated that even a transient gradient of this chemokine...
established prior to DNA vaccination favors the accumulation, activation and expansion of tumor-specific T cells. This is consistent with previous data demonstrating that CCL21 can promote the clonal expansion of T cells. Thus, our data clearly demonstrate the efficacy of priming malignant lesions with specific chemokines prior to the administration of a therapeutic DNA anticancer vaccine. The optimization of this approach is likely to result in the development of a generic and cost-effective immunotherapeutic regimen for the treatment of unresectable (metastatic) tumors.

Currently, DNA-based anticancer vaccines are most commonly administered via the intramuscular route, a setting in which multinucleated, elongated muscle cells express target antigens to high levels, favoring antigen uptake and cross-presentation by intramuscular DCs. On the contrary, the intradermal route allows for direct antigen presentation via MHC class I mechanism by DNA-transfected cutaneous antigen-presenting cells (APCs), including Langerhans cells and DCs. We therefore hypothesized that chemokine-mediated recruitment of immature DCs to the vaccine administration site may favor direct antigen presentation to T cells by vaccinated DCs. We were also convinced that the concurrent recruitment of T cells may further promote antigen presentation at the vaccination site. In support of these notions, we have recently demonstrated that the simultaneous recruitment of DCs and T cells to the skin prior to DNA vaccination, allows for extranodal antigen presentation via MHC class I molecules, T-cell activation, expansion, and antigen-specific cytotoxic immune response in both prophylactic and therapeutic settings (Fig. 1B).

In summary, further optimization of the priming procedures is likely to allow for the efficient recruitment of immature DCs and naive T cells to the cutaneous tissue, possibly resulting in the formation of transient lymph node-like structures similar to those observed in mucosal tissues, or for the intratumoral accumulation of T cells, are expected to improve the efficacy of therapeutic DNA-based anticancer vaccines. It is also plausible that optimizing the composition of DNA-based vaccines, for instance by including various immunostimulatory epitopes or interferon-responsive factors, and/or administering them in the context of CTLA4 inhibition would promote the DC-mediated activation of tumor-specific CTLs and hence the elicitation of therapeutically relevant tumor-specific immune response.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were to be disclosed.
References
1. Alexeev V, Pidich A, Kemp D, Igoucheva O. Recombinant DNA technology in emerging modalities for melanoma immunotherapy. In: Huyhn G (ed) Melanoma: from early detection to treatment. Intech: Rijeka, Croatia, 2013, pp 175-194
2. Sondak VK, Smalley KS, Kudchadkar R, Grippon S, Kirkpatrick P. Ipilimumab. Nat Rev Drug Discov 2011; 10:411-2; PMID:21629286; http://dx.doi.org/10.1038/nrd3463
3. Alexeev V, Mucci T, Igoucheva O. Immunotherapeutic strategies for the treatment of malignant melanoma. G Ital Dermatol Venereol 2008; 143:139-49; PMID:18833640
4. Novak L, Igoucheva O, Cho S, Alexeev V. Characterization of the CCL21-mediated melanoma-specific immune responses and in situ melanoma eradication. Mol Cancer Ther 2007; 6:1755-64; PMID:17575105; http://dx.doi.org/10.1158/1535-7163.MCT-06-0709
5. Igoucheva O, Grazzini M, Pidich A, Kemp DM, Larijani M, Farber M, Lorton J, Rodeck U, Alexeev V. Immunoeediting and eradication of orthotopic melanoma using a chemokine-enhanced DNA vaccine. Gene Ther 2013; 20:939-48; PMID:23552473; http://dx.doi.org/10.1038/gt.2013.37
6. Wu A, Zeng Q, Kang TH, Peng S, Roosinovich E, Pai SI, Hung CF. Innovative DNA vaccine for human papillomavirus (HPV)-associated head and neck cancer. Gene Ther 2011; 18:304-12; PMID:20981112; http://dx.doi.org/10.1038/gt.2010.151
7. Park JY, Jin DH, Lee CM, Kang MJ, Lee SY, Shin HS, Chung YH, Kim KY, Kim SS, Lee WB, et al. CD4+ TH1 cells generated by Ii-PADRE DNA at prime phase are important to induce effectors and memory CD8+ T cells. J Immunother 2010; 33:510-22; PMID:20463596; http://dx.doi.org/10.1097/CJI.0b013e3181d75ce
8. Flanagan K, Moroziewicz D, Kwak H, Höreig H, Kaufman HL. The lymphoid chemokine CCL21 costimulates naive T cell expansion and Th1 polarization of non-regulatory CD4+ T cells. Cell Immunol 2004; 231:75-84; PMID:15919372; http://dx.doi.org/10.1016/j.cellimm.2004.12.006
9. Rangel-Moreno J, Morron-Quirox JE, Hartson L, Kusser K, Randall TD. Pulmonary expression of CXC chemokine ligand 13, CC chemokine ligand 19, and CC chemokine ligand 21 is essential for local immunity to influenza. Proc Natl Acad Sci USA 2007; 104:10577-82; PMID:17563386; http://dx.doi.org/10.1073/pnas.0700591104
10. McDonald KG, McDonough JS, Wang C, Kucharcik T, Williams IR, Newberry RD. CC chemokine receptor 6 expression by B lymphocytes is essential for the development of isolated lymphoid follicles. Am J Pathol 2007; 170:1229-40; PMID:17392163; http://dx.doi.org/10.2353/ajpath.2007.060817