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TRIMELVax: A Novel Innate Immune-Engaging Vaccine for Malignant Melanoma Targeting Neutrophil-Driven Antigen Presentation and T-Cell Activation

Flavio Salazar-Onfray[1,2,3]

[1] *Disciplinary Program of Immunology, Faculty of Medicine, University of Chile, Chile;*
[2] *Millennium Institute for Immunology and Immunotherapy, University of Chile, Chile;*
[3] *Division of Infectious Diseases, Karolinska University Hospital, SE-171 77 Solna, Sweden.*

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***Correspondence:** Flavio Salazar-Onfray Disciplinary Program of Immunology, Faculty of Medicine, University of Chile, Chile; Millennium Institute for Immunology and Immunotherapy, University of Chile, Chile; Division of Infectious Diseases, Karolinska University Hospital, SE-171 77 Solna, Sweden.
E-mail: fsalazaronfray@gmail.com
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Abstract

TRIMELVax is an innovative immunotherapeutic vaccine for malignant melanoma, which combines heat shock-conditioned human melanoma cell lysates with a mollusk hemocyanin as an adjuvant. Preclinical studies demonstrated significant effectiveness in reducing tumor growth and improving survival in mice with melanoma and colorectal tumors. However, the precise immunological mechanisms behind its anti-tumor effects have remained unclear. We focused on understanding how TRIMELVax induces inflammation at the injection site, recruits innate immune cells, triggers DC migration to draining lymph nodes, and affects tumor microenvironment and growth. To achieve this, C57BL/6 mice were injected in the footpad with TRIMELVax, PBS, or control vaccines, and then the skin and the popliteal lymph node were harvested for qPCR or FACS analysis. Results showed that TRIMELVax rapidly induced a specific pattern of proinflammatory cytokines and chemokines, leading to a differential acute innate immune response in the injection site. Neutrophils, type 1 macrophages, monocytes, cDC1, Langerhans cells, and monocyte derived-DCs were recruited to the footpad, while type 2 macrophages decreased. This early inflammation facilitated a superior migration of cDC1 and a new subtype of antigen-presenting neutrophils to the draining lymph node compared to controls. Depleting neutrophils before vaccination reduced DC migration, especially cDC1, to the draining lymph node and suppressed TRIMELVax's ability to control tumor growth, demonstrating that vaccine-induced neutrophils play a fundamental role in TRIMELVax's mechanism of action. At the tumor microenvironment level, it was observed that TRIMELVax induces a more intense infiltration of CD8+ T lymphocytes than controls, with a low level of exhaustiveness and greater cytotoxic capacity. A phase I clinical trial in twenty nivolumab-refractory patients showed that TRIMELVax is well tolerated with no grade 3-5 side effects and induces a Delayed-Type hypersensitivity reaction against melanoma antigens after four doses of the vaccine with an impact on disease stability and patient survival. In summary, TRIMELVax triggers a rapid and potent activation of the innate immune system, which seems crucial for a more effective adaptive immune response against aggressive melanoma tumors. These results underscore the promise of TRIMELVax as a potential immunotherapeutic approach for melanoma treatment.