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ORIGINAL ARTICLE

Immunity to the melanoma inhibitor of apoptosis protein (ML-IAP; livin) in patients with malignant melanoma

Jun Zhou · Noah K. Yuen · Qian Zhan · Elsa F. Velazquez · George F. Murphy · Anita Giobbie-Hurder · F. Stephen Hodi

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Abstract Therapeutic targeting of melanoma antigens frequently focuses on the melanocyte differentiation or cancer-testis families. Antigen-loss variants can often result, as these antigens are not critical for tumor cell survival. Exploration of functionally relevant targets has been limited. The melanoma inhibitor of apoptosis protein (ML-IAP; livin) is overexpressed in melanoma, contributing to disease progression and treatment resistance. Improved understanding of the significance of ML-IAP immune responses in patients has possible therapeutic applications. We found ML-IAP frequently expressed in melanoma metastases by immunohistochemistry. To assess spontaneous immunity to ML-IAP, an overlapping peptide library representing full-length protein was utilized to screen cellular responses in stage I–IV patients and healthy controls by ELISPOT. A broad array of $CD4^+$ and $CD8^+$ cellular responses against ML-IAP was observed with novel class I and class II epitopes identified. Specific HLA-A*0201 epitopes were analyzed further for frequency of reactivity. The generation of specific $CD4^+$ and cytotoxic T cells revealed potent functional capability including cytokine responsiveness to melanoma cell lines and tumor cell killing. In addition, recombinant ML-IAP protein used in an ELISA demonstrated high titer antibody responses in a subset of patients. Several melanoma patients who received CTLA-4 blockade with ipilimumab developed augmented humoral immune responses to ML-IAP as a function of treatment which was associated with beneficial clinical outcomes. High frequency immune responses in melanoma patients, associations with favorable treatment outcomes, and its essential role in melanoma pathogenesis support the development of ML-IAP as a disease marker and therapeutic target.

Keywords Melanoma · ML-IAP · Livin · Immune responses

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J. Zhou · F. S. Hodi (✉)
Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA
e-mail: stephen_hodi@dfci.harvard.edu

J. Zhou · F. S. Hodi
Melanoma Disease Center, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA, USA

N. K. Yuen
John A. Burns School of Medicine, University of Hawai'i at Manoa, Honolulu, HI 96813, USA

Q. Zhan · E. F. Velazquez · G. F. Murphy
Department of Pathology, Brigham and Women's Hospital, Boston, MA 02115, USA

A. Giobbie-Hurder
Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA

Introduction

Many melanoma antigens have been identified that are the targets of both cellular and humoral immune responses. The melanocyte differentiation antigens expressed in both melanomas and normal melanocytes have been extensively studied as both the targets of spontaneous immune responses as well as utilized in strategies to augment immunity with therapeutic intent [1]. In addition, the cancer-testis antigens, such as MAGE [2, 3] and NY-ESO-1 [4, 5], have