



Epigenetic Therapy, an Appealing Strategy to Improve Cancer Immunotherapy

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Comment on:

Li BH et al. Induction of a specific CD8+ T-cell response to cancer/testis antigens by demethylating pre-treatment against osteosarcoma. *Oncotarget* 2014; 5: 10791-802.

Introduction

Conventional chemotherapeutic regimens against tumors are subject to chemoresistance and drug-related toxicity. T cell-based immunotherapy is a particularly promising strategy for the treatment of malignant tumors because of its inherent high specificity and lymphocytes' ability to traffic to distant tumor cells [1]. However, most tumors epigenetically silence the expression of neo-antigens or "non-self" proteins and the lack of satisfactory immunotherapeutically targetable epitopes expressed consistently and uniformly limits its application [2].

Cancer/testis antigens (CTAs), almost exclusively expressing in tumor cells, can be the encouraging targetable antigens [3]. Nevertheless, the CTA expression may also be silenced in tumors, compromising the CTA-based immunotherapy. Then how to elevate the CTA expression becomes the key point for CTA specific immunotherapy. Epigenetic plays an important role in regulating gene expression and a key mediator of gene silencing is the protein DNA methyl-transferase 1 (DNMT1). Demethylating agents such as decitabine (DAC) are potent inhibitor of DNA methylation and restore the normal function of promoter region to enhance gene transcription and expression [4].

A recent study by Li BH and colleagues [5] showed adoptive immunotherapy combining with demethylating treatment had the potential for non-surgical therapeutic strategy against osteosarcoma. Building on their work, the authors demonstrated expression of CTAs, including MAGE-A family and NY-ESO-1 in osteosarcoma cell line

can be elevated after treatment with DAC. Moreover, the elevated CTA expression could effectively facilitate CTA specific CD8+ T-cell-mediated tumor cell killing *in vitro* and *in vivo*. Their results highlighted the synergistic role that demethylating treatment could play with specific immunotherapy and be considered as a promising strategy for patients.

However, the authors may overlook the phenomenon that DAC could be rapidly metabolized into inactive uridine counterparts by cytidine deaminase (CDA), an enzyme highly expressed in the liver and intestine [6]. So the demethylating effect of DAC would be strengthened by combining with CDA inhibitors and bring more promising results in treating malignant tumors.

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