Austin Journal of Dermatology

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Austin Publishing Group

Editorial

Tumor Promoter or Tumor Suppressor: A Question for Epigenetic Regulatory Factors

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Received: March 06, 2018; **Accepted:** March 13, 2018; **Published:** March 20, 2018

Editorial

Epigenetics is defined as the gene expression alterations, properly leading to a phenotype change, without DNA sequence alteration [1]. In cancer, epigenetic alterations are changes in DNA and histone modifications, which cause promoting oncogenic genes and suppressing tumor suppressor genes, as well as other cell homeostasis events leading to a normal cells becoming tumorigenic. The deregulation of epigenetic modifications or epigenetic regulatory factors plays an important role in cancer initiation and progression. However, functions of many epigenetic regulatory factors are complex on tumorigenesis, sometimes showing opposite roles in different cancers.

Melanoma takes part of less than 10% of all skin cancers. However, because of the high metastatic potential and resistance to chemotherapy and radiotherapy, melanoma is the most deadly form of skin cancer [2]. Recent study reveal that melanoma harbor 4.4% to 15.0% DOT1L mutations [3]. Those mutations impair DOT1L histone methyltransferase function and decrease the H3K79 methylation, which promotes melanoma development in transgenic mouse model through induction of insufficient DNA repair upon UVR treatment. However, compared with the protective role of DOT1L/H3K79 methylation in melanocytes from development of melanoma, DOT1L interacts with oncogenic MLL-fusion protein to promote leukemia formation [4]. This discovery point to the complex function of epigenetic regulatory factors, which termed as "gatekeeper". The function of epigenetic regulatory factors always shows the dependence on the cellular context and tumor types. For example, PCR2 mutations with activating and loss-of-function are both observed in different cancer types. Activating mutations of EZH2 drive melanoma formation [5]. However, loss-of-function mutations of PRC2 component EZH2 cause myeloid malignancies [6]. Moreover, SUZ12 inactivation functions to enhance Ras oncogene function, suggesting SUZ12 tumor suppressor function [7]. These differences reflect tissue-specific and context-dependent roles for PRC2. Therefore, the specific molecular consequence of epigenetic regulator factors is still required for investigated within different cancer, including melanoma. With the fast developing of next-generation genome sequencing, mutations of epigenetic regulatory are promising to be identified, with not only the novel mutations occurring in cancer but also those mutations that are co-occurring or mutually excluded. These would contribute to our understanding of chromatin effector and their regulated signaling pathways network on promoting cancer initiation and progression. Moreover, these researches would reveal genetic markers for the responsiveness to certain treatment with subgroup cancer patients.

Immune checkpoint blockade targeting inhibitory receptors, e.g. PD-1 receptor, on T cells induces durable responses for cancer patients. The function of cytotoxic T cells, the key effectors for tumor immunity and cancer clearance, is impacted by tumor cells. For example, some melanoma cells increase expression of PD-L1, which interacts with its receptor PD-1 and inhibits T cell function [8]. The clinical studies show that there are approximately 30% melanoma patients are responsive to these immunotherapies, with most patients fail to these treatment [9]. The newly discovery through a genome-scale CRISPR-Cas9 screen have identified chromatin modular play an essential role for resistance to immunotherapy [10]. This study point to the significance of PBAF complex, especially the component of Pbrm1, Arid2 and Brd7, which belongs to SWI/SNF chromatin remodeling complex, to tumor immunity and immune checkpoint blockade therapy. The same conclusion was reported in another group that PBRM1 mutations improved responses of patients to PD-1 or PD-L1 blockade treatment [11]. Most work on primary and acquired resistance to Checkpoint Inhibitors (CPI) are on overcoming T cell. Those two newly studies point to that inactivating mutations of PBAF components develop a more efficient anti-tumor immunity microenvironment, in which cytotoxic T cell function was enhanced under immunotherapy. The interesting story is that frequent mutations of PBAF were observed in human cancers and PBAF complex is believed to function as a tumor suppressor in those cancers. For example, Arid 2 loss-of-function mutations were identified in 7% melanoma, and together with other component mutations of SWI/SNF complex harboring a loss-of-function mutation was observed in up to 13% of melanoma samples. Those mutations of SWI/SNF components were identified as the driver mutations to promote melanomagenesis [12].

The functions of epigenetic regulatory factors in cancer are complex. With fast growing of the cancer genomic sequencing and chromatin techniques, novel mutations in cancers have been identified and predicated for diagnostic and/or genetic markers for responsiveness. However, it is important to study the background mutations or cancer-types for those certain functions, since the same mutations of epigenetic regulatory factor may show different function in distinct cancer text. In coming years, targeting alterations of epigenetic regulatory factors will probably be tested in cancer clinical trials and/or genetic markers for therapeutic design. Moreover, the mechanisms for cancer- or mutation-associated epigenetic alterations will be elucidated with details, which will provide insights into epigenetic-based medicine.

Citation: Zhu B. Tumor Promoter or Tumor Suppressor: A Question for Epigenetic Regulatory Factors. Austin J Dermatolog. 2018; 5(1): 1084.

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Austin J Dermatolog - Volume 5 Issue 1 - 2018
ISSN : 2381-9197 | www.austinpublishinggroup.com

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