Immunomodulation of HDAC Inhibitor Entinostat Potentiates the Anticancer Effects of Radiation and PD-1 Blockade in the Murine Lewis Lung Carcinoma Model

Yeeun Kim, Kyunghee Park , Yeon Jeong Kim, Sung-Won Shin, Yeon Joo Kim, Changhoon Choi, and Jae Myoung Noh

Student: Kam-Hong Kam Advisor: Michael Chan Date : 2023/04/21

(1)簡述論文的重大發現

本論文使用 HDAC 抑制劑 Entinostat,以增強放射治療和 PD-1 inhibitor 治療在小鼠肺癌中的抗癌效果，並且促進免疫反應和腫瘤細胞死亡。這種 triple therapy 有望在治療肺癌或其他類型的癌症患者中提高治療效果。

(2)對論文內容的疑問

雖然這項研究在小鼠模型中展示出有希望的結果，但需要進一步的研究來確定這種方法在人類患者中的安全性和有效性。需要進行臨床試驗來評估使用 Entinostat 與放射線和 PD-1 阻斷劑組合治療人類肺癌或其他類型的癌症的潛力。

(3)論文的缺點與評論

研究使用老鼠肺癌模型來探討組合療法的效果。但無法完全反映疾病的複雜性。儘管存在某些潛在限制，該研究仍可能提供有關癌症潛在新療法的方向。未來的研究可以建立在這些發現基礎之上，以提供更具有決定性的證據來證實該治療方法的安全性和有效性。

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Yeeun Kim [1,†], Kyunghee Park [2,†], Yeon Jeong Kim [2], Sung-Won Shin [1], Yeon Joo Kim [1], Changhoon Choi [1,*] and Jae Myoung Noh [1,3,*]

[1] Department of Radiation Oncology, Samsung Medical Center, Seoul 06351, Republic of Korea
[2] Samsung Genome Institute, Samsung Medical Center, Seoul 06351, Republic of Korea
[3] Department of Radiation Oncology, Sungkyunkwan University School of Medicine, Seoul 06351, Republic of Korea
* Correspondence: changhoon1.choi@samsung.com (C.C.); rodrno@skku.edu (J.M.N.)
† These authors contributed equally to this work.

Abstract: Although the combination of radiotherapy and immunotherapy has proven to be effective in lung cancer treatment, it may not be sufficient to fully activate the antitumor immune response. Here, we investigated whether entinostat, a histone deacetylase inhibitor, could improve the efficacy of radiotherapy and anti-PD-1 in a murine syngeneic LL/2 tumor model. A total of 12 Gy of X-rays administered in two fractions significantly delayed tumor growth in mice, which was further enhanced by oral entinostat administration. Flow cytometry-aided immune cell profiling revealed that entinostat increased radiation-induced infiltration of myeloid-derived suppressor cells and $CD8^+$ T cells with decreased regulatory T-cells (Tregs). Transcriptomics-based immune phenotype prediction showed that entinostat potentiated radiation-activated pathways, such as JAK/STAT3/interferon-gamma (IFN-γ) and PD-1/PD-L1 signaling. Entinostat augmented the antitumor efficacy of radiation and anti-PD-1, which may be related to an increase in IFN-γ-producing $CD8^+$ T-cells with a decrease in Treg cells. Comparative transcriptomic profiling predicted that entinostat increased the number of dendritic cells, B cells, and T cells in tumors treated with radiation and anti-PD-1 by inducing MHC-II genes. In conclusion, our findings provided insights into how entinostat improves the efficacy of ionizing radiation plus anti-PD-1 therapy and offered clues for developing new strategies for clinical trials.

Keywords: entinostat; radiation; anti-PD-1; antitumor immunity; lung cancer

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1. Introduction

Lung cancer is the second most common cancer worldwide and its incidence continues to increase. Radiation therapy (RT) is a major component of the multimodal treatment for patients with solid cancers, including lung cancer. RT is a double-edged sword that induces an antitumor immune response and promotes immune suppression [1]. For example, RT encourages the recruitment of cytotoxic killer T cells and immunosuppressive cells, such as myeloid-derived suppressive cells (MDSCs) and regulatory T cells (Tregs). Immune checkpoint inhibitors (ICIs) designed to block the programmed cell death-1 (PD-1) and programmed cell death-ligand 1 (PD-L1) pathways have revolutionized lung cancer treatment. Combined with the PD-1 signaling blockade, ICIs reinvigorate RT-induced immune suppression, resulting in a better outcome. The phase 3 PACIFIC study showed that concurrent chemoradiation followed by consolidation with durvalumab (anti-PD-L1) resulted in longer progression-free survival and a higher overall survival rate than placebo [2,3]. Nevertheless, the combination of RT and ICIs may not be sufficient to fully