EZH2 inhibits NK cell–mediated antitumor immunity by suppressing CXCL10 expression in an HDAC10-dependent manner

Suresh Bugide, Romi Gupta, Michael R. Green, and Narendra Wajapeyee

Proceedings of the National Academy of Sciences (PNAS)
Doi:10.1073/pnas.2102718118/-/DCSupplemental.
July, 2021

Student: Ciao-Ni Chen Advisor: Dr. Michael Chan Date: 2022/10/21

1. 簡述論文的重大發現：

肝細胞癌 (HCC) 是一種肝癌， 5 年生存率較差，目前對於 HCC 有效的治療有限，因此迫切需要找到新的治療方式。在幾種癌症類型中觀察到 EZH2 可能具有致癌性突變或是過表達，作為致癌基因發揮作用。基於這些結果，目前已經開發幾種 EZH2 的抑制劑作於治療藥物，並進行多種癌症的臨床試驗，證實了 EZH2 是一種具有臨床價值的癌症治療靶點。

在作者先前研究中已經發現 EZH2 可以調控自然殺手 (NK) 細胞的抗腫瘤活性，而對於其涉及的機制尚未清楚。此篇研究中作者發現 EZH2 抑制劑可以通過調節趨化因子 CXCL10 募集自然殺手細胞到腫瘤部位，以此達到抗腫瘤功效。作者利用 EZH2 抑制劑處理肝癌細胞及 mouse model，可以發現處理過後增強趨化因子 CXCL10 的表達，並增加了自然殺手募集至腫瘤部位，抑制了腫瘤發展。另外先前研究表明 EZH2 的轉錄基因表達和 histone acetylation 有關。因此，作者進一步探討其機制，發現在肝癌細胞 knockdown HDAC10 後，降低 CXCL10 promoter 上 EZH2 的募集，增加 CXCL10 的表達，從而增加自然殺手的遷移能力，促進抗腫瘤的能力。

2. 對論文內容的提問：

在本篇論文中只探討了 EZH2 抑制劑調節 CXCL10 的表達，並增加自然殺手細胞的募集，然而其他趨化因子是否也會涉及此機制？另外，EZH2 除了調控自然殺手細胞，是否也會調節其他的免疫細胞？

3. 論文的缺點與評論：

本篇作者針對 EZH2 抑制劑透過增加自然殺手細胞的募集達到抗腫瘤的效果，為 HCC 治療上提供新的治療標的。

EZH2 inhibits NK cell–mediated antitumor immunity by suppressing CXCL10 expression in an HDAC10-dependent manner

Suresh Bugide[a], Romi Gupta[a], Michael R. Green[b,1], and Narendra Wajapeyee[a,1]

[a]Department of Biochemistry and Molecular Genetics, University of Alabama at Birmingham, Birmingham, AL 35233; and [b]Department of Molecular, Cell and Cancer Biology, University of Massachusetts Medical School, Worcester, MA 01605

Contributed by Michael R. Green, June 22, 2021 (sent for review February 10, 2021); reviewed by Sushanta K. Banerjee, Girdhari Lal, and Ajay P. Singh

Enhancer of zeste homolog 2 (EZH2) is a histone H3 lysine 27 methyltransferase that has been shown to function as an oncogene in some cancers. Previous reports have largely focused on the ability of EZH2 to regulate cell-intrinsic tumor regulatory pathways as its mechanism-of-oncogenic action. However, the role that EZH2-mediated immune suppression plays in its oncogenic activity is not fully known. In particular, the role of natural killer (NK) cells in EZH2-driven tumor growth remains incompletely understood. Here, we demonstrate that genetic or pharmacological inhibition of EZH2 induces reexpression of the chemokine CXCL10 in hepatic tumor cells. We find that histone deacetylase 10 (HDAC10) is necessary for EZH2 recruitment to the *CXCL10* promoter, leading to *CXCL10* transcriptional repression. Critically, CXCL10 is necessary and sufficient for stimulating NK cell migration, and EZH2's ability to inhibit NK cell migration via CXCL10 suppression is conserved in other EZH2-dependent cancers. NK cell depletion in an immunocompetent syngeneic mouse model of hepatic tumorigenesis reverses the tumor inhibitory effects of an EZH2 inhibitor (GSK343), and inhibitor-mediated reexpression of CXCL10 is required for its tumor suppressive effects in the same mouse model. Collectively, these results reveal a decisive role for NK cells and CXCL10 in mediating the oncogenic function of EZH2.

EZH2 | hepatocellular carcinoma | NK cells | HDAC10 | CXCL10

Enhancer of zeste homolog 2 (EZH2) encodes a histone methyltransferase that constitutes the catalytic component of polycomb repressive complex 2 (PRC2). The gene silencing activity of PRC2 depends on its ability to trimethylate lysine 27 of histone H3 (H3K27me3), which occurs via the catalytic SET domain of the EZH2 subunit and at least two other PRC2 subunits, including suppressor of zeste 12 (SUZ12) and embryonic ectoderm development (EED) (1–3). In particular, the carboxyl-terminal domain of EED binds specifically to histone tails carrying trimethyl-lysine residues associated with repressive chromatin marks, which in turn, leads to allosteric activation of the methyltransferase activity of PRC2 (4).

The presence of gain-of-function oncogenic mutations in the *EZH2* gene or EZH2 overexpression is observed in several cancer types, and in some cases, EZH2 also functions as an oncogene (5). These observations have led to the development of several potent and clinically efficacious EZH2 and EED inhibitors, many of which are already undergoing clinical testing for treating a wide variety of cancers (5). Based on the results of these clinical trials, one such EZH2 inhibitor, tazemetostat (Tazverik), has already been approved by the US Food and Drug Administration (US FDA) for treating follicular lymphoma and epithelioid sarcoma (6, 7). Collectively, these observations confirm that EZH2 is a druggable target with clinical value for cancer therapy.

The host immune response to cancer cells is a potent mechanism for tumor suppression. In this regard, cells of both the adaptive immune system (e.g., T cells and B cells) and the innate immune system (e.g., natural killer [NK] cells and macrophages) have been shown to play important roles in tumor initiation and progression (8). Therefore, a number of cancer therapeutic agents function to elicit tumor inhibitory immune responses that, in some cases, underpin their anticancer activity (9–11). Previous studies exploring the mechanisms of EZH2-mediated oncogenesis have largely focused on the cell-intrinsic mechanisms by which EZH2 regulates expression of genes that are necessary for cancer cell proliferation and survival to promote tumor development and progression (12, 13). However, the relative contribution of cell-extrinsic tumor regulatory pathways, including host immune response, relative to cell-extrinsic pathways, such as those that promote cell proliferation and survival, for mediating EZH2-driven oncogenesis, is not known.

We previously demonstrated that EZH2 promotes tumor development through a cell-extrinsic mechanism involving inhibition of the antitumor activity of NK cells (14). NK cells are components of the innate immune response that play a key role in eradicating infected and stress-damaged cells (15). These cells are also critical for inhibiting tumor initiation and progression (16, 17). There are two main mechanisms that regulate the antitumor activity of NK cells. These include the pathways that directly regulate NK cell–mediated tumor cell eradication, and those that control NK cell migration and recruitment to tumor sites, which are also necessary for their antitumor activity. The regulation of these NK cell activities is achieved, in part, by modulating the expression of NK cell–activating and repressing ligands on tumor cells (16). In our previous study, we demonstrated that EZH2

Significance

Hepatocellular carcinoma (HCC), a type of liver cancer, has a poor 5-y survival rate and current therapies provide only marginal clinical benefits to most HCC patients. Therefore, new therapeutic approaches are needed for HCC treatment. Natural killer (NK) cells are cells of the innate immune system that can inhibit tumor development and progression. We find that pharmacological inhibition of EZH2 results in NK cell–mediated hepatic tumor growth inhibition in mice, which occurs, in part, due to the increased expression of the chemokine CXCL10, leading to increased NK cell migration. These results have implications for EZH2-dependent tumors, in which NK cell–mediated tumor clearance can be induced using EZH2 inhibitors.

Author contributions: S.B., R.G., and N.W. designed research; S.B. performed research; R.G., M.R.G., and N.W. contributed new reagents/analytic tools; S.B., R.G., M.R.G., and N.W. analyzed data; and S.B., R.G., M.R.G., and N.W. wrote the paper.

Reviewers: S.K.B., VA Medical Center and University of Kansas Medical Center; G.L., National Centre for Cell Science; and A.P.S., University of South Alabama.

The authors declare no competing interest.

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[1]To whom correspondence may be addressed. Email: nwajapey@uab.edu or michael.green@umassmed.edu.

This article contains supporting information online at https://www.pnas.org/lookup/suppl/doi:10.1073/pnas.2102718118/-/DCSupplemental.

Published July 23, 2021.

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