Commentary

The promise of using histone deacetylase inhibitors in combination treatment against breast cancer and other solid tumors

Nirmal Perera, Alexander Hergovich

Tumour Suppressor Signalling Networks Laboratory, UCL Cancer Institute, University College London, London, UK

Correspondence to: Alexander Hergovich. UCL Cancer Institute, University College London, 72 Huntley Street, WC1E 6BT, London, UK. Email: a.hergovich@ucl.ac.uk.

Provenance: This is a Guest Commentary commissioned by Section Editor Zi-Guo Yang, (Key Laboratory of Carcinogenesis and Translational Research, Breast Center, Peking University Cancer Hospital & Institute, Beijing, China).

Comment on: Zeng H, Qu J, Jin N, *et al.* Feedback Activation of Leukemia Inhibitory Factor Receptor Limits Response to Histone Deacetylase Inhibitors in Breast Cancer. Cancer Cell 2016;30:459-73.

Submitted Dec 08, 2016. Accepted for publication Dec 08, 2016.

doi: 10.21037/cco.2017.01.05

View this article at: http://dx.doi.org/10.21037/cco.2017.01.05

In eukaryotes, DNA bound to histones forms chromatin. Histone acetylation occurs on lysines in the N-terminal tails of histones, leading to chromatin relaxation and elevated gene expression. Histone deacetylases (HDACs) catalyze the deacetylation of histones and are associated with tumorigenesis through the repression of tumor suppressor gene expression. HDAC inhibitors promote histone acetylation and consequently allow re-expression of tumor suppressor genes, which can repress malignancies (1).

Significantly, the US Food and Drug Administration (FDA) has already approved the three HDAC inhibitors vorinostat, romidepsin and belinostat for the treatment of cutaneous and peripheral T-cell lymphomas. HDAC inhibitors are epigenetic drugs targeting specific parts of cancer cell signaling (1). In contrast, standard chemotherapy indiscriminately kills rapidly dividing cancerous and non-cancerous cells, which can cause undesired side effects and anticancer therapy resistance. Therefore, the past 20 years have seen the development of target-directed approaches for the clinical treatment of the most frequent malignancies in the world such as breast cancer. Tailored therapies were developed based on the status of receptors for estrogen, progesterone, and HER2 (human epidermal growth factor 2). However, in spite of significantly improved earlier diagnosis and the development of targeted therapeutics, the mortality rate in breast cancer has only decreased by about one third over the past decades. Two main reasons are (I) the emergence of anticancer drug resistance and (II) the lack of specific therapies for triple-negative breast cancers (TNBC), a breast cancer subtype that is hormone receptor negative and characterized by poor prognosis due to rapid disease progression (2). Therefore, we need to discover new therapeutic approaches to overcome drug resistances and efficiently target TNBC cells. Recent research has led to the testing of epigenetic modulators, such as HDAC inhibitors, in the treatment of breast cancer cells, with some promising results showing positive effects associated with low side effects, although patients with TNBC, particularly those with BRCA1/2 mutations (3), still face more limited treatment options and have a worse prognosis than patients who are hormone receptor positive. Nevertheless, combinations of targeted therapies involving HDAC and PARP inhibitors are promising options against breast cancers, especially TNBC (2).

HDAC inhibitor monotherapy is effective against hematological malignancies, however ineffective against solid tumors such as TNBC (1). A recent study provided a mechanistic explanation for this lack of responsiveness (4). Zeng *et al.* tested the response of various human cancer cells to the HDAC inhibitor vorinostat (aka SAHA), discovering why breast cancer cells show a limited response to HDAC inhibition (4). More specifically, they found that cytokine-cytokine receptor pathway and STAT3 (signal transducer and activator of transcription 3) signaling were reprogrammed upon HDAC inhibition. In particular, HDAC inhibition could promote leukemia inhibitory factor

receptor (LIFR) expression, which stimulated JAK1 (Janus kinase 1)-STAT3 signaling to drive expression of anti-apoptotic genes such as BCL2 or MCL-1, finally resulting in reduced anticancer drug response (4). Noteworthy, STAT3-mediated anti-apoptotic signaling limited the response to HDAC inhibitors in breast cancer cells irrespective of hormone receptor status (4). The observed HDAC inhibitor induced upregulation of LIFR (4) is in full agreement with previous findings (5).

Significantly, Zeng *et al.* further found that HDAC inhibition enhanced histone acetylation at the LIFR promoter supported by the BET (bromodomain and extra terminal domain) protein BRD4 (4). Therefore, Zeng *et al.* tested JQ1, a pharmacological BRD4 inhibitor (6), in combination with vorinostat, revealing that breast cancer cell growth was inhibited upon combined BRD4 and HDAC inhibition (4). This observation is fully supported by a previous study that also focused on breast cancer cells (7) as well as studies of pancreatic carcinoma, acute lymphoblastic leukemia and acute myeloid leukemia cells (8-10). In other words, different pre-clinical studies have demonstrated that the use of HDAC inhibitors together with therapeutics targeted against BRD4 signaling should be considered for the treatment of solid tumors and hematological malignancies.

Based on the discovery that vorinostat-induced LIFR upregulation can activate JAK1-STAT3 signaling to promote the expression of anti-apoptotic genes (4), Zeng *et al.* also tested the response of breast cancer cells to vorinostat in combination with ruxolitinib (INCB018424), a pan-JAK1/2 inhibitor recently approved by the FDA for the treatment of myelofibrosis (11). Strikingly, this combination therapy resulted in increased apoptosis and reduced proliferation of breast cancer cells, with 3 out of 4 TNBC patient derived xenograft models showing a significant tumor growth inhibition in mice (4). Therefore, the pre-clinical work by Zeng *et al.* [2016] indicates that clinical studies should be seriously considered in which FDA-approved targeted therapeutics such as HDAC and JAK1/2 inhibitors are utilized in combination therapy to treat patients suffering from TNBC and possibly also other solid tumors, in addition to combined HDAC and JAK1/2 inhibition in myelofibrosis (12,13).

In this regard, it is noteworthy that poly (ADP-ribose) polymerase (PARP) inhibitors can also synergize with HDAC inhibitors in the treatment of numerous cancer cell types (14-22). For example, it was observed that pan-HDAC inhibition can induce "BRCAness" in TNBC cells, resulting in a sensitization of TNBC cells to PARP inhibition (14-16). Mechanistically, HDAC inhibition can downregulate DNA double-strand break (DSB) repair components and cause PARP "trapping", consequently resulting in impaired DSB repair, finally inducing the formation of unrepaired DSBs (16,19,20,23-25). Thus, pre-clinical studies suggest that the clinical use of combined HDAC and PARP inhibition should be considered for the treatment of TNBC (14-16), advanced prostate cancer (17), leukemia (18,19), malignant melanoma (20), glioblastoma (21), and hepatocellular carcinoma (22).

Taken together, pre-clinical studies have established a rationale for combined administration of HDAC inhibitors with FDA-approved targeted therapeutics such a ruxolitinib (JAK1/2 inhibitor) or olaparib (PARP inhibitor). In particular, based on the study by Zeng *et al.* [2016] it will be very interesting to explore the therapeutic options of combined HDAC and JAK1/2 inhibition in the treatment of currently difficult to treat solid tumors in the clinic.

Acknowledgements

We are very grateful to Joanna Lisztwan and all members of the Hergovich laboratory for their critical review of the commentary.
Funding: The Hergovich laboratory has been supported by the Wellcome Trust (090090/Z/09/Z), BBSRC (BB/I021248/1), Worldwide Cancer Res (AICR; 11-0634), UCL Cancer Research UK Centre funding, and the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. West AC, Johnstone RW. New and emerging HDAC inhibitors for cancer treatment. The J Clin Invest 2014;124:30-9.
2. Sharma P. Biology and Management of Patients With Triple-Negative Breast Cancer. Oncologist 2016;21:1050-62.
3. Lord CJ, Ashworth A. BRCAness revisited. Nat Rev Cancer 2016;16:110-20.
4. Zeng H, Qu J, Jin N, et al. Feedback activation of

leukemia inhibitory factor receptor limits response to histone deacetylase inhibitors in breast cancer. Cancer Cell 2016;30:459-73.
5. Blanchard F, Kinzie E, Wang Y, et al. FR901228, an inhibitor of histone deacetylases, increases the cellular responsiveness to IL-6 type cytokines by enhancing the expression of receptor proteins. Oncogene 2002;21:6264-77.
6. Filippakopoulos P, Qi J, Picaud S, et al. Selective inhibition of BET bromodomains. Nature 2010;468:1067-73.
7. Borbely G, Haldosen LA, Dahlman-Wright K, et al. Induction of USP17 by combining BET and HDAC inhibitors in breast cancer cells. Oncotarget 2015;6:33623.
8. Fiskus W, Sharma S, Qi J, et al. Highly active combination of BRD4 antagonist and histone deacetylase inhibitor against human acute myelogenous leukemia cells. Mol Cancer Ther 2014;13:1142-54.
9. Loosveld M, Castellano R, Gon S, et al. Therapeutic targeting of c-Myc in T-cell acute lymphoblastic leukemia, T-ALL. Oncotarget 2014;5:3168-72.
10. Mazur PK, Herner A, Mello SS, et al. Combined inhibition of BET family proteins and histone deacetylases as a potential epigenetics-based therapy for pancreatic ductal adenocarcinoma. Nat Med 2015;21:1163-71.
11. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366:799-807.
12. Baffert F, Evrot E, Ebel N, et al. Improved Efficacy Upon Combined JAK1/2 and Pan-Deacetylase Inhibition Using Ruxolitinib (INC424) and Panobinostat (LBH589) in Preclinical Mouse Models of JAK2V617F-Driven Disease. Blood 2011;118:798.
13. Wang Y, Fiskus W, Chong DG, et al. Cotreatment with panobinostat and JAK2 inhibitor TG101209 attenuates JAK2V617F levels and signaling and exerts synergistic cytotoxic effects against human myeloproliferative neoplastic cells. Blood 2009;114:5024-33.
14. Ha K, Fiskus W, Choi DS, et al. Histone deacetylase inhibitor treatment induces 'BRCAness' and synergistic lethality with PARP inhibitor and cisplatin against human triple negative breast cancer cells. Oncotarget 2014;5:5637-50.
15. Min A, Im SA, Kim DK, et al. Histone deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA), enhances anti-tumor effects of the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib in triple-negative breast cancer cells. Breast Cancer Res 2015;17:33.
16. Wiegmans AP, Yap PY, Ward A, et al. Differences in expression of key DNA damage repair genes after epigenetic-induced BRCAness dictate synthetic lethality with PARP1 inhibition. Mol Cancer Ther 2015;14:2321-31.
17. Chao OS, Goodman OB. Synergistic loss of prostate cancer cell viability by coinhibition of HDAC and PARP. Mol Cancer Res 2014;12:1755-66.
18. Jasek E, Gajda M, Lis GJ, et al. Combinatorial effects of PARP inhibitor PJ34 and histone deacetylase inhibitor vorinostat on leukemia cell lines. AntiCancer Res 2014;34:1849-56.
19. Robert C, Nagaria PK, Pawar N, et al. Histone deacetylase inhibitors decrease NHEJ both by acetylation of repair factors and trapping of PARP1 at DNA double-strand breaks in chromatin. Leuk Res 2016;45:14-23.
20. Krumm A, Barckhausen C, Kücük P, et al. Enhanced Histone Deacetylase Activity in Malignant Melanoma Provokes RAD51 and FANCD2-Triggered Drug Resistance. Cancer Res 2016;76:3067-77.
21. Rasmussen RD, Gajjar MK, Jensen KE, et al. Enhanced efficacy of combined HDAC and PARP targeting in glioblastoma. Mol Oncol 2016;10:751-63.
22. Zhang JX, Li DQ, He AR, et al. Synergistic inhibition of hepatocellular carcinoma growth by cotargeting chromatin modifying enzymes and poly (ADP-ribose) polymerases. Hepatology 2012;55:1840-51.
23. Adimoolam S, Sirisawad M, Chen J, et al. HDAC inhibitor PCI-24781 decreases RAD51 expression and inhibits homologous recombination. Proc Natl Acad Sci U S A 2007;104:19482-7.
24. Kachhap SK, Rosmus N, Collis SJ, et al. Downregulation of homologous recombination DNA repair genes by HDAC inhibition in prostate cancer is mediated through the E2F1 transcription factor. PloS One 2010;5:e11208.
25. Palmieri D, Lockman PR, Thomas FC, et al. Vorinostat inhibits brain metastatic colonization in a model of triple-negative breast cancer and induces DNA double-strand breaks. Clin Cancer Res 2009;15:6148-57.

Cite this article as: Perera N, Hergovich A. The promise of using histone deacetylase inhibitors in combination treatment against breast cancer and other solid tumors. Chin Clin Oncol 2017;6(1):9. doi: 10.21037/cco.2017.01.05

