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 unrepaird 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.

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Footnote

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