Editorial

iMedPub Journals
www.imedpub.com

Journal of Clinical Epigenetics
ISSN 2472-1158

2018
Vol.4 No.2:8

DOI: 10.21767/2472-1158.100093

HDAC Inhibitors in Solid Tumors: An Incomplete Story

Ramchandra V Amnekar[1, 2] and Sanjay Gupta[1, 2]*

1 Epigenetics and Chromatin Biology Group, Gupta Laboratory, Cancer Research Centre, Advanced Centre for Treatment Research and Education in Cancer, Tata Memorial Centre, Kharghar, Navi Mumbai, MH, 410210, India
2 Homi Bhabha National Institute, Training School Complex, Anushakti Nagar, Mumbai, MH, 400085, India

***Corresponding author:** Sanjay Gupta

sgupta@actrec.gov.in

Homi Bhabha National Institute, Training School Complex, Anushakti Nagar, Mumbai, MH, 400085, India.

Citation: Amnekar RV, Gupta S (2018) HDAC Inhibitors in Solid Tumors: An Incomplete Story. J Clin Epigenet Vol.4 No.2:8

Received: March 19, 2018; **Accepted:** March 22, 2018; **Published:** March 26, 2018

In the Field of Observation, Chances Favor the Prepared Minds – Louis Pasteur

With the vast experience of the last several decades, now it has become clear that epigenetic changes like post-translational histone modifications (PTMs) define the hallmarks of cancer. Histone acetylation, a well-studied PTM in cancer, is controlled by the opposing activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs) [1]. In 1971, Charlotte Friend's serendipitous voyage to decipher the mechanism of DMSO induced erythroid differentiation in murine erythroblastic leukemia, paved the way for development of SAHA: a potent inhibitor of cell proliferation and inducer of cell death. By 1998, HDACs were found to be the target of SAHA and by 2006 FDA approved SAHA (Vorinostat) for the treatment of cutaneous T cell lymphoma, making it one of the first generation epi-drug along with 5'-azacytidine. HDAC's are NAD^+ or Zn^{2+} dependent enzymes catalyzing deacetylation of histones and non-histone proteins. Depending on their substrate specificity and cellular localization they have been classified under four classes [2].

Acetylation of histones on cis-acting regulatory elements like enhancer and promoters and the associated chromatin changes is at the heart of transcription and gene reprogramming. The prognostic utility of site specific histone acetylations *viz* H3K9ac, H3K18ac, H4K12ac, H4K16ac has been demonstrated through their correlation with clinicopathological parameters in case of breast, lung, prostate and gastric cancer [3]. This hypoacetylation could be an outcome of decreased levels of HATs or inactivation as in case of hMOF or conversely an increase in HDAC's or HDAC activity [4]. Infact, increased Class I and Class II HDACs has been demonstrated to be an indicator in case of colon, pancreatic, gastric and ovarian cancers for tumor aggressiveness, impact on survival, invasive potential and dedifferentiated state of tumors [5].

Epigenetic processes being reversible, epi-drugs like HDACi are envisaged as the new arsenal to combat the altered epigenome and gene expression in cancer. The effects of HDACi may range from hyperacetylation of histones/non-histone proteins to re-expression of tumor suppressors like p21, p16 leading to apoptosis or cell cycle arrest or by induction of differentiation as in case of chondrosarcomas [6] and colon cancer cells [7]. Today, pan HDAC inhibitors like Vorinostat and Romidepsin have shown promising results as single agents in hematological malignancies and also in cell line studies on breast, prostate and gastric cancers [8]. However, the translation of these *in vitro* and pre-clinical studies into clinics in case of solid tumors has been abortive owing to their ineffectiveness and toxicities involved. This warrants the need to investigate the confounding factors.

Pleiotropic function of HDAC's in different physiological processes warrants the use of selective inhibitors, minimizing off target effect. This has been a major concern for the FDA approved HDACi which cannot discriminate between the different classes of HDACs. Further, the trials carried out during the last few decades are on terminally ill patients or patient who has received prior chemotherapy, thus having less tolerability to epi-drugs. Also, trials failed to sub-categorize the patients on the basis of their HDAC or the histone acetylation status. This need of patient stratification is further supported by the fact that colon and endometrial cells with inactivating HDAC1 mutation failed to respond to TSA treatment [9]. In 2008, Weichert et al. conducted a retrospective analysis in a 143 patient training cohort and 150 patient validation cohort, wherein expression of Class I HDACs was evaluated for gastric cancer. Around 78% and 65% patients in the training and validation cohort showed high expression of either all three or one of the Class I HDACs respectively. Further,

this high expression co-related with lymph node metastasis and poor survival of patients. It would be imperative to consider the high HDAC expression group for HDACi treatment, rather considering all patients [10]. Thus, efforts should be envisaged in selecting the right targetable tumors as HDACi might be useful only in those tumors where HDAC's are the key players in pathogenesis.

The outcome of HDACi treatment is also dependent on the levels of thioredoxin (TRX) gene or other ROS scavenging agents like superoxide dismutase. HDACi treatment is associated with increased reactive oxygen species specifically in tumor cells. This has been attributed to the biased role of HDACi, wherein they induces expression of TRX gene in normal cells, mitigating the increased ROS generated. However, in tumor cells they induce the expression of TRX binding protein: a negative regulator of TRX, making tumor cells susceptible to ROS mediated cell death [11]. A high level of TRX or other ROS scavenging agents like superoxide dismutase which is observed in certain cancer may predispose the tumor to HDACi resistance [11]. Thus, additional determinants need to be studied and validated before stratification.

Besides patient stratification, modulating the chromatin architecture by HDACs to increase the binding affinity of chemotherapeutic drug is another rational approach. Cancer cells in general are hypo-acetylated with condensed chromatin and hence refractile to DNA damaging agent, thus demanding a high dosage which in real scenario is not well tolerated. Combination of HDAC inhibitors with platin-based chemotherapeutic drugs have been successfully validated in breast, gastric and lung cancer cell lines [12-14]. This would demand low doses of the drugs making therapy more effective and well tolerable.

If stratification is requisite than novel and non-invasive diagnostic methods to monitor the levels of HDACs is necessary. Recently, we have demonstrated the utility of serum based diagnosis of HDAC levels in cancer patients of various types [15]. So the story is yet to be complete and there is no need to despair. A holistic approach is what today's prepared minds (our clinicians and researchers) need to take to make HDAC inhibitors for solid tumor treatment a success. This would involve integration across the tier right from diagnosis for patient stratification; to judicial selection of HDAC inhibitors in a combinatorial fashion with local administration would be effective way to cross the barrier.

References

1 Cohen I, Poręba E, Kamieniarz K, Schneider R (2011) Histone modifiers in cancer: Friends or foes. Genes Cancer 2: 631-647.

2 Marks PA, Breslow R (2007) Dimethyl sulfoxide to vorinostat: Development of this histone deacetylase inhibitor as an anticancer drug. Nat Biotechnol 25: 84-90.

3 Khan SA, Reddy D, Gupta S (2015) Global histone post-translational modifications and cancer: Biomarkers for diagnosis, prognosis and treatment. World J Biol Chem 6: 333-345.

4 Wang Y, Zhang R, Wu D, Lu Z, Sun W, et al. (2013) Epigenetic change in kidney tumor: Downregulation of histone acetyltransferas MYST1 in human renal cell carcinoma. J Exp Clin Cancer Res 32: 8.

5 Moradzadeh M, Tabarraei A, Sadeghnia HR (2015) The role of histone deacetylase (HDAC) as a biomarker in cancer. J Mol Biomark Diagn 5: 240.

6 Sakimura R, Tanaka K, Yamamoto S, Matsunobu T, Li X, Hanada M et al. (2007) Epigenetic change in kidney tumor: Downregulation of histone acetyltransferase MYST1 in human renal cell carcinoma. The effects of histone deacetylase inhibitors on the induction of differentiation in chondrosarcoma cells. Clin Cancer Res 32: 8.

7 Lea MA, Ibeh C, Shah N, Moyer MP (2007) Induction of differentiation of colon cancer cells by combined inhibition of kinases and histone deacetylase. Anticancer Res 27: 741-748.

8 Nervi C, De Marinis E, Codacci-Pisanelli G (2015) Epigenetic treatment of solid tumours: A review of clinical trials. Clinical Epigenetics 7: 127.

9 Ropero S, Fraga MF, Ballestar E, Hamelin R, Yamamoto H, et al. (2006) A truncating mutation of HDAC2 in human cancersconfers resistance to histone deacetylase inhibition. Nat Genet 38: 566-569.

10 Weichert W, Röske A, Gekeler V, Beckers T, Ebert MP, et al. (2008) Association of patterns of class I histone deacetylase expression with patient prognosis in gastric cancer: A retrospective analysis. Lancet Oncol 9: 139-148.

11 Marks PA (2006) Thioredoxin in cancer -Role of histone deaceylase inhibitors. Semin Cancer Biol 16: 436-443.

12 Wawruszak A, Luszczki JJ, Grabarska A, Gumbarewicz E, Dmoszynska-Graniczka M, et al. (2015) Assessment of interactions between cisplatin and two histone deacetylase inhibitors in MCF7, T47D and MDA-MB-231 human breast cancer cell lines: An isobolographic analysis. PLoS One 10: e0143013.

13 Mutze K, Langer R, Becker K, Ott K, Novotny A, et al. (2010) Histone deacetylase (HDAC) 1 and 2 expression and chemotherapy in gastric cancer. Ann Surg Oncol 17: 3336-3343.

14 To KK, Tong WS, Fu LW (2017) Reversal of platinum drug resistance by the histone deacetylase inhibitor belinostat. Lung Cancer 103: 58-65.

15 Reddy D, Khade B, Pandya R, Gupta S (2017) A novel method for isolation of histones from serum and its implications in therapeutics and prognosis of solid tumours. Clin Epigenetics 9: 30.