H3K18Ac as a Biomarker in Cancer Progression

Subjects: Oncology

Contributor: Anna Wawruszak , Marta Hałasa , Małgorzata Guz , Joanna Kałafut , Andrzej Stepulak , Marek Cybulski ,

Acetylation and deacetylation are posttranslational modifications (PTMs) which affect the regulation of chromatin structure and its remodeling. Acetylation of histone 3 at lysine placed on position 18 (H3K18Ac) plays an important role in driving progression of many types of cancer, including breast, colon, lung, hepatocellular, pancreatic, prostate, and thyroid cancer.

H3K18Ac cancer cells

1. Prostate Cancer

Microarray-based comparative analysis of HAT activity in the hormone-sensitive (HS) prostate cancer cell line (LNCaP) and its castrate-resistant (CR) daughter cell line (C4−2) has revealed increased HAT activity against specific histone sites of H3 in the CR cell line compared to its HS equivalent [1]. The progression of HS to CR is accompanied by histone H3 lysine 18 (H3K18) hyperacetylation, upregulation of p300 activity, and downregulation of SIRT2 protein expression. These findings suggest that enhanced HAT activity in C4-2 cells can be assigned to activated, acetylated p300, and that SIRT2 regulates the acetylation level of the activated acetyl-p300 form [1]. The expression of histone H3K18Ac acetylation, and proteins that regulate its acetylation (P300) and deacetylation (SIRT2), has been evaluated in benign prostatic hyperplasia (BPH), high grade prostatic intraepithelial neoplasia (HGPIN), prostate cancer (PCa), and metastases [2]. The levels of H3K18Ac were found to be higher in primary cancers and metastases compared to benign tissues and increased H3K18Ac identified patients at increased risk of PCa recurrence. Moreover, downregulation of P300 protein expression in PCa and metastases and a progressive loss of SIRT2 compared to benign, malignant, and metastatic tissues has been observed. Analysis of genomic and clinical data in The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) has revealed that the HAT P300 and its target H3K18Ac increase during prostate cancer progression, while the HDAC SIRT2 decreases. Gain of H3K18Ac and loss of SIRT2 reflect P300 mediated hyperacetylation, and their determination may help identify patients likely to benefit from therapy with HAT inhibitors [2]. It has been demonstrated that SIRT7 plays a vital role in the aggressiveness of prostate cancer, meaning it is a promising predictive marker for aggressive prostate cancer [3]. SIRT7 levels have been found to be elevated in tumors and positively associated with the tumor grade. The knock down of SIRT7 inhibits the migration of two androgen-independent prostate cancer cells (DU145 and PC3), although the overexpression of the native protein, but not the mutated form, promotes cell migration and invasion of the poorly aggressive, androgen-dependent LNCaP cell line.

SIRT7 overexpression induces resistance of cells to docetaxel, which indicates that SIRT7 deacetylase activity is associated with resistance to chemotherapy [3].

2. Pancreatic Cancer

The influence of acetylation and deacetylation, which regulates the expression of oncogenes and tumor suppressor genes, on pancreatic carcinogenesis is not well known. It has been shown [4]. that low expression of H3K18 acetylation in patients with stage I and II pancreatic adenocarcinomas is an independent predictor of poor survival. In contrast to other research [5], high H3K18Ac expression in pancreatic cancer has been found to be an independent prognostic factor for poorer survival, and H3K18Ac expression is lower in nonmalignant tissues compared to the primary tumors and metastases [5].

3. Colon Cancer

Expression of H4K12Ac and HDAC2, but not H3K18Ac, has been found to rise from normal tissue through adenoma to moderately and well-differentiated colorectal carcinoma (CRC), suggesting that HDAC2 and H4K12Ac together may play a role in the progression of colon cancer. Additionally, HDAC2 has the diagnostic power to differentiate between cancer and non-cancer diagnosis. The acetylation of H4K12 and H3K18 is decreased in poorly differentiated compared to moderately and well differentiated cancer cells [6]. Selective agents are being sought that might target abnormal patterns of histone modification as a means of destroying cancer cells. The differentiation status of cancer cells is important in regard to chromatin modification, and, hence, further studies will expand the current work using wide-genome array-based techniques to investigate histone modification and HDAC2 expression in colorectal adenoma and CRCs with different levels of differentiation. The results to date are encouraging because they demonstrate that aberrant expression of HDAC2 frequently occurs in patients with CRC, providing potential biomarkers for use in future clinical trials. Another study performed on colon cancer has demonstrated that GPR109A, the receptor for short-chain fatty acids, functions as a tumor inhibitor in CRC, and the IFNγ can be used to activate GPR109A transcription silenced by DNA methylation. The treatment of tumor cells with IFNγ removes the silencing of GPR109A without changing the methylation of its promoter, suggesting that histone acetylation may be critical in the IFNγ-induced expression of GPR109A. It has been discovered that IFNγ rapidly activates pSTAT1, which binds to the p300 promoter to activate its transcription, upon which p300 binds to the GPR109A promoter to induce H3K18 hyperacetylation, resulting in activation of GPR109 transcription. This study has shown that the IFNγ-producing cells of the host immune system counteract the silencing of GPR109A mediated by DNA methylation to suppress cancer development [7].

4. Breast Cancer

It is known that specific marks such as H3K18Ac are associated with transcriptionally active gene promoters. It has been discovered that most breast tumors score low for H4K16Ac, whereas H3K18ac and H4K20Me3 are expressed at relatively high levels. Low levels of H3K18Ac are associated with high tumor grade, and high

expression of histone modifications is correlated with cancers positive for steroid receptors (androgen receptor, estrogen receptor, and progesterone receptor), increased expression of E-cadherin and BRCA1, and low p53 and HER-2 expressions. These findings may explain the poor prognosis of breast cancer patients with low levels of histone modifications and underline the biological importance of histone modifications. Indeed, decreased levels of histone modifications have been correlated with an unfavorable patient outcome, and the increased level of H3K18Ac detection has been associated with more advantageous breast cancer-specific survival (BCSS), longer disease-free survival (DFS), and metastatic-specific survival (MSS). Importantly, multivariate analysis has shown that the H3K18ac level is independent of other key prognostic factors including tumor size, histologic grade, and lymph node stage, with respect to BCSS and DFS. However, the correlations between histone modifications and patient outcome have been seen to be diminished in patients treated with hormonal therapy or chemotherapy. Nonetheless, this research supports the evidence that global hypoacetylation of H3K18 is demonstrative of cell transformation and may be a crucial prognostic marker in breast cancer [8].

5. Hepatocellular Carcinoma

It has been reported that SIRT7 has a high selectivity for acetylated H3K18 and that it supports malignant phenotype. It has been observed that HBx oncoprotein of hepatitis B virus (HBV) stabilizes SIRT7 and stimulates H3K18 deacetylation, and depletion of SIRT7 decreases cell viability and transformation. These findings show that SIRT7 is an important regulator of HBx-driven oncogenic transformation [9]. In other research, high expressions of SIRT7 and H3K18Ac in hepatocellular carcinoma (HCC) were associated with worse patient overall survival (OS), and H3K18Ac levels turned out to be an independent prognostic factor in multivariate analysis. SIRT7 expression and higher H3K18ac levels were observed in HCC cells compared to non-tumor hepatocytes, and SIRT7 expression was weakly correlated with H3K18Ac. These results suggest that other mechanisms may be involved in deacetylation of H3K18Ac in HCC [10]. Another study [11] has shown that up-regulation of the acetylation of histone 3 at the maternally expressed 3 (Meg3) differentially methylated region (DMR) increases the level of miR-376a that contributes to the development of HCC. Interestingly, HDAC9, a histone deacetylase responsible for H3K18 deacetylation, was established as the target of miR-376a, and its inhibition was found to increase the expression of miR-376a by up-regulating the global histone H3K18Ac. Finally, both miR-376a and HDAC9 were inversely correlated in HCC [11].

6. Lung Cancer

It has been demonstrated [12] that overexpression of inhibitor of growth 5 (ING5) leads to p300 HAT activation and increased acetylation of p300 target proteins (p53 at K382 and H3 at K18) in the human NSCLC A549 cell line. C646, a specific p300 HAT inhibitor, has been found to reduce ING5-induced acetylation of p53K382 and H3K18 and subsequent expression of Bax and p21 proteins. These findings suggest that ING5 functions as a tumor suppressor by regulating expression of many genes through specific lysine acetylation and that it inhibits invasiveness of lung cancer cells [12].

7. Thyroid Cancer

It has been shown [13] that levels of H3K9-K14Ac are higher in thyroid follicular adenomas and carcinomas (papillary, follicular, and undifferentiated) than in normal tissues. Similarly, acetylated H3K18 levels have been found to increase in adenomas and cancers (except undifferentiated tumors) compared to normal tissues, indicating that reduction of H3K18Ac may play a role during thyroid cancer progression. The induction of RAS, BRAF, and RET–PTC oncogenes that are typically activated in thyroid cancers leads to an increase in either H3K9–K14ac or H3K18ac levels in rat thyroid cell lines. Moreover, thyroid stimulating hormone (TSH) increases levels of H3K18Ac in non-tumorigenic FRTL-5 rat thyroid cells, showing that hormonal stimulation and oncogene activation in the course of neoplastic transformation can modify levels of histone acetylation in thyroid cells [13].

References

1. Lee, J.-H.; Yang, B.; Lindahl, A.J.; Damaschke, N.; Boersma, M.D.; Huang, W.; Corey, E.; Jarrard, D.F.; Denu, J.M. Identifying Dysregulated Epigenetic Enzyme Activity in Castrate-Resistant Prostate Cancer Development. ACS Chem. Biol. 2017, 12, 2804–2814.
2. Damodaran, S.; Damaschke, N.; Gawdzik, J.; Yang, B.; Shi, C.; Allen, G.O.; Huang, W.; Denu, J.; Jarrard, D. Dysregulation of Sirtuin 2 (SIRT2) and histone H3K18 acetylation pathways associates with adverse prostate cancer outcomes. BMC Cancer 2017, 17, 874.
3. Haider, R.; Massa, F.; Kaminski, L.; Clavel, S.; Djabari, Z.; Robert, G.; Laurent, K.; Michiels, J.-F.; Durand, M.; Ricci, J.-E.; et al. Sirtuin 7: A new marker of aggressiveness in prostate cancer. Oncotarget 2017, 8, 77309–77316.
4. Manuyakorn, A.; Paulus, R.; Farrell, J.; Dawson, N.A.; Tze, S.; Cheung-Lau, G.; Hines, O.J.; Reber, H.; Seligson, D.B.; Horvath, S.; et al. Cellular histone modification patterns predict prognosis and treatment response in resectable pancreatic adenocarcinoma: Results from RTOG 9704. J. Clin. Oncol. 2010, 28, 1358–1365.
5. Juliano, C.N.; Izetti, P.; Pereira, M.P.; dos Santos, A.P.; Bravosi, C.P.; Abujamra, A.L.; Prolla, P.A.; Osvaldt, A.B.; Edelweiss, M.I.A. H4K12 and H3K18 Acetylation Associates With Poor Prognosis in Pancreatic Cancer. Appl. Immunohistochem. Mol. Morphol. 2016, 24, 337–344.
6. Ashktorab, H.; Belgrave, K.; Hosseinkhah, F.; Brim, H.; Nouraie, M.; Takkikto, M.; Hewitt, S.; Lee, E.L.; Dashwood, R.H.; Smoot, D. Global Histone H4 Acetylation and HDAC2 Expression in Colon Adenoma and Carcinoma. Dig. Dis. Sci. 2009, 54, 2109–2117.
7. Bardhan, K.; Paschall, A.V.; Yang, D.; Chen, M.R.; Simon, P.S.; Bhutia, Y.D.; Martin, P.M.; Thangaraju, M.; Browning, D.D.; Ganapathy, V.; et al. IFN Induces DNA Methylation-Silenced GPR109A Expression via pSTAT1/p300 and H3K18 Acetylation in Colon Cancer. Cancer Immunol. Res. 2015, 3, 795–805.

8. Elsheikh, S.E.; Green, A.R.; Rakha, E.A.; Powe, D.G.; Ahmed, R.A.; Collins, H.M.; Soria, D.; Garibaldi, J.M.; Paish, C.E.; Ammar, A.A.; et al. Global Histone Modifications in Breast Cancer Correlate with Tumor Phenotypes, Prognostic Factors, and Patient Outcome. Cancer Res. 2009, 69, 3802–3809.
9. Pandey, V.; Kumar, V. Stabilization of SIRT7 deacetylase by viral oncoprotein HBx leads to inhibition of growth restrictive RPS7 gene and facilitates cellular transformation. Sci. Rep. 2015, 5, 14806.
10. Lee, H.S.; Jung, W.; Lee, E.; Chang, H.; Choi, J.H.; Kim, H.G.; Kim, A.; Kim, B. SIRT7, H3K18ac, and ELK4 Immunohistochemical Expression in Hepatocellular Carcinoma. J. Pathol. Transl. Med. 2016, 50, 337–344.
11. Zheng, Y.; Chen, H.; Yin, M.; Ye, X.; Chen, G.; Zhou, X.; Yin, L.; Zhang, C.; Ding, B. MiR-376a and Histone Deacetylation 9 Form A Regulatory Circuitry in Hepatocellular Carcinoma. Cell. Physiol. Biochem. 2015, 35, 729–739.
12. Zhang, T.; Meng, J.; Liu, X.; Zhang, X.; Peng, X.; Cheng, Z.; Zhang, F. ING5 differentially regulates protein lysine acetylation and promotes p300 autoacetylation. Oncotarget 2018, 9, 1617–1629.
13. Puppin, C.; Passon, N.; Lavarone, E.; Di Loreto, C.; Frasca, F.; Vella, V.; Vigneri, R.; Damante, G. Levels of histone acetylation in thyroid tumors. Biochem. Biophys. Res. Commun. 2011, 411, 679–683.