Review

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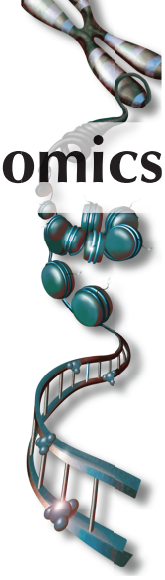
Epigenomics



The bitter side of epigenetics: variability and resistance to chemotherapy

Nabil Hajji*[,1], Daniel J García-Domínguez[2], Lourdes Hontecillas-Prieto[2], Kevin O'Neill[1], Enrique de Álava[2] & Nelofer Syed[1]

[1]The John Fulcher Molecular Neuro-Oncology Laboratory, Division of Brain Sciences, Imperial College London, London, UK

[2]Institute of Biomedicine of Seville (IbiS), Virgen del Rocío University Hospital/CSIC/University of Seville/CIBERONC, Spain

*Author for correspondence: n.hajji@imperial.ac.uk

One of the major obstacles to the development of effective new cancer treatments and the main factor for the increasing number of clinical trial failures appears to be the paucity of accurate, reproducible and robust drug resistance testing methods. Most research assessing the resistance of cancers to chemotherapy has concentrated on genetic-based molecular mechanisms, while the role of epigenetics in drug resistance has been generally overlooked. This is rather surprising given that an increasing body of evidence pointing to the fact that epigenetic mechanism alterations appear to play a pivotal role in cancer initiation, progression and development of chemoresistance. This resulted in a series of clinical trials involving epi-drug as single treatment or combined with cancer conventional drugs. In this review, we provided the main mechanisms by which the epigenetic regulators control the resistance to cancer drugs.

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Histone deacetylases expression contributes to cancer development & drug resistance

Histone lysine modifications directly influence activation and repression of transcription and are also essential for higher chromatin order structure; depending on which residue is modified and at what position in the gene such a residue is located [1]. Histone deacetylases (HDAC) and histone acetyltransferases (HAT) control the acetylation state of lysine residues, including those situated in the N-terminal 'tails' of the histones [2]. HATs fulfill simultaneously the function of transcription coactivators, while HDACs are co-repressors [3]. Overall, post-translational modifications of histones create an epigenetic mechanism for the regulation of a variety of normal and disease-related processes. Histone modification patterns based on acetylated H3 Lysine K18 can predict the risk of tumor recurrence for cancer [2] and global hypoacetylation of H4K12 is considered to be informative of tumor stage [4]. Furthermore, increased global histone H3 lysine 4 trimethylation (Me_3-K4 H3) and histone H3 serine 10 phosphorylation (P-S10 H3) were observed accompanying development of the resistance phenotype [5]. Interestingly, we and others found that the global loss of H4K16 acetylation can be used as a hallmark for multidrug resistant cancer cells [6]. Moreover, the loss of H4K16 acetylation together with H4K20 trimethylation has been suggested also to be common hallmarks of cancer cells [4].

Aberrant expression patterns of HDACs are implicated in a number of cancers, for example, SIRT1 (HDAC Class III), and it is consistently up-regulated in malignant cells or tissues from patients with leukemia, glioblastoma, prostate, colorectal or pancreatic cancer and is the only HDAC that is significantly overexpressed in leukemia lymphoblasts as compared with normal lymphoblasts [7]. We recently showed that the reduction in HDAC2 expression level plays an essential role in *in vitro* and *in vivo* cancer response to DNA-damaging agents alone or combined with HDAC inhibitors [8]. Furthermore, sustained-suppression of HDAC2 in lung cancer results in regression of tumor cell growth and activation of cellular apoptosis via p53 and Bax activation and Bcl2 suppression [9].

Increasing number of studies that have reported that specific inhibition of certain HDACs (e.g., Sirt1) leads to down-regulation of multidrug resistance protein 1 (MDR1) [10] and promotes cell death by acetylating the DNA-damage-protecting protein NBS1 [11]. In light of this, we showed that hMOF (HAT) and SIRT1 (HDAC)

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Table 1. Major epigenetic changes in cancer that play important role in drug resistance.

Alterations	Major regulator	Principal mechanism of drugs resistance		Ref.
		Targets genes	Alteration of biological processes	
Histones post-translational modifications	Histone acetyltransferase			
	– hMOF	– H4K16 acetylation and NRF2	– Sensitization of multidrug-resistant cancer cells	[6,12]
	– CBP/P300	– *ZEB1*	– Resistance to chemotherapeutic agents	[13]
	– HAT1	– Glucose metabolism genes: *LDHA*, *GLUT1*, *PKM2* and *FBP1*	– Cisplatin resistance	[14]
	– TIP60	– *MDR1*/ *BMI1*	– Cisplatin cross-resistance acquisition	[15]
	Histone deacetylase			
	– HDAC1, HDAC2	– *YKL*-40	– Deregulation of NF-kB	[16]
	– HDAC2	– *p53*, *Bax* and *Bcl2*	– Apoptosis	[9]
	– Sirt1	– *MDR1* and *NBS1*	– Cell death	[10,11]
	– HDAC3	– *p53*, *Bax* and *Bcl2*	– Proliferation, invasion and increases drug-resistance	[17]
	– HDAC1	– NA	– Resistance to proteasome inhibitors	[18]
	– HDAC1, 3, 6 and 8	– *ABCG2*	– Multidrug-resistant phenotype	[5]
	Histone methyltransferases			
	– EZH2	– HOX genes (*HOXB7* and *HOXA9*)	– Increase drug-resistance	[19]
	– G9a	– *IL8*/*CXCR1*/2	– Autocrine stimulation to increase drug resistance	[20]
	– NSD2	– Hexokinase 2 and glucose-6-phosphate dehydrogenase	– Glycolysis and the pentose phosphate pathway activation	[21]
	– MLL1	– *MDR1*	– Multidrug-resistant phenotype	[22]
	– EHMT1/EHMT2	– *PARP* cleavage and *procaspase*-3	– Apoptosis	[23]
	Histone demethylases			
	– JARID1B	– Mitochondrial ATP-synthase	– Mitochondrial respiratory chain and oxidative energy metabolism	[24]
	– KDM1	– *PELP1*/*ER*	– Endocrine therapy-resistant	[25]
	– KDM3B	– *MAGEA1* and *ANGPT1* among others	– Relapse and developing drug resistance	[26]
	– KDM5A	– *p21* and *BAK1*	– Apoptotic cell death	[27]
DNA methylation modifications	Hypermethylation	– Silencing of tumor suppressors: *E-cadherin*, *pRB*, *P53*, *PTEN*, *BRCA1*, *BRCA2*, *P16* and *CDKN2A*	– Tumorigenesis induction, cell-cycle- deregulation and apoptosis inhibition	[28,29]
		– Inhibition of negative regulators of drugs resistance genes: miRN-129–5p	– Transporter efflux pumps	[30]
		– Repression of *AR* gene	– Resistance to androgen deprivation therapy in prostate cancer	[31]
	Hypomethylation	– Disrupt X-chromose imprinting in *IGF2* locus	– Promote growth and anti-apoptosis in an autocrine manner	[32,33]
		– Increasing genomic instability: *p53* mutation enhances genomic instability	– Mitotic recombination, deletion and translocations, chromosomal rearrangements	[29,34]
		– Activating proto-oncogenes	– Carcinogenesis induction	[35]
		– Overexpression of the multi-drug resistance genes: *MDR1* and other ABC transporters	– Transporter efflux pumps	[36,37]
	Combination of hyper- and hypomethylation alterations	– Hypomethylation of the sulfatase 2 and hypermethylation of estrogen receptor α gene	– Loss of estrogen responsiveness: apoptosis and cell–cell contact deregulations	[38]
miRNAs	– miR-21	– *BCL2*	– Apoptosis (cisplatin)	[39]
	– miR-125b	– *E2F3*	– Cell proliferation and apoptosis (5-fluorouracil)	[40]
	– miR-425-5p	– *PDCD10*	– Cell death (5-fluorouracil and oxaliplatin)	[41]
	– miR-484	– Cytidine deaminase	– Cell proliferation and cell cycle (gemcitabine)	[42]
	– miR-193a-3p	– *ING5*	– DNA damage response pathway (paclitaxel)	[43]
Crosstalk	– DNA methylation provides a platform for methyl-binding proteins	– *MBD1*, *MBD2*, *MBD3*, and *MeCP2*	– Recruiting histone-modifying enzymes to coordinate chromatin dynamics	[44]
	– Hypermethylation of miR-129–5p	– ABC transporters	– Transporter efflux pumps (5-fluorouracil, vincristine and cisplatin)	[30]
	– miR-193a-3p methylation	– *SRSF2*	– Oxidative stress pathway (5-fluorouracil)	[45]

MiRNA: MicroRNA.

expression levels are critical parameters in HDAC inhibitor-mediated sensitization of multidrug-resistant NSCLC and neuroblastoma cancer cells to topoisomerase II inhibitor and increased chromatin relaxation through the global H4K16 acetylation [6]. The results of this study provide a mechanism and justify the ongoing clinical trials on neuroectodermal tumors using combined treatment (VPA) HDACi class I and VP16 (www.clinicaltrials.gov). More HDACs and HTs have been identified in different types of cancer to play important role in drug resistance (Table 1).

The alteration of these histone-modifying enzymes expression involves the regulation of crucial drug response genes and subsequently induces alteration of key biological process that controls cancer sensitivity (Table 1).

The overexpression of certain HDACs in cancer cells is implicated in genotoxic insult protection, silencing of tumor suppressor genes, alteration of DNA repair pathways, and increased resistance to DNA-damaging agents by the activation of nonhistone proteins that are required for DNA stability [46]. For instance, SIRT1 plays a vital role in maintaining genomic integrity by deacetylating the excision DNA repair protein APE1 [46]. It has been shown that, increased deacetylation of APE1 by SIRT1 during genotoxic stress increases efficiency repair of APE1. However, APE1's acetylation by p300 impaired MDR1 activation and sensitizes the cells to cisplatin or etoposide [47].

These outcomes are to a large extent cell-type specific and have raised the potential that the HDACis may represent a promising new class of antineoplastic agents which may reverse chemo-resistance and stratify patients according to potential for chemoresponse in cancer.

HDAC inhibitors have been shown to be effective therapeutic anticancer agents via multiple mechanisms, inducing cell-cycle arrest, intrinsic and extrinsic apoptotic mechanisms, mitotic cell death, autophagic cell death, reactive oxygen species, inhibiting angiogenesis and improving NK cell-mediated tumor immunity [48]. These diverse effects on cancer cells make HDAC inhibitors attractive agents not only for monotherapy but also for combination therapy with other anticancer modalities. HDACis can modulate cellular responses to cancer conventional treatment. Although many combination strategies have been shown to be both effective and synergistic, the exact mechanism(s) for this synergy are poorly understood and likely different according to the combination regimen utilized [6].

DNA methylation & drug resistance

Another epigenetic mechanism that has been shown to be associated with drug resistance is the covalent modification that occurs by the addition of methyl group at the 5-carbon of cytosine in a DNA CpG dinucleotide and catalyzed by DNA methyltransferases (DNMTs) enzyme. Genomic DNA sequencing analysis has shown elevated rates of abnormal CpG promoter methylation (5–10%) in several types of cancer [35]. There are three fundamental associations between drug resistance and DNA methylation status; drug resistance associated with hypo or hypermethylated genes, cellular heterogeneity and induction of tumor cells sensitivity through adjuvant treatments (Table 1).

The main DNA methylation alteration associated with drug resistance is the hypermethylation of the CpG islands on gene promoters of certain genes. This contributes for instance, to carcinogenesis through silencing of tumor suppressor genes (e.g., E-*cadherin*, *pRB*, *P53*, and *CDKN2A*) [28]. Cancer cells are proficient in silencing tumor suppressor genes by hypermethylation and subsequently increases tumor cell proliferation and survival. For instance, the tumor suppressor gene *TP53* is considered as veritable 'Swiss Army knife' of cellular regulation and one of the major regulators of apoptosis in response to chemotherapy. It is well known that silenced *TP53* expression in cancer by hypermethylation renders it nonfunctional and drug resistance can follow as a consequence of evading apoptosis.

The hypermethylated androgen receptor gene promoter causes resistance to anti-androgens in prostate cancer (CaP) [31]. Hypermethylated promoters in *MLH1*, *WTH3* and *BMP6* genes are also involved in breast adenocarcinoma drug resistance [38]. Furthermore, the hypermethylation of *C22orf2* and *BCL2*-like 11 promoters by DNMT1 reduced their expression and subsequently contributed to resistance to tyrosine-kinase inhibitors in chronic myeloid leukemia [49].

On the other hand, a global DNA hypomethylation in cancer targets diverse genomic sequences, including repetitive elements, transposons, intronic CpG dinucleotides, and gene deserts, increasing genomic instability and activating proto-oncogenes [28]. DNA hypomethylation may also be involved in anticancer drug resistance, which leads to an accumulation of the multidrug resistance genes as *MDR1* in breast cancer or in oral squamous cell carcinoma (cisplatin resistance inductor) [28]. Glioma tumor cells resistant to conventional drugs showed a significant DNA hypomethylation compared with their counterpart nonresistant tumor cells *in vitro* [50]. Besides, drug resistance could be driven by the combination of hyper- and hypomethylation alterations depending where the alteration of DNA methylation occurs. For instance, the *sulfatase2* precursor gene hypomethylation and the hypermethylation of *estrogen receptor* α gene induced loss of estrogen responsiveness by estrogen metabolism deregulation in MCF-7 drug-resistant cells [38].

DNA methylation modulators have shown to sensitize the multidrug-resistant tumor cells to conventional treatment. For instance, increased global methylation level was reduced in recurrent cases of colorectal cancer by utiliizing 5-aza-2′-deoxycytidine that restores colorectal cancer sensitivity to 5-FU [51]. Furthermore, this demethylating agent

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has been used in ovarian cancer to overcome acquired resistance to carboplatin [52]. In addition, demethylation agent also restored the sensitivity to cisplatin, taxol, and oxaliplatin in cervical cancer [53]. However, the use of DNA methylation regulation agents could activate unwanted genes, including new drug resistance genes and others that induce tumor progression.

MicroRNA & drug resistance in cancer

MicroRNAs (miRNAs) are small noncoding RNAs (19–25 nucleotides in length) implicated in most physiological processes and are tightly related with several diseases, including cancer [54]. The first evidence of a correlation between miRNAs and cancer was reported in 2002. Calin *et al.*, describe deletions and down-regulation of miR-15a and miR-16-1 in approximatively 68% of chronic lymphocytic leukemia patients [55]. After these initial observations, miRNAs have been shown to play an important role during tumorogenesis, act as either tumor suppressors or oncogenes depending on the cellular context and the expression of the miRNA targets in the concrete malignant tissues [56]. The involvement of miRNAs in resistance to anticancer drugs is emerging field. Several studies indicate that a significant changes in miRNA expression profiles occur in drug-resistant cancer cells in comparison with parental drug-sensitive cancer cells [57] and other studies shown that the alteration of specific miRNAs expression, such as miR-21, miR-221/222, miRNA let-7 family, are responsible for drug resistance in tumor cells [39]. One of the most important links between miRNA function and cancer drug resistance is represented by the effect on the expression of tumor suppressor genes. Those miRNAs are considered as oncogenes and usually promote tumor development by inhibiting tumor suppressor genes and/or genes that control cell differentiation or apoptosis [58].

Many reported research findings showed that certain miRNA influence cancer chemoresistance and the difference in their expression occurs simultaneously rather than by an individual chemoresistance miRNA mechanism (Table 1). In recent years, researchers linked miRNA dysregulated expression with different cellular pathways that are directly influencing tumor chemoresistance. MiRNAs activity affects apoptotic pathway, proliferation response to DNA damage, and regulation of multidrug resistance genes [41–43]. The complexity of understanding miRNA regulation in cancer is due to the high number of target genes that can be regulated by one single miRNA as predicted by bioinformatics analysis. Additionally, by the fact that that each cell type of cancer may be defined by a unique set of miRNAs that controls drug resistance.

Epigenetic mechanisms crosstalk in cancer drug resistance

The heterogeneity of epigenetic regulation mechanisms defines a disease spectrum in many tumors. This has increased cancer complexity and altered our understanding of tumor behavior. However, the heterogeneity provides the implication for epi-drugs and multimodality treatment programs.

It has been demonstrated that epigenetic abnormalities have an important role in the plasticity of cell states during tumorigenesis and this could lead to acquired drug resistance. Reversible states of cells that survive to chemotherapeutic drugs exposure may drive multistep epigenetic fixation of gene expression changes during the acquisition of drug resistance [59]. Heterogeneity in a tumor cell population, based on dynamic variation in epigenome configurations, is thought to provide a nongenetic variance source for selection of drug-resistant cells [60].

The mainstream of epigenetic and drug resistance in cancer research field stresses the importance of individual epigenetic mechanisms. However, the interaction between different regulators of epigenetic mechanisms in cancer drug resistance is overlooked despite strong evidence of these interactions. For instance, hypermethylation has been shown to affect the expression of miR-129-5p that modulates the level of the multidrug resistance ABC transporters (ABCB1, ABCC5 and ABCG1) genes in gastric cancer [30]. Interestingly, miRNAs can directly target HATs/HDACs and subsequently influence the level of histone acetylation and transcription factor activation. Furthermore, miRNAs can affect the level of *DNMT* expression. Recently, Masoumeh *et al.* found in tissues and cells of pancreatic cancer that miR-377 expression was inversely correlated with *DNMT1* expression. Downregulating *DNMT1* expression by miR-377 led to reactivation of tumor suppressor genes *BNIP3* and *SPARC* via promoter DNA hypomethylation and subsequently, reduction of proliferation and apoptosis induction in PC cells [61].

The emerging strategies to regulate epigenetic regulators in cancers include the activation or inactivation of their expression to increase drug effectiveness. This indicates that these regulators can be considered as sensitive biomarkers for drug resistance and as a potential therapeutic target to break drug resistance. However, a deeper understanding of epigenetic crosstalk could increase the efficiency and the use of selective and combined epigenetic drugs for therapeutic use.

Executive summary

- Epigenetic alterations contribute to the modulation of crucial mechanisms of cancer drug resistance.
- The alteration of histone-modifying enzymes expression modifies cancer drug response genes by the regulation of key biological process that controls cancer sensitivity.
- DNA hypermethylation or hypomethylation contribute to cancer drug resistance by the activation of tumor suppressor gene or inactivation of proto-oncogene respectively.
- Histone deacetylases inhibitors and DNA de-methylating agents have shown to sensitize the multidrug-resistant tumor cells to conventional treatment.
- MiRNAs regulate cancer drug resistance as oncogenes and tumor suppressors by negatively inhibiting tumor suppressor genes and/or genes that control cell differentiation or apoptosis.
- The understanding of epigenetic mechanisms crosstalk in cancer drug resistance will help to increase targets selectivity and therapeutic efficacy against cancer cells.

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