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Metabolomics of Drug Resistance in Cancer: The Epigenetic Component

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Drug resistance is an important concern in practical medicine, with special relevance in cancer (chemotherapy resistance). Although the molecular mechanisms of drug resistance are still obscure, there is evidence that genetic variation in pathogenic, metabolic, and transporter genes, under the influence of epigenetic events (DNA methylation, chromatin/histone remodeling, miRNA dysregulation), may contribute to drug resistance. Three types of drug efflux pumps, the multidrug resistance gene 1 (MDR1/ABCB1)-encoded P glycoprotein, the multidrug resistance-associated protein (MRP/ABCC1) and breast cancer resistance protein (BCRP/ABCG2) may play an important part in the intrinsic or acquired defense of cells against drugs. Multidrug resistance is often associated with an ATP-dependent decrease in cellular drug accumulation which is attributed to the overexpression of ABC transporter proteins [1,2].

SNPs of the *ABCB1* (T1236C, G2677T/A and C3435T) and two SNPs of the *ABCG2* (G34A and C421A) genes influence resistance and/or good response to imatinib mesylate (IM) in chronic myeloid leukemia (CML) treatment. The frequency distribution of *ABCG2* 421 CC, CA and AA genotypes are different between IM good responders and resistant patients. Resistance is associated with patients who are homozygous for the *ABCB1* 1236 CC genotype. For *ABCB1* G2677T/A polymorphism, a better complete cytogenetic remission is observed in patients with the TT/AT/AA variant. The *ABCB1* haplotype C1236G2677C3435 is linked to a higher risk of IM resistance, while the *ABCG2* diplotype A34A421 correlates with a good response to IM. *ABCG2* 421C>A is associated with a major molecular response and *ABCB1* 2677G>T/A is associated with a lower molecular response [3]. *SLC22A1-ABCB1* haplotypes may also influence IM pharmacokinetics in Asian CML patients [4].

Epigenetic modifications are associated with drug resistance [5]. The acquisition of drug resistance is tightly regulated by post-transcriptional regulators such as RNA-binding proteins (RBPs) and miRNAs, which change the stability and translation of mRNA-encoding factors involved in cell survival, proliferation, epithelial-mesenchymal transition, and drug metabolism [6]. Increased *ABCB1* transcript expression coincident with acquisition of resistance to epirubicin or paclitaxel was temporally associated with hypomethylation of the *ABCB1* downstream promoter in the absence of gene amplifications or changes in mRNA stability. Changes in *ABCB1* promoter methylation, *ABCB1* promoter usage and *ABCB1* transcript expression can be temporally and causally correlated with the acquisition of drug resistance in breast tumor cells [7]. About two-thirds of all breast cancers are ERα-positive and can be treated with the antiestrogen tamoxifen, and over 30% of women treated with tamoxifen develop drug resistance. Aberrant DNA methylation, together with other pharmacogenetic factors [8], is thought to play a role in this resistance [9]. ERα-positive TMX2-11-resistant cells have 4,000 hypermethylated sites and ERα-negative TMX2-28-resistant cells have over 33,000. The tamoxifen-resistant cell lines share 3,000 hypermethylated and 200 hypomethylated CpGs. The *ZNF350* and *MAGED1* genes are hypermethylated, and treatment with 5-aza-2'deoxycitidine causes a significant reduction in promoter methylation and a corresponding increase in expression in TMX2-28 [9].

MDR1 promoter methylation is frequent in prostate carcinoma where *MDR1* downregulation is mainly due to histone post-translational modifications. This occurs concomitantly with aberrant promoter methylation, substantiating the association with decreased expression of P-gp. Histone active marks H3Ac, H3K4me2, H3K4me3, H3K9Ac, and H4Ac are increased at the *MDR1* promoter after exposure to trichostatin A alone or combined with 5-aza-2'deoxycytidine [10].

RASSF10 is located on chromosome 11p15.2, a region that shows frequent loss of heterozygosity (LOH) in several cancer types. RASSF10 suppresses colorectal cancer growth by activating P53 signaling. RASSF10 is methylated in 82.6% of human primary hepatocellular carcinoma cells (HCC) and methylation of RASSF10 is associated with tumor size and TNM stage. Restoration of RASSF10 expression suppresses cell proliferation, induces apoptosis and G2/M phase arrest, sensitizes cells to docetaxel, and activates P53 signaling in HepG2 and QGY7703 cells [11].

Bromodomain and extra-terminal (BET) domain proteins have emerged as promising therapeutic targets in cancer. BET inhibitors directly target bromodomain proteins that bind acetylated chromatin marks. Resistance to I-BET, the prototypal BET inhibitor, confers cross-resistance to chemically distinct BET inhibitors such as JQ1, as well as resistance to genetic knockdown of BET proteins. Chromatin-bound BRD4 is globally reduced in resistant cells, whereas the expression of key target genes remains unaltered, highlighting the existence of alternative mechanisms to regulate transcription. Resistance to BET inhibitors is in part a consequence of increased Wnt/β-catenin signaling, and negative regulation of this pathway results in restoration of sensitivity to I-BET [12].

Despite alteration of DNA methylation or histone modifications, deregulated miRNA expression patterns of tumor cells have been identified as interfering with drug response [13]. Efflux pumps of the ABC transporter family are subject to miRNA-mediated gene regulation. ABC transporters are embedded in a concerted and miRNA-guided network of concurrently regulated proteins that mediate altered drug transport and cell survival under changing environmental conditions. miR-27a, miR-137, miR-145, miR-200c, miR-298, miR-331-5p, miR-451, and miR-1253 are associated with reduced *ABCB1* expression, and miR-27a, miR-138, miR-296, and miR-451 are associated with increased *ABCB1* expression [14].

The bladder cancer (BCa) cell line 5637 is significantly more

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sensitive to the cytotoxicity of five chemotherapeutic agents than H-bc cells. The inhibitor of growth 5 (*ING5*) gene is upregulated in 5637 cells compared with H-bc cells, indicating that it has an inhibitory role in BCa chemoresistance. SiRNA-mediated inhibition of ING5 increases the chemoresistance and inhibits the DNA damage response pathway in 5637 cells. Conversely, forced expression of EGFP-ING5 decreases the chemoresistance and activates the DNA damage response pathway in H-bc cells. *ING5* gene expression is inhibited by miR-193a-3p and is instrumental in the role of miR-193a-3p in activating BCa chemoresistance [15].

Lung cancer cells show inherent and acquired resistance to chemotherapy. The level of HDACs 1, 2, 3 and 4, DNA methyltransferase, acetylated H2B and acetylated H3 are lower in A549DOX11 (doxorubicin-resistant) compared to A549 lung adenocarcinoma cell lines. Fourteen miRNAs are dysregulated in A549DOX11 cells; of these 14 miRNAs, 4 (has-mir-1973, 494, 4286 and 29b-3p) show a 2.99-4.44-fold increase in their expression. This is associated with reduced apoptosis and higher resistance of A549DOX11 cells to doxorubicin and etoposide [16].

The oncogenic isoform of HER2, HER2Δ16, is expressed with HER2 in nearly 50% of HER2-positive breast tumors where HER2Δ16 drives metastasis and resistance to multiple therapeutic interventions including tamoxifen and trastuzumab. Expression of HER2Δ16 oncogene alters expression of 16 microRNAs (especially, miR-7 tumor suppressor) to promote endocrine resistance [17]. 123 differentially-expressed miRNAs were identified in the cells resistant to vinorelbine (NVB). MAPK, mTOR, Wnt, and TGF-beta signaling pathways and several target genes such as *CCND1, GRB2* and *NT5E* may associate with drug resistance of breast cancer cells to NVB [18].

Expression of miR-520g is correlated with drug resistance of colon cancer cells. Ectopic expression of miR-520g confers resistance to 5-fluorouracil (5-FU) - or oxaliplatin-induced apoptosis and reduces the effectiveness of 5-FU in the inhibition of tumor growth. Changes in circulating miRNA-126 during treatment are related to the response to chemotherapy and bevacizumab in patients with CRC. miR-203 enhances 5-fluorouracil chemosensitivity via the downregulation of TYMS in colorectal cancer. miR-320 expression level is found to be down-regulated in human colon cancer. The oncogene *FOXM1* is a direct target of miR-320. miR-320 and FOXM1 protein have a negative correlation in colon cancer tissues and adjacent normal tissues. miR-320-FOXM1 axis may overcome chemoresistance of colon cancer cells [19].

miR-16 is downregulated in paclitaxel-resistant lung cancer cells. It is also the target of the anti-apoptotic protein Bcl-2 in paclitaxel-resistant lung cancer cells. The combined overexpression of miR-16 and miR-17 and subsequent paclitaxel treatment greatly sensitizes paclitaxel-resistant lung cancer cells to paclitaxel by inducing apoptosis via caspase-3-mediated pathway. The loss of miR-199b-5p due to progressive epigenetic silencing leads to the activation of the JAG1-mediated Notch1 signaling cascade, thereby leading to the development of acquired chemoresistance in ovarian cancer. miR-199b-5p is downregulated in cisplatin-resistant ovarian cancer cells and is clinically associated with advanced and poor survival ovarian cancers. The promoter region of miR-199b-5p is hypermethylated, and the loss of miR-199b-5p can be restored by 5-Aza-dC-mediated demethylation. JAG1 is a primary target of miR-199b-5p [20].

These examples illustrate the complexity of the metabolomics of drug resistance in different cancer cells and the potential influence that epigenetic intervention may provide as a future anti-cancer strategy [21,22].

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