Epigenetic and transcriptional changes following treatment with DNA methylation inhibitor, 5-aza-deoxycytidine (DAC)

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Epigenetic mechanisms, such as altered DNA methylation, are important contributors to cancer initiation and progression. These DNA methylation changes are reversible and as such DNA demethylating agents are of therapeutical potential. 5-aza-deoxycytidine (DAC) has been FDA-approved for treatment of myelodysplastic syndrome and recent research shows the benefits may be transferable to solid tumors. However, the exact mechanisms of DAC effects on tumor cells are still unknown while immune-stimulatory properties have recently been discussed. Head and neck squamous cell carcinoma (HNSCC) is considered to be the sixth most common cause of cancer-related mortality worldwide; its survival rates are relatively low and have not improved over the last four decades despite new chemotherapy-based treatments. Therefore, there is a justified need for predictive biomarkers and complementary treatments. Here, we use HNSCC cell lines as a model to study genome-wide effects of DAC on DNA methylation, DNA hydroxymethylation, DNase I-hypersensitive sites (regulatory elements) and transcriptional output. Using genome-wide DNase-1-seq methods, we identified HNSCC-specific regulatory elements and compare them with the genomic distribution of 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) marks obtained through 5MeDIP-seq and 5hMeDIP-seq, respectively. We demonstrate that treatment with DAC, even at low doses (100 nM) significantly alters the epigenetic landscape in HNSCC cells with a change to around 50% of regulatory elements and 40% of 5hmC sites. Furthermore, DAC treatment leads to demethylation of ERV1 sequences with corresponding increased expression of ds RNA potentially leading to viral mimicry. In addition, SINE/Alu elements are significantly affected by DAC treatment and show different mechanism of demethylation than other repeat sequences which involves hydroxymethylation pathway. In agreement with above findings DAC treatment primarily causes an increase in expression of immune system-related genes. Identification of changes induced by DNA demethylation could potentially hold therapeutic value.

Recent Publications

Biography
Malgorzata Wiench is a Lecturer in Cancer Biology at University of Birmingham. Uniquely based between the School of Dentistry and the Institute of Cancer and Genomic Medicine, she aims to understand the mechanisms by which chromatin organization and DNA methylation regulate gene expression in health and disease and to develop the basis for patient-tailored epigenetic cancer therapies. The investigations focus on the role of nuclear receptors, DNA methylation and hydroxymethylation in the functioning of distal regulatory elements. She has received grants from the Marie Curie Action (FP7) and Royal Society.