Inhibition of DNA methylation does not overcome docetaxel resistance in human breast cancer cells

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Introduction

Resistance mechanisms to the chemotherapeutic drug docetaxel are poorly understood.

DNA methylation can alter gene expression by gene silencing.

Altered gene expression is associated with chemotherapy drug resistance in various different cancer types.

Gene expression alterations due to epigenetic events is one underlying mechanism of chemotherapy drug resistance in cancer.

Aim

Investigate the effect of decitabine, a DNA methylation inhibitor, on the response to docetaxel in docetaxel-resistant human breast cancer cells.

Methods

- Docetaxel-sensitive & docetaxel-resistant MCF-7 & MDA-MB-231 breast cancer cells were treated with or without 8 µM decitabine.
- Global methylation and DNA methyltransferase (DNMT) activity was measured using an ELISA-based assay.
- *DNMT* gene expression was measured by qRT-PCR.
- MTT assay was used to measure cell viability.

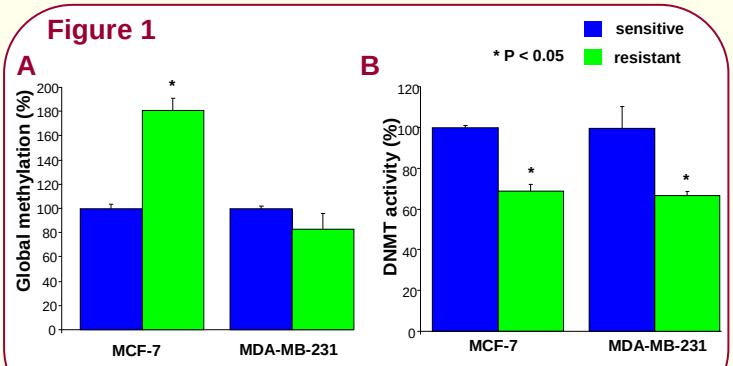
Results

- Global methylation was increased in docetaxel-resistant MCF-7 cells but decreased in MDA-MB-231 cells compared to parental sensitive cell lines (**Figure 1A**).
- DNMT activity (**Figure 1B**) and *DNMT1* and *DNMT3b* gene expression (data not shown) was decreased in both docetaxel-resistant cell lines.
- Decitabine decreased DNMT activity (**Figure 2**) but increased *DNMT* gene expression (**Figure 3A**) in MCF-7 docetaxel-resistant cells whereas both DNMT activity (**Figure 2**) and *DNMT* gene expression (**Figure 3B**) were decreased in MDA-MB-231 cells.
- Decitabine treatment significantly increased resistance to docetaxel in MCF-7 cells but had no effect on MDA-MB- 231 cells (**Figure 4**).

Conclusions

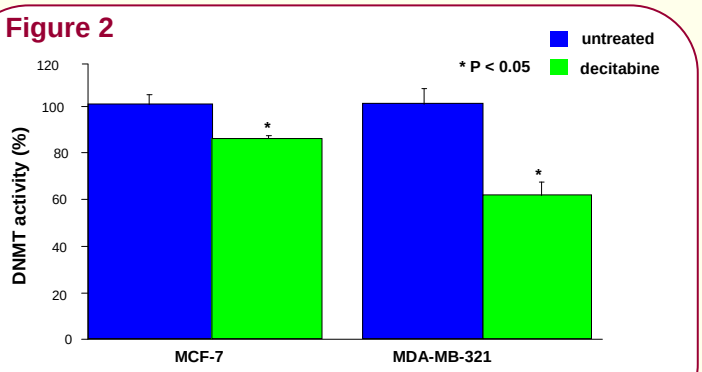
- Altered global methylation, DNMT activity and *DNMT* gene expression is associated with docetaxel resistance in human breast cancer cells.
- Decitabine treatment does not overcome resistance to docetaxel but increased resistance after treatment in MCF-7 cells.

Figure 1



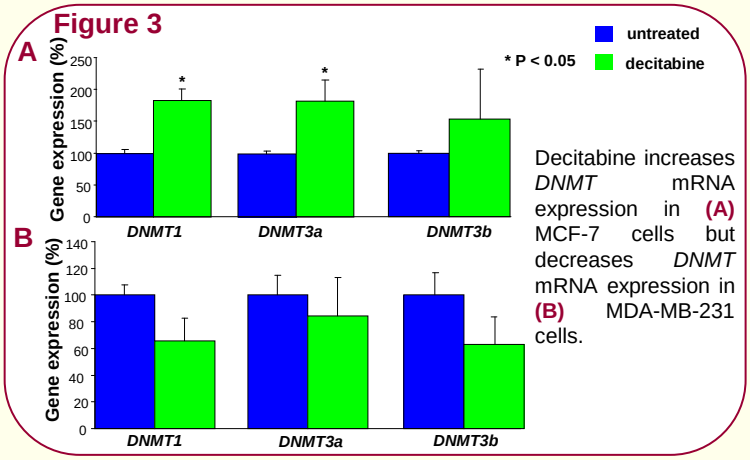
(A) Global methylation and **(B)** DNMT activity is associated with docetaxel resistance in breast cancer cells.

Figure 2



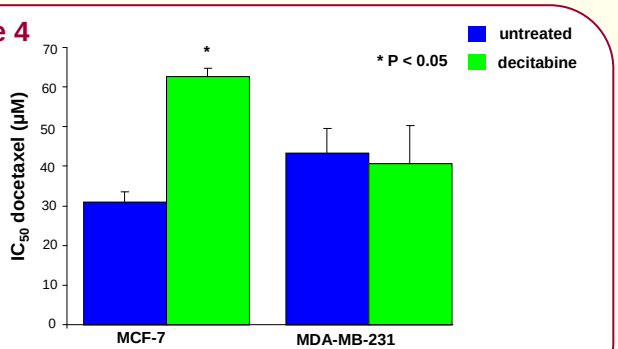
Decitabine decreases DNMT activity in docetaxel resistant breast cancer cells.

Figure 3



Decitabine increases *DNMT* mRNA expression in **(A)** MCF-7 cells but decreases *DNMT* mRNA expression in **(B)** MDA-MB-231 cells.

Figure 4



Decitabine increases docetaxel resistance in MCF-7 docetaxel-resistant cells.

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