P36 p300 up-regulation by docetaxel contributes to chemotherapy resistance in prostate cancer

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Introduction & Objectives: Administration of the microtubule inhibitor docetaxel is a common treatment for castration-resistant prostate cancer (PCa), which leads to a minor survival benefit. However, after a short period of time chemotherapy resistance emerges and the underlying mechanisms are still not fully elucidated. The histone acetyltransferase p300 has previously been correlated to PCa progression. This study aimed to determine whether p300 plays a role in chemotherapy resistance.

Materials & Methods: Publicly available datasets of patients with metastatic PCa that suffered from relapse after docetaxel treatment were analyzed concerning p300 levels. Expression of p300 was measured by qPCR or Western blot in absence or presence of docetaxel. p300 knockdown was achieved by doxycycline-inducible shRNA expression in stably transduced cells. Clonogenic assays were performed to determine colony formation efficiency. Cell Migration and invasion were analyzed by wound scratch and Boyden chamber assays. Expression levels of downstream targets c-Myc, Vimentin and E-Cadherin were determined by qPCR or Western Blot.

Results: Analysis of docetaxel-treated patients revealed significantly higher p300 mRNA expression compared to control patients. In line with this, docetaxel-resistant cells showed significantly increased p300 protein expression compared to docetaxel-sensitive counterparts. Docetaxel treatment of PCa cells for 72 hours resulted in elevated expression of p300 and its downstream target c-Myc at mRNA and protein level. In docetaxel-sensitive cells p300 knockdown did not influence the total number of colonies. However; interestingly, p300 knockdown in docetaxel-resistant cells significantly decreased the clonogenic potential. Downregulation of p300 in docetaxel-resistant cells also decreased cell migration and invasion ability.

Conclusions: Taken together, we showed that docetaxel treatment increases p300 expression in PCa cells and patients. In contrast to docetaxel-sensitive cells, docetaxel-resistant cells showed reduced colony formation potential as well as decreased cell migration and invasion ability upon p300 knockdown. Based on our findings, we suggest that p300 contributes to chemotherapy resistance and could be a possible target in docetaxel-resistant patients. However, docetaxel resistance in PCa is heterogeneous and appropriate patient selection is crucial in advancing personalized medicine.