The stepwise evolution of the exome during acquisition of docetaxel resistance in breast cancer cells

**Background:** Resistance to taxane-based therapy in breast cancer patients is a major clinical problem that may be addressed through insight of the genomic alterations leading to taxane resistance in breast cancer cells. In the current study we used whole exome sequencing to discover somatic genomic alterations, evolving across evolutionary stages during the acquisition of docetaxel resistance in breast cancer cell lines. Results: Two human breast cancer in vitro models (MCF-7 and MDA-MB-231) of the step-wise acquisition of docetaxel resistance were developed by exposing cells to 18 gradually increasing concentrations of docetaxel. Whole exome sequencing performed at five successive stages during this process was used to identify single point mutational events, insertions/deletions and copy number alterations associated with the acquisition of docetaxel resistance. Acquired coding variation undergoing positive selection and harboring characteristics likely to be functional were further prioritized using network-based approaches. A number of genomic changes were found to be undergoing evolutionary selection, some of which were likely to be functional. Of the five stages of progression toward resistance, most resistance relevant genomic variation appeared to arise midway towards fully resistant cells corresponding to passage 31 (5 nM docetaxel) for MDA-MB-231 and passage 16 (1.2 nM docetaxel) for MCF-7, and where the cells also exhibited a period of reduced growth rate or arrest, respectively. MCF-7 cell acquired several copy number gains on chromosome 7, including ABC transporter genes, including ABCB1 and ABCB4, as well as DMTF1, CLDN12, CROT, and SRI. For MDA-MB-231 numerous copy number losses on chromosome X involving more than 30 genes was observed. Of these genes, CASK, POLA1, PRDX4, MED14 and PIGA were highly prioritized by the applied network-based gene ranking approach. At higher docetaxel concentration MCF-7 subclones exhibited a copy number loss in EZF4, and the gene encoding this important transcription factor was down-regulated in MCF-7 resistant cells. Conclusions: Our study of the evolution of acquired docetaxel resistance identified several genomic changes that might explain development of docetaxel resistance. Interestingly, the most relevant resistance-associated changes appeared to originate midway through the evolution towards fully resistant cell lines. Our data suggest that no single genomic event sufficiently predicts resistance to docetaxel, but require genomic alterations affecting multiple pathways that in concert establish the final resistance stage.

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