Review

UHN Microarray Centre

Resisting Arrest : Using microarrays to decipher the genetic signatures of drug resistance for breast cancer cells

Review of Feature Article: Villeneuve, D.J. *et al*. cDNA microarray analysis fo isogenic paclitaxel- and doxorubicin-resistant breast tumor cell lines reveals distinct drug-specific genetic signatures of resistance. Breast Cancer Research and Treatment, 2006, 96:17-39.

One of the goals in cancer treatment is to provide patients with "tailor-made" chemotherapeutic drug regimens, an approach that will result in more effective and efficient treatment with fewer side effects. cDNA microarray analysis is widely used to classify tumours based on their expression profiles and predict patient prognosis to specific cancers. However, one of the problems with predicting patient prognosis is the inability to differentiate between genes that affect patient prognosis and genes that play a role in the response to certain drugs. From a clinical standpoint, identifying genes whose expression correlates with tumour cell sensitivity to specific chemotherapeutic agents would better enable us to predict patient response and deliver more personalised medicine. From a research standpoint, identifying these genes would provide insight into the possible mechanisms through which tumours acquire resistance to certain drugs and would also advance chemotherapeutic drug discovery.

Villeneuve *et al.* used cDNA microarrays to identify drug-specific changes in gene expression that accompany the establishment of resistance to paclitaxel or doxorubicin, two common chemotherapeutic agents, in highly controlled *in vitro* studies. It is thought that the genes identified in the genetic signatures may allow for prediction of patient response to paclitaxel and doxorubicin. The significance of this study is that it is the first microarray analysis to compare gene expression amongst a series of isogenic drug-resistant tumour cell lines, such that drug-specific genomic signatures of resistance could be obtained and verified by Q-PCR and immunoblotting experiments.

This study used the MCF-7 breast tumour cell line, which has well-characterised estrogen receptors and has been used extensively to model breast cancer cell growth, derived from epithelial tissue. Using cDNA microarray analysis of wildtype MCF-7 breast tumour cells and isogenic paclitaxel-resistant (MCF-7_{TAX}) or doxorubicin-resistant (MCF-7_{DOX}) derivative cell lines, Villeneuve *et al.* identified drug-specific changes in gene expression that accompany the establishment of resistance to paclitaxel and doxorubicin.

Of the genes identified as "resistant", the majority were drug-specific and coded for proteins involved in drug transport, drug metabolism, growth, survival, and cell death. Of the 35 genes identified by microarray and Q-PCR experiments to comprise the paclitaxel resistance signature, 11 genes were found to be "highly paclitaxel-specific". And of the 33 genes identified to comprise the doxorubicin resistance signature, 11 genes were found to be "highly doxorubicin-specific".

Although Villeneuve *et al*. set out to find drug-specific genetic signatures of resistance to paclitaxel and doxorubicin, they found the MCF-7_{DOX} cell line has significant cross-resistance to paclitaxel. Since one third of genes that have changing expression upon selection for resistance to paclitaxel exhibit similar changes in expression for resistance to doxorubicin, and vice versa, these genes could prove to be general instead of specific predictors of drug resistance. It would be interesting to repeat this set of experiments using the UHN Human 19k array (which contains 19,008 ESTs), as a larger and more diverse genetic signature could have been found for each drug-resistant cell line if an array representing more genes was used.

While this study was the first to compare gene expression amongst a series of isogenic drug-

resistant tumour cell lines using microarray analysis, another study has also demonstrated that studies using MCF-7 cells could be used to support clinical data suggesting the importance of certain genes in the acquisition of resistance to another chemotherapy drug (docetaxel) and in the prediction of response to this drug in breast cancer patients[2]. Another study by Villeneuve *et al.* is currently underway to examine the utility of the identified genes as biomarkers for prediction of resistance to anthracyclins and taxanes in breast cancer tumours.

By identifying genes that play a role in the response to certain drugs, researchers will learn more about the mechanisms through which tumours acquire resistance to certain drugs and, eventually, predict patient response to certain drugs.

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References:

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