

The research was based on the hypothesis that the development of drug resistance in breast cancer is due to a network of drug-induced alterations in gene expression. This was to part fund a continuing project that used cDNA microarray analysis to compare gene expression in breast cancer cells treated with the anticancer drug doxorubicin.

Aims

1. Compare gene expression in parental and drug resistant breast cancer cell lines at the RNA level
2. Confirm altered expression in candidate genes implicated in the development of drug resistance
3. Use tumour bank samples to study the expression of candidate genes in tumours known to either respond or develop resistance to chemotherapy using doxorubicin.

Outcomes

Aim 1 was completed by mid 2005 with a number of candidate genes identified for further study. Due to time and budgetary constraints two candidates were chosen for aim 2. Aim 2 was completed by the mid 2006 and one of the candidate genes (peroxiredoxin III) was confirmed to be up-regulated at both the RNA and protein levels. This is significant as peroxiredoxin III is thought to be a potent antioxidant. One of the toxic effects of doxorubicin is as an oxidant and if antioxidants are activated, this could be one mechanism by which cells become drug resistant. A tumour bank study (aim 3) was postponed as essential reagents were unavailable. These have now been sourced and the tumour bank study is planned for late in 2007 subject to the acquisition of suitable funding. In order to progress the research, an alternative study was then planned. Blood samples will be taken from patients undergoing chemotherapy with either doxorubicin or epirubicin (a doxorubicin analogue with the same mechanism of action) both before and after chemotherapy and if possible after follow treatments. Levels of peroxiredoxin III will be measured at both the protein and RNA levels in extracts from white blood cells and these will then be correlated to response to chemotherapy. Making the shift from cultured cells to white blood cells required re-optimisation of all our established procedures and in particular obtaining stable RNA was problematic. These problems have now been resolved and an application to carry out this work using human cancer patients has been submitted for ethical approval. It is envisaged that this work will be started early in 2007.

This research has identified a potential new target for the development of anticancer therapies. The work in both human subjects and archival tumour tissue will be critical in confirming our essentially "in vitro" observations. Nevertheless the funding provided by the Cancer Research Charitable Trust has enabled us to complete the first phase of this research and has been invaluable in allowing us to both complete the initial study and providing us with a starting point for further research.

I would like to take this opportunity to thank the Cancer Research Charitable Trust for supporting this research.

Kathryn Stowell
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