Researcher Profile

Dr. Amadeo Parissenti

Multidrug resistance in breast cancer and PKC signalling

Identifying the mechanisms by which tumour cells acquire resistance to chemotherapy drugs will enable the development of effective strategies to reverse or minimise drug resistance in cancer patients. Dr. Parissenti and his colleagues have identified genes that may play a role in the onset of resistance to the taxane and anthracycline classes of chemotherapy drugs in breast cancer cells. Using UHN cDNA arrays, Dr. Parissenti's team has published a study that identified distinct drug-specific gene signatures of resistance to paclitaxel and doxorubicin in breast tumour cell lines. Using tumour core biopsies from patients with locally advanced/inflammatory breast cancer enrolled in a recently completed clinical trial by the National Cancer Institute of Canada (MA.22), his group is now examining by microarray and quantitative PCR the utility of these genes (and others) to predict response to epirubicin/docetaxel chemotherapy. Another recent study by his group concluded that resistance in breast tumour cells to anthracyclines and taxanes is acquired at a certain threshold drug concentration and that the onset of drug resistance is not always correlated with the induction and activity of drug transporters. Rather, a variety of mechanisms appear to be at play at or before the acquisition of drug resistance.

Dr. Parissenti is also looking at the possibility that aldoketoreductases (AKRs) may confer anthracycline resistance and that the inhibition of AKRs may be a new approach to combat drug resistance. AKRs convert anthracyclines like doxorubicin and epirubicin to less potent hydroxy metabolites and may also play a role as scavengers of reactive oxygen species generated by anthracyclines and other classes of chemotherapy agents. His group recently published data that used UHN arrays to identify and characterise the role of AKR1C2, AKR1C3, and other drug dose-dependent genes in the acquisition of anthracycline resistance. This study found that the expression of certain genes (such as those coding for AKRs and other proteins involved in drug transport, drug metabolism, redox reactions, cell signaling, transcription, cell proliferation, apoptosis, and immune response) correlated with the onset and magnitude of anthracycline resistance in breast tumour cells. Surprisingly, soley by inhibiting the 1C family of AKRs, the sensitivity to doxorubicin in doxorubicin-resistant cells was almost completely restored.

Dr. Parissenti and his colleagues are also studying the role of Protein Kinase C (PKC) in the control of cellular growth and the development of cancer. While examining the structure-function relationships for PKC, his group has identified regions within the PKC regulatory domain (outside of the pseudosubstrate sequence) that are important for inhibition of the catalytic domain. Dr. Parissenti's team is currently elucidating the precise mechanism by which PKC inhibits cell growth and how the cytoskeletal protein calponin induces autophosphorylation of PKC. His group is also investigating agents like calphostin C, a PKC inhibitor, which can effectively kill drug-resistant breast tumour cells.

Dr. Amadeo Parissenti is a Professor in the Department of Chemistry and Biochemistry, Laurentian University (Sudbury) and is a Professor in the Division of Medical Sciences at the newly established Northern Ontario School of Medicine. He is also Chair in Cancer Research at the Sudbury Regional Hospital. In 2007, he was appointed a member of the Ontario Institute for Cancer Research's Clinical Investigation Advisory Board (CIAB).

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