Novel Methods for Predicting and Treating Tumors Resistant to Drug, Immunotherapy, and Radiation

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Technology description

Despite advances in development of diagnostic tools and therapies for cancer, one of the greatest challenges in the treatment of cancer is overcoming tumor recurrence and multi-drug resistance (MDR) to drug, immunotherapy, and radiation treatment. Overall, less than one-third of patients respond to current chemotherapy, and most will recur and acquire multi-drug resistance after initial successful treatments. In the US, 500,000 solid cancers and 89,000 blood cancers are untreatable due to MDR. Based on experimental models, researchers have identified a wide variety of single gene-mediated drug resistance, which unfortunately have weak relationships with the drug resistance in human malignancies. This is partly because the methods used to identify the drug-resistant mechanisms have been based on tumor models that do not reflect the in vivo sensitivity to treatment. Gene expression signatures, identified primarily through mathematical and statistical models, have greater predictability of the treatment response of tumors. Unfortunately, such gene expression signatures have limited application because they are not relevant to particular therapeutic targets that can guide treatment decision or further drug discovery.Using 3D tumor models of breast cancer, UCSF researchers have identified a gene/protein that is necessary and sufficient for inducing MDR in breast cancer tissue. Blocking expression of this gene using RNAi led to increased sensitivity of the tumor cells in response to drug, immunotherapy, and radiation treatment, which resulted in more than 50% increase in cell death. Furthermore, over-expression of the gene in the tumor cells led to increased resistance to treatment. The UCSF researchers also observed that the gene-induced resistance is found independent of the tumor model used. Additionally, the UCSF researchers have shown that the MDR resistance mediated by the identified gene/protein depends on its ability to interact with a second protein. Blocking such interaction by mutating a critical residue at the protein-protein interface, or blocking expression of the second protein using RNAi, lead to increased sensitivity to treatment and more than 100% increased cell death. Therefore, disrupting the interaction of these two genes can lead to novel cancer treatments and/or adjuvant therapy to sensitize MDR tumors to primary treatment. Such drug screening and drug design strategy may lead to drug candidates that have higher specificity and greater therapeutic index against MDR tumors.

UCSF researchers have identified biomarkers for the diagnosis and prognosis of malignant tumors (including primary and metastatic tumors and cancers) resistant to anti-tumor therapeutics or that will develop resistance to anti-tumor therapeutics. These biomarkers are also useful in the diagonosis and

prognosis of multidrug resistant (MDR) tumors. This technology also provides methods of sensitizing treatment of MDR turmors to anti-cancer therapeutics.

Application area

Diagnose multi-drug resistant tumors and guide treatment decisions for personalized therapy.
Targets for novel drug development.
Screening assay for adjuvant therapy that sensitizes resistant tumors to first-line treatment.

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