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Cancer characteristics that may compromise drug efficacy

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In the first-line defense against cancer, the gradual replacement of conventional chemotherapy with molecularly targeted agents has opened the possibility to tailor drug treatments to particular tumors. However, this transition necessitates the characterization of the molecular lesions that are causative for the transformation of healthy cells into cancerous cells, because drugs need to be matched with the underlying carcinogenic defect to be effective. Two additional caveats, caused by unique genetic changes in the primary tumors and in their metastases, can affect drug transport and metabolism and need to be taken into consideration.

- We performed a comprehensive molecular analysis of a recurrent sarcoma with the aim of supporting treatment decisions. The investigation identified a likely culprit for the disease in a point mutation within FAF1, which may cause a loss of apoptotic function consecutive to transforming DNA damage. The associated upregulation of gene products that regulate migration and invasion, as well as gene products for extracellular matrix molecules and their modulators, reflected the invasive nature of this cancer. Of note, the RNA levels for genes that regulate transport and metabolism were extensively skewed in the tumor tissue as compared to muscle and bone. While the study informed on potential challenges to chemotherapy posed by drug transport and drug metabolism pharmacogenetics, it fell short of identifying a suitable drug target for therapy.
- The aberrant expression or splicing of metastasis genes conveys to primary cancers the ability to break through tissue barriers and disseminate. Established metastases differ from their original tumors by silencing genetic programs for extracellular matrix interactions and by activating genes associated with tissue remodeling and the oxidative metabolism. Cancer metastases to distinct target organs differ significantly in their gene expression profiles among each other and from the primary tumor. By contrast, metastases to the same target organ, derived from various primary tumors, share gene expression signatures. The results imply the possibility that chemotherapy of metastatic cancer may be more efficacious if selected to match the metastatic site affected rather than the organ of origin of the primary tumor. An advanced molecular treatment strategy for cancer will rely on the molecular definition of drug target, drug transport, and drug metabolism pharmacogenetics in the primary tumor. Consecutive to cancer dissemination, it will also require adjustments to account for the genetic changes in the metastases.

Biography

Georg F Weber attended medical school in Wuerzburg, Germany. He worked at the Dana-Farber Cancer Institute, Harvard Medical School from 1990 through 1999 and is currently on the faculty at the University of Cincinnati. Georg F Weber has published close to 90 scientific reports, including many in the most respected professional journals, and various monographs, most recently textbooks on molecular oncology and anti-cancer drugs. He holds several patents. As a component of his mission to research cancer dissemination, Georg F Weber is the founder and chief executive officer of MetaMol Theranostics, a company specialized in diagnosis and treatment of cancer metastasis.

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