How the hepatocyte resembles a drug-resistant cancer cell

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Current Major Challenges in Translational Cancer Research

- To identify causes of cancer and intercede to prevent initiation or development (prevention)

- To enumerate and verify molecular alterations that can be used as targets for cancer-specific therapy and use these to improve treatment of cancer (targeted cancer therapy)

- To discover why some cancers fail to respond to therapy and/or relapse after treatment (drug resistance) and to find ways to improve responses
Drug Resistance in Cancer

- May reflect resistance to single agents generally by altering targets, or affect multiple drugs used simultaneously: known as multidrug resistance (MDR). Can be intrinsic or acquired.
- MDR affects all classes of drugs, including newly designed targeted drugs
- Just as oncogene targets have been catalogued, we need to enumerate all mechanisms of drug resistance in cancer to solve this problem and circumvent resistance
Major Strategy

- To determine the clinical relevance of genes whose expression has been found in cultured cancer cells to confer drug resistance
Mechanisms of resistance to anti-cancer drugs

- Reduced apoptosis
- Altered cell cycle checkpoints and/or growth pathways
- Increased metabolism of drugs
- Increased or altered targets
- Increased repair of damage
- Compartmentalization

Decreased Uptake--100’s of Solute carriers

Increased Efflux--48 ABC transporters incl. ABCB1, ABCC1, ABCG2
The Hepatocyte and the Cancer Cell: Dr. Jekyll and Mr. Hyde
Jean-Pierre Gillet, Michael M. Gottesman, and Mitsunori Okabe

- Edited by Irwin M. Arias
- 2009 John Wiley and Sons, Ltd.
Multidrug resistant cancers are hepatocyte wannabes*

Hepatocellular cancer responds poorly to chemotherapy because the hepatocyte from which it is derived expresses many drug resistance genes

*A wannabe (slang for "want to be") is a person with an ambition to be someone or something that she/he is not.
Steps Demonstrating Relevance of Expression of MDR Genes in Clinical Cancers

- Established that mRNA expression is a surrogate for function of MDR gene products in the NCI-60 cell lines
- Developed a sensitive, specific, robust assay for MDR mRNAs to use in clinical cancers (Taqman Low Density Array, TLDA)
- Studied cancers in which intrinsic and/or acquired resistance contributes to treatment failure and correlated expression of drug-resistance genes with response to therapy (with Jean-Pierre Gillet)
Importance of new technology to address need for better assays of gene expression in clinical samples: TLDA (TaqMan Low Density Array: a microfluidic technology) has a much greater dynamic range than microarray.

Expression of ABCB1 detected in NCI-60 cell lines

Orina et al., Mol Cancer Ther. 2009 Jul;8(7):2057-66
Previous genomic expression profiling has focused on the predictive power of gene signatures for overall survival of patients with hepatocellular carcinoma (HCC).

Attention has also been directed towards gene signatures associated with the carcinogenic process, from preneoplastic lesions to neoplastic stages, including very early HCC to metastatic tumors, from patients with hepatitis c virus (HCV) infection.

We were interested in addressing multidrug resistance mechanisms in clinical samples of normal liver and HCC, mainly associated with hepatitis B virus (HBV).
Conclusions from Clinical Studies on Drug Resistance: Hepatoma

- There are substantial differences in MDR gene expression between normal hepatocytes and HCC (Jekyll and Hyde hypothesis)

- In HCC, there is a 45 MDR gene signature that distinguishes poor prognosis from better prognosis

- Using the connectivity map, it is possible to find drugs that shift the signature in some cultured cells from poor prognosis to improved outcome patterns

- Treatment of cultured hepatomas with these drugs makes them more sensitive to other anti-cancer drugs
Implications of these studies for drug-induced liver injury

- Some drugs may affect transcription of genes that determine sensitivity or resistance to cytotoxic drugs in the liver
- Conversely, an understanding of DILI could contribute to improved treatment of hepatomas and other drug-resistant tumors
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