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Biosketch

Neil Kaplowitz MD is Director of the USC NIDDK-sponsored Research Center for Liver Diseases in its 21st year of funding. He holds two endowed chairs, the Brem Professor of Medicine and the Budnick Chair in Liver Diseases, and is Chief of the Division of Gastrointestinal and Liver Diseases. He is also Professor of Physiology & Biophysics and Pharmacology & Pharmaceutical Sciences at the Keck USC School of Medicine and School of Pharmacy.

Dr. Kaplowitz has received a number of important honors and distinctions including election to membership in the American Society for Clinical Investigation and the Association of American Physicians. He is recipient of the Western Gastroenterology Research Prize, the William S. Middleton Award, the Solomon A. Berson Medical Alumni Achievement Award in Clinical Science from his alma mater, the Merit Award from the National Institutes of Health, the Mayo Soley Award from WSCI, the AASLD Distinguished Achievement Award, and the ALF Distinguished Scientific Achievement Award. He has served as the President of the American Association for the Study of Liver Diseases, and Vice-Chair for Research of the American Liver Foundation. He has also served as Associate Editor of leading medical and scientific journals such as Hepatology, Gastroenterology and the American Journal of Physiology.

In recent years he has focused on the role of signal transduction, ER and mitochondrial stress in the pathogenesis of liver injury. He has published more than 200 peer-reviewed, scientific articles, 150 scholarly reviews and has edited seventeen books related to liver diseases.

Abstract: Adaptations to cellular stress - role in susceptibility to DILI?

The initiation of cellular stress by drugs may promote cell death and/or inflammation or increase the susceptibility to the toxic effects of the innate or adaptive immune system. Parent drugs or metabolites can induce cellular stress through promotion of ROS production, chemical modification of proteins (covalent binding, or targeting intracellular or organelles such as endoplasmic reticulum (ER) and mitochondria as well as signal transduction and transcription. There are many adaptive responses to these individual stressors. Adaptive responses dampen toxicity and promote survival. ROS production through redox cycling of drugs, impairment of mitochondrial election transport, or release from inflammatory cells is modulated by the activation of NRF2, a transcription factor, which controls a set of genes which determine antioxidant defense. Mitochondrial impairment is modulated fission-fusion, mitophagy, mitochondrial unfolded response (UPRMT), and mitochondrial biogenesis: the latter two are controlled by activation of transcription factors specific to mitochondrial stress. ER stress is a universal accompaniment of covalent binding which leads to accumulation of malfolded proteins. This elicits an adaptive response (UPRER) initiated by transcription factors or kinases in the ER which signal the nucleus to produce chaperone proteins which protect the ER. In addition, protein

synthesis is temporarily inhibited and selective mRNAs are degraded to limit the overload of the ER with client proteins. Organellar stress and ROS also activate many signal transduction kinases which promote of toxicity (JNK) or defense (ERK, PKA, AKT, AMPK). In addition, the programmed death pathways that participate in DILI are dampened by the adaptive responses noted above. How do we place all these toxic stresses and their adaptive responses in context of DILI? Clearly, the potential for genetic and environmental modulation of the adaptive responses to cellular stress could be a very important factor in both direct (intrinsic) toxicity of drugs (e.g. APAP, valproate, amiodarone) and idiosyncratic toxicity. In the latter case, it is conceivable that dampening stress may diminish danger signals which co-stimulate adaptive immunity promote “clinical” adaptation or improve the cellular fitness of the liver to withstand immune mediated toxicity to the liver (minimize susceptibility), thereby minimizing the severity of injury.