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Mouse models for evaluation of the risk factors for human hepatocellular carcinoma

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Abstract

Transgenic and knockout mouse models are used to test the epidemiologic evidence that the major risk factors for human HCC are male gender, age, hepatitis injury, alfatoxin (AFB1) exposure and alcohol consumption. Using a large cohort of mice bred to carry various risk factors we found that male gender, age, p53 loss or mutation and hepatitis injury each increased AFB1 hepatocarcinogenicity. On careful analysis of the states of the increased sensitivity a common factor found was increased proliferation of hepatocytes; especially in the sensitivity of newborn mice. A major difference between newborn and adult mice is the low level of glutathione-S-transferase, namely mGSTA3 in newborn, as compared to adult mice. To test this further we produced an mGSTA3 knockout (KO) mouse line. This is essentially a “humanized” mouse in respect to AFB1 metabolism as humans do not have the equivalent of mGSTA3. Our preliminary studies show that the KO mice are highly sensitive to AFB1 by DNA-AFBO adduct formation, oval cell generation and production of HCCs. Thus, the mGSTA3 KO mouse provides a model to test the hypothesis that low levels of AFB1 exposure combined with alcohol exposure may act synergistically to cause HCC. In addition, the unique finding of large numbers of oval cells after AFB1 exposure in the KO mouse will allow us to determine the role of oval cells in development of HCC.

Biography

Dr. Sell is a board certified pathologist and immunologist. He has published over 400 papers and 12 books. His paper with Barry Pierce (Lab. Invest. 70:6-21, 1994.) was selected as an AACR scientific landmark. Among his findings are: development of delayed hypersensitivity before antibody formation (1959). the role of the thymus in development of immune competence (1964); first identification of immunoglobulin on the surface of B cells (1965; Current contents citation classic, 1984); classification of immunopathological reactions (1971); development of a radioimmunoassay for alphafetoprotein (1972); identification of liver stem cells during chemical hepatocarcinogenesis and in response to injury (1972-94); role of endocytosis in activation of B cells (1974); recognition that the chancre of syphilis is a delayed hypersensitivity reaction (1979); role of mGSTA3 in detoxification of aflatoxin (2004); and characterization of breast cancer stem cells (2012).