Methodological Heterogeneity in Hepatocellular Carcinoma Research: Where Are We?

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ducible in clinical studies.

Other animal models include: infection-associated (HCV core transgenic mouse, HCV core, E1, E2 transgenic mouse, chronic H. hepaticus infected mouse, HBx/c-Myc transgenic mouse, HBV, LHBs transgenic mouse, HBV HBx transgenic mouse); inflammation-associated (Mdr2 knockout mouse, fatty liver shionogi [FLS] mouse, hepatocyte - specific conditional NEMO knockout mouse [NEMO<sup>LPC-KO</sup>]); carcinogen-induced (Diethyl nitrosamine [DEN] treated rodents, choline deficient diet, carbon tetrachloride [CCl<sub>4</sub>] treated rodents); transgenic mouse models (SV40-antigen transgenic mouse, β catenin/H-ras double transgenic mouse, TGF-α/c-Myc double transgenic mouse, c-Met conditional knockout mouse [MetLivKO]); and others (Immunotolerized rat model, chimeric mouse model, uPA/SCID mouse model, and GBV-B). Aside these models of HCC, there are etiology-specific models such as those of alcohol and LPS.

The argument has always been made that since more than two thirds of HCC incidence is causally associated with hepatitis B and C viral infections, HBV-and HCV-induced rodent models of HCC must be used as standard models of HCC. In as much as this may be partly understandable, many legitimate issues remain. For instance HCC is caused by multiple etiologies which in most cases work synergistically. How can unique individual contributions of each etiological factor be produced by one model? Is there a window of intense contribution to HCC pathogenesis that reflects kind of etiology? If yes, do current models of HCC incorporate this? What manifest as human HCC is a product of many etiologies acting in complex ways that cannot be easily replicated in an experimental model.

As we look into the future efforts must focus on designing new experimental models of HCC that will substantially address the deficiencies of existing in vitro and in vivo models and at the same time take into account the multi-etiologic, time course and complex pathology of HCC. At least such an ideal model can accurately recreate pathological and molecular features of human HCC. This may in a way close up the usual disconnect between pre-clinical and clinical studies with respect to efficacy of newly discovered small molecules (NDSMs) with potential anti-HCC effects.

BIBLIOGRAPHY


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