Title: STUDIES ON GENETIC AND VIRAL FACTORS ASSOCIATED WITH HEPATOCELLULAR CARCINOMAS IN INDIAN POPULATION.

Supervisor: Prof. LUQMAN A KHAN
Head of the Department, Biosciences, Jamia Millia Islamia, New Delhi

Co-supervisor: Dr. S. K. SARIN
Director, Prof and Head, Department of Gastroenterology
G.B. Pant Hospital, New Delhi

Thesis submitted by: SUJOY BOSE

Abstract:

Studies on genetic and viral factors associated with hepatocellular carcinomas in Indian population.

Hepatitis B virus (HBV) causes hepatocellular carcinoma (HCC). Literature suggests that the disease progression is multifactorial, including viral and genetic factors. The present study aimed to investigate the role of key signal transducer (of Ras-MAPK/AKT, iNOS/NO and Wnt-β-catenin pathways), in the progression of chronic HBV related advanced liver disease to HCC in Indian population , and also on development of a novel cholangi-oarcinma cell line of Indian origin. Patients {CHBV (n=25), cirrhosis (n=15) and HCC (n=30)} were selected on the basis of inclusion and exclusion criteria from the out patient department of Gastroenterology, G. B. Pant hospital, New Delhi. The outcome of the present study may be summarized as: **(1)** HBV genotype D was the most prevalent in HCC. **(2)** Integration and localization of HBV x-gene was found in 2/8 (25%) and 10/12 (83.33%) cases. **(3)** The novel observation of downregulation (normal liver> CHBV> cirrhosis > HCC) of RAS expression in HCC cases is supportive of a tumor suppressive activity of the wild type form of the proto-oncogene in HCC. (**4**) Multiple pathways downstream of RAS, i.e. RAF-MAPK/AKT pathway, Wnt-β-catenin pathway, NFkBp65 activation, p53 downregulation, deregulation in cell cycle checkpoints, differential growth factor activation etc definitely contribute towards hepatocarcinogenesis, and our findings provide crucial insights in delineating the paradox behind the steps leading to hepatocarcinogenesis. The summation of all the events points towards a multistep deregulation in the signal transduction mechanism as 'multiple genetic hits' under HBV assault leading to hepatocarcinogenesis. (**5**) Activation of the MAPK and AKT pathways independent of RAS and iNOS/NO signaling independently contributes towards HCC development. (**6**) We have established and used a standardized, reproducible culture system of cholangiocarcinoma that may serve as a suitable human model system in systems biology, studying HBV/HCV mediated signaling deregulations etc.