

Proteomics for the early diagnosis and treatment of hepatocellular carcinoma

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The incidence of primary cancer has been increasing globally and now-a-days it constitutes the 5th most frequent cancer of humans representing around 5% of all cancers worldwide. Chronic HBV infection assumes greater significance because of its reported association with cirrhosis, and more ominously hepatocellular carcinoma or HCC. Hepatitis B infection constitutes a major global problem with nearly 400 million infected individuals. It contributes to a significant degree of morbidity on account of the associated chronicity that develops in 5-10% of infected adults and more than 90% of infected neonates. Globally, around one million people suffering from HBV-related chronic hepatitis and HCC die per year. Despite the availability of an effective prophylactic vaccine against hepatitis B for over 20 years, effective treatment of the chronic disease and associated HCC remains elusive. Therefore, identification of the cellular mediators and effectors of HCC is an important medical objective for developing new diagnostic tools and therapeutic strategies against it. Molecular biomarkers hold great promise for refining our ability to establish early diagnosis and prognosis for HCC, and to predict response to therapy. Proteomics is a rapidly expanding discipline that is expected to change the way in which disease can be diagnosed, treated and monitored in the near future. The proteomic analysis of serum and tumors should allow accurate prediction of what is happening at the protein level in a cancer cell or a body fluid proteome. It is the

hope that, by deciphering the alterations in serum and liver proteome, biomarkers and patterns of biomarkers will be found that should be helpful in improving early detection, diagnosis and treatment monitoring of HCC. In the last few years, HCC has been extensively investigated using different proteomic approaches on HCC cell lines, animal models, and in human tumor tissues. Though a new generation of HCC markers awaits validation in properly controlled clinical studies, an overview of the recent development in this area will be presented.

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The Gambia hepatitis intervention study (GHIS)

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The Gambia Hepatitis Intervention Study (GHIS) is a collaborative undertaking by the International Agency for Research on Cancer, The Government of the Republic of

The Gambia and the Medical Research Council of the United Kingdom. This programme was launched in 1986 with the objective of evaluating the efficacy of Hepatitis B (HB)

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vaccination in childhood in the prevention of HB infection, chronic liver disease and primary liver cancer in a population at high risk. The implementation of this trial involves three overlapping phases:

Phase I (1986-1990): Vaccination of approximately 60,000 children. HB vaccine, which was approved by the World Health Organisation, was integrated into the Gambian Expanded Programme of Immunisation (EPI) in a phased manner over a four-year period from July 1986 to February 1990. During this period, two groups of children were recruited, one comprising about 60,000 children who received all vaccines in the EPI schedule plus the HB vaccine, the other comprising a similar number of children who received all vaccines except HB. Since February 1990, HB vaccination is offered to all newborns as part of the EPI schedule in The Gambia.

Phase II (1991-1997): Estimate of efficacy of HB vaccine against infection and chronic carriage. Longitudinal and cross-sectional surveys were carried out in selected groups of vaccinated (Group 1) and unvaccinated (Group 2). These two subsets have provided evidence of the short-term efficacy of HB vaccine in preventing infection and chronic carriage. By the end of the first decade of life, the vaccine prevents 84% and 94% of HBV infections and chronic carriage, respectively, despite waning antibody levels during the period.

Phase III (since 1998): Long-term follow-up through Cancer Registration. The aim of this phase is to carry

out a surveillance of the population of The Gambia, to identify cases of chronic liver disease (cirrhosis) and liver cancer. A linkage is made between the records of cases occurring in subjects within the age-range of the GHIS cohort, and the GHIS database of vaccinated children, to determine whether the individual belongs to the vaccinated or unvaccinated cohort. The components of Phase III are:

1. Detection and ascertainment of cancer cases and cases of chronic liver disease in the population of The Gambia, through support to liver cancer diagnosis in the public and private health sector, and support to Laboratory and Histopathology Services.
2. Registration of cancer cases and of cases of chronic liver disease through the National Cancer Registry (NCR), a population-based cancer registry established in 1986.
3. Record linkage of identified cases with the GHIS database of vaccinated/non-vaccinated children, so that the net effect of HB vaccination in preventing liver cancer can ultimately be assessed.

In parallel with the development of the three phases above, the GHIS framework has fostered studies on viral, environmental and genetic factors in hepatocellular carcinoma, biomarkers of HB Infection and aflatoxin exposure, long term efficacy of HB vaccination and monitoring of breakthrough injections.

HCC Biomarkers in China and Taiwan

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A number of different types of biomarkers have been used to understand the etiology and progression of hepatocellular cancer (HCC). Perhaps the most well known are the serum/plasma markers of HBV or HCV infection. These markers include analysis of viral DNA or proteins or antibodies produced against the viral proteins. HBV surface antigen

(HBsAg) is most frequently used to determine chronic infection with high or low viral replication, while HBeAg is a measure of chronic infection with high viral replication. Analysis of antibodies includes measurement of anti-HBV core antigen, anti-HBV e antigen and anti-HBsAg. The response to immunization can be monitored by analysis of anti-HBsAg.

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