



## Multistep Process of Hepatocarcinogenesis

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Professor Ng graduated from the Faculty of Medicine in this University in 1980. She joined the Department of Pathology at The University of Hong Kong in 1981 and is currently a clinical Professor. She has a secondary appointment as Honorary Consultant in Pathology at Queen Mary Hospital.

Her primary research is in liver cancer, a disease prevalent both worldwide and locally. Significantly, she has established useful pathological and biological parameters for management of patients with this cancer. Her long-term objective of her research is to understand why liver cancer develops and to elucidate the molecular mechanisms in this cancer. Her laboratory is involved in the identification and molecular characterization of a number of tumor suppressor genes and oncogenes. In addition, she has been the chief pathologist of the liver transplant team at The University of Hong Kong-Queen Mary Hospital since the first successful liver transplantation in 1991.

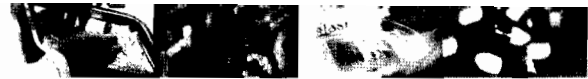
With over 300 publications with more than 200 peer-reviewed papers, she ranks among the world's top 1% in the ISI list of most cited scientists in clinical medicine. In recognition of her original research, she was awarded the Croucher Senior Medical Fellowship 2005-2006 and Outstanding Researcher Award by The University of Hong Kong in 2005.

Hepatocellular carcinoma (HCC) is one of the commonest malignancies worldwide and also in Southeast Asia and Hong Kong. Similar to other cancers, hepatocarcinogenesis is of a multistep process. However, systematic analysis using a genetic or molecular approach to accurately delineate the different steps/stages of HCC development is scarce. Studies to systematically evaluate the allelic alterations in the multi-steps in hepatocarcinogenesis including chronic hepatitis/cirrhosis, dysplastic nodules, primary and metastatic HCCs are very much awaited.

Cirrhosis is known to be a premalignant lesion for HCC. To delineate the frequency of allelic losses in chronic hepatitis and cirrhosis when compared with the corresponding normal DNA, genome-wide allelotyping is a good means. The frequency of loss of heterozygosity (LOH) in cirrhotic/chronic hepatitis livers is not too high, and in our cases, the fractional allelic loss index was 0.005. In contrast, LOH is a common occurrence in the predominantly hepatitis B virus-associated HCCs, as reported in many studies. In our HCCs, the fractional allelic loss index was in the range of 0.4.

The development of dysplastic nodule has been the subject of study with regard to its role in hepatocarcinogenesis. Reports in the allelic losses in DN are scanty. But we have observed the overall fractional allelic loss index of dysplastic nodules is in between that of cirrhosis and HCC. Significantly, there is a stepwise increase of fractional allelic loss index from low-grade to high-grade dysplastic nodules.

The molecular relationship between multiple tumor nodules in HCC within individual patients was also determined with both LOH assay and comparative genomic hybridization. The results indicated that in about 40% of patients, the multiple HCCs had different clonalities, hence of multicentric origin, whereas in the remaining 60% patients, the multiple HCCs had similar clonal relationship, hence of intrahepatic metastasis. Assessment of DNA alterations allowed precise determination of the clonality of multiple HCCs within one patient. Also, a cut-off value of 30% of discrepancy of LOH patterns between the nodules was found to distinguish



intrahepatic metastasis and multicentric occurrence. Consistently, those multinodular HCCs with <30% discrepancy, i.e. intrahepatic metastasis, had significantly more frequent venous invasion and tumor microsatellite formation. Thus, the discrepancy of LOH results between primary and metastatic HCCs was less than 30%. From our study, large-scale genetic deletions as reflected by genome-wide allelotyping were not common in metastatic HCCs.

Overall, hepatocarcinogenesis is a multistep process accompanied by stepwise increase in allelic losses, showing significant difference in different pathological disease stages. Such allelic losses can promote tumor development and progression.