

**NUS Graduate School for Integrative Sciences and Engineering
Research Project Write-up**

Title of Project : Identification and functional characterization of mutations and/or polymorphisms in FAT10 gene to elucidate the role of these mutations/polymorphisms in the carcinogenesis process.

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Short Description

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide, especially in the Asia Pacific region. To elucidate the molecular events underlying HCC development, our laboratory utilized cDNA microarrays to isolate novel differentially expressed genes in match tumor/adjacent normal tissues. One of the differentially expressed genes, FAT10, is particularly intriguing because its gene expression is highly up-regulated in most tumor tissue and it was not previously associated with cancer.

FAT10 is a member of the ubiquitin-like modifier (UBL) family of proteins and has been implicated to play important roles in inflammatory response, apoptosis and mitosis. FAT10 expression was reported to be generally and synergistically inducible by cytokines IFN γ and TNF α but not IFN α (5). Recently, we demonstrated the up-regulation of *FAT10* gene expression in 90% of hepatocellular carcinoma patients as well as other cancers (4) and found that FAT10 is negatively regulated by p53 (6). Both these observations are published in the journal *Oncogene*. We have also demonstrated that over-expression of the FAT10 gene results in dysregulated mitosis and aneuploidy (7)

In this project, the student will identify and characterize mutations/polymorphisms that occur in the FAT10 gene in HCC patients so as to better understand its dysregulation and role in the hepatocarcinogenesis process.

Objectives

- 1) Screen for mutations/polymorphisms in the FAT10 gene in HCC patients through sequencing of ~100 HCC patients.
- 2) Determine the effect of mutations/polymorphisms at the FAT10 promoter region on FAT10 promoter activity or expression.
- 3) Determine the effect of non-synonymous FAT10 mutations/polymorphisms on the FAT10 function including its subcellular localization, apoptosis and cell-cycle (mitotic) profiles as well as chromosome stability.
- 4) Perform a preliminary study to test for association between haplotype of polymorphisms at the promoter or within exons of the FAT10 gene and risk for the development of HCC.

These specific aims will test the following hypotheses:

- 1) Mutations/polymorphisms at the FAT10 promoter region of HCC patients may account for differences in the expression of the FAT10 gene
- 2) Non-synonymous mutations/polymorphisms within the FAT10 gene may affect the function of the FAT10 gene.
- 3) Polymorphisms in the FAT10 gene may be associated with differential risk for the development of HCC.

The understanding of how mutation/polymorphisms within this gene may influence FAT10 expression and function will facilitate the design of better strategies targeting this gene for HCC cancer diagnosis and therapy.

References

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- 2) Dongwei Zhang, Kuan-Teh Jeang, **Caroline G.L. Lee***. P53 negatively regulates the expression of FAT10, a gene upregulated in various cancers. ***Oncogene*** 25, 2318–2327 (2006)
- 3) Jianwei Ren, Alison Kan, Siew Hong Leong, London L.P.J Ooi, Kuan-Teh Jeang, Samuel S. Chong, Oi Lian Kon and **Caroline G.L. Lee***. FAT10 plays a role in the regulation of chromosomal stability. *The Journal of Biological Chemistry* 281: 11413 - 11421 (2006)
- 4) Chuan-Bian Lim, Dongwei Zhang and **Caroline GL Lee***. FAT10, a gene up-regulated in various cancers, is cell-cycle regulated. *Cell Division* 1:20 (2006).