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

Title of Project : Molecular elucidation of proteins that interact with FAT10 in the carcinogenesis process

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Short Description

Hepatocellular carcinoma (HCC) is a 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 IFNγ and TNFα but not IFNα (5). Recently, we demonstrated the up-regulation of *FAT*10 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 (manuscript in submission).

FAT10, being a member of the UBL family of proteins may represent novel targets for cancer treatment. FAT10 comprises two-ubiquitin-like moieties fused in tandem. Although FAT10 was reported to bind MAD2 non-covalently, target proteins that are covalently conjugated to FAT10 have yet to be identified. Our ultimate goal is to elucidate the physiological link between FAT10 and carcinogenesis. Our specific aim is to identify the downstream targets of FAT10 and characterize their interactions. As HCC, a difficult cancer to treat, remains a major problem in this region of the world, the identification of novel HCC-associated genes and the elucidation of the pathway by which these genes are involved in the carcinogenesis process will enable us to develop more specific markers for cancer diagnosis as well as develop target-specific therapies for the treatment of cancer

Objectives

1) Identify targets that bind to FAT10
2) Determine if the conserved C-terminal Gly-gly residues are important for the binding of the targets of FAT10
3) Evaluate the functional significance of the interaction between FAT10 and the identified targets

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)