OMICS Group Conferences
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Global Cancer Conference & Medicare Summit
September 15-17, 2014 Hyderabad International Convention Centre, India

Combinatorial association of liver specific vehicular system and tumor dependent expression of dsRNA inducing histone and DNA methylation of c-Myc P2 promoter in hepatocellular carcinoma cells

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For hepatocellular carcinoma (HCC) therapy, an ideal targeting system could involve a liver specific vehicular system coupled with a therapeutic modality active only under tumorigenic condition. One such liver targeting entity is a reconstituted Sendai viral envelop, known as Sendai virosome, containing the surface fusion (F) proteins which interact with the asialoglycoprotein receptors (ASGPRs) of hepatocytes. Transcriptional gene silencing (TGS), compared to post transcriptional gene silencing (PTGS), is heritable and does not require continuous supply of the effectors si/shRNA molecules, leading to long term transcriptional repression of the target gene. Utilizing such F-virosomal delivery system, HCC specific fusion cassettes of alpha-fetoprotein (AFP) promoter, with different tumour specific enhancers, was used to express shRNA targeting proto-oncogene c-Myc P2 promoter for induction of TGS in neoplastic liver cells. The combinatorial association of Sendai F-virosomes with the AFP promoter/enhancer expression system ensured that the c-Myc TGS inducing shRNA was active only in transformed liver cells. We demonstrated that such c-Myc shRNA expression system was efficient in inducing cell type as well as tumour specific activation of cell death in hepatocarcinoma cells. This was due to the methylation of both histone (H3K9Me2 and H3K27Me3) and CpG islands, with decreased histone 3 acetylation, around the target c-Myc P2 promoter. Moreover, this could serve as an added advantage over other gene therapeutic approaches, since persistent c-Myc inactivation is required for HCC suppression. Additionally, the Sendai F-virosome/AFP promoter/enhancer system could also be used to introduce genes specifically in embryonic liver and to tackle recalcitrant cancer cells with de-regulated c-Myc.

Biography

Mohammad Khalid Zakaria has completed his PhD on Cancer Therapeutics from All India Institute of Medical Sciences (A.I.I.M.S), New Delhi in October 2013. He has published in reputed international peer reviewed journals, is a co-author in an international patent and has qualified all national level entrance examinations aiding in financial assistance for PhD tenure. Academically he always has been among the top 2 students of the class, during masters and graduation, and is a good speaker as well. He has also won many journal club and seminar presentation awards.

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