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Targeting hepatocellular carcinoma cells by tumor biomarker α-fetoprotein based transcriptional interference system

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α-fetoprotein (AFP) is significantly expressed by the fetal liver and yolk sac during embryonic development. Following child birth, by various complex mechanisms, the level of AFP becomes un-detectable. Contrastingly, during hepatocellular carcinoma (HCC), the AFP expression is re-activated to several folds. Hence, AFP serves as a biomarker for the detection of HCC. Utilizing such tumor specific activation of AFP, the minimal AFP promoter region, in combination with various tumor specific enhancers, was utilized to drive the expression of dsRNA within hepatoma cells. The expressed dsRNA, specially designed against a proto-oncogene (c-Myc) promoter region rather than transcript, surprisingly recruited various epigenetic silencing factors such as DNA methyl transferases (DNMTs) and histone deacytylases (HDACs) at the target c-Myc promoter locus of the transformed cells. This resulted in c-Myc promoter hyper methylation (CpG sites) and heterochromatization (H3K9Me2/H3K27Me3), ultimately resulting in heritable and long term transcriptional repression. Survival assays and Flow cytometric analysis, post epigenetic repression of c-Myc in hepatoma cells, showed decreased cell survival and increased apoptosis. The therapeutic potential of this system was further enhanced by utilizing a para-influenza virus known as Sendai. We transformed this Sendai virus into liver specific Sendai fusion (F) virosome. The F-virosomes were tested for structure/function by fluorimetric/de-quenching assays and the F-proteins of the virosomes were demonstrated to interact with the asialoglycoprotein receptors (ASGPRs) of the hepatocytes. The hepatoma specific AFP promoter/enhancer driven dsRNA system was packaged and delivered into the tumor cells by these F-virosomes. Moreover, epigenetically c-Myc suppressed hepatoma cells were sensitized to sub-lethal doses of 5-Fluorouracil (5-FU) and Cisplatin. This approach could be utilized to minimize therapeutic dosage requirements and side effects of chemotherapy, introduce genes specifically within the embryonic liver and to target re-calcitrant hepatoma cells with de-regulated c-Myc.

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A comprehensive analysis of LACK (*Leishmania* homologue of receptors for activated C kinase) in the context of visceral leishmaniasis

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The *Leishmania* homologue of activated C kinase (LACK) a known T cell epitope from soluble *Leishmania* antigens (SLA) that confers protection against *Leishmania* challenge. This antigen has been found to be highly conserved among *Leishmania* strains. LACK has been shown to be protective against *L. donovani* challenge. A comprehensive analysis of several LACK sequences was completed. The analysis shows a high level of conservation, lower variability and higher antigenicity in specific portions of the LACK protein. This information provides insights for the potential consideration of LACK as a putative candidate in the context of visceral Leishmaniasis vaccine target.

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