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Cholesterol-conjugated let-7a mimics: Antitumor efficacy and toxicity in preclinical xenograft models of human Hepatocellular carcinoma

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Therapy with let-7 miRNAs is a potential strategy for human hepatocellular carcinoma (HCC). A major challenge for the clinical utility of let-7 miRNAs is the lack of an effective, non-toxic carrier. Recently we confirmed the antitumor efficacy and potential off-target effects of cholesterol-conjugated let-7a mimics (Chol-let-7a) in preclinical models. Subcuneous and orthotopic xenograft were treated with Chol-let-7a or negative control miRNA through local injections or systemic delivery. Ultrasonography was used to evaluate tumor growth and metastasis. Histopathology and ultrastructural features of the liver and kidney were used to evaluate toxicity after systemic treatment. Chol-let-7a inhibited HCC growth (Inhibitory rate, 56.3%) and tumor invasion when delivered by means of local injection in a subcutaneous xenograft model. Chol-let-7a was shown to effectively carry let-7a to the target tumors and produce satisfactory antitumor effects (Inhibitory rate, 66.5%) in an orthotopic xenograft model when administered systemically. In addition, Chol-let-7a-treated tumor cells showed no significant atypia and mitoses were very rare per unit of measurement in most areas after systemic therapy. Let-7a-treated xenografts revealed a significant upregulation of let-7a miRNA, and downregulation of three ras genes and ras proteins, especially n-ras/N-RAS was most strongly affected at the transcript and post-transcriptional levels. After continuous Chol-let-7a treatment, only some non-specific reaction changes were observed in liver and kidney in nude mice. These results suggested that Chol-let-7a produces inhibitory effects when administered locally and systemically. Chol-let-7a induced mild damage in liver and kidney after long-term treatment. Thus, systemically delivered *Chol-let-7a* is a promising therapeutic drug candidate for HCC.

Biography

Jian Guan received her MD from Peking Union Medical College (PUMC) in 2001 and completed Postdoctoral research work in Law Institute of Chinese Academy of Social Sciences. She is Associate Professor, department of pathology & Professor, department of scientific research & Lawyer, PUMC Hospital. She is Deputy Secretary-General, Chinese Society of Medical Science Research Administration. Her research interests are mainly in molecular oncology, medical ethics and IP. She has published more than 30 papers in reputed journals and has been serving as an Editorial Board Member of *"Advance of Cancer" and "Chinese Medical Research Management"*.

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