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MINI REVIEW

The Growth of Hepatocellular Carcinoma Can be Inhibited by Encapsulation of TGFβ1 Antagonists

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Mini Review

Physiological behavior of invasive hepatocellular carcinoma (HCC) is in the state of rapid division, aggressive growth and wide dispersion [1]. They are complicated with forming new blood vessels (angiogenesis) [2], separating from mother tumor (migration) and forming new tumor (metastasis). Unfortunately, HCCs are able to enhance their survival growth in spite of their hypoxic tumor environment by increasing their glycolysis rate [3]. HCCs can furthermore resist drug therapies because cells grew in distance far away from blood vessels that can be exposed to low concentrations of drug related to limited drug access [4]. Moreover, some drugs might be less active in hypoxic, acidic or nutrient-deprived microenvironments [5]. Additionally, there are barriers formed by extracellular matrix like collagen fibers, matrix metalloproteinase to prevent drug penetration and diffusion. Un similar to other carcinomas, since mutations in specific oncogenes or tumor suppressors drive tumor initiation and progression. The majority of HCCs are multifactorial and primarily due to infections with hepatitis B virus (HBV), or hepatitis C virus (HCV). However, worldwide cases of non-viral HCC are on the rise due to growing numbers of patients with metabolic liver diseases [6]. The advanced HCCs regardless of type are highly malignant cancer and are characterized by their innate resistance to chemotherapeutic agents that are widely and effectively treatments can be used in other cancer types [7]. HCCs are characteristically hyper-vascular tumor [2] suggesting their growths are associated with neovascularization within growing tumor nodules. However, advanced infiltrative HCCs seldom show hyper-vascularity, although grow more rapidly than mass forming types. Therefore, cancer cells in these advanced infiltrative HCCs are likely to generate signals that enable them to survive in hypoxic conditions [3]. Previous reports revealed to significant insight into the Transforming Growth Factor-β (TGF-β) signal transduction network. TGF-β is a multifunctional ubiquitous polypeptide cytokine that binds and activates a membrane receptor serine/threonine kinase complex [8]. Many studies revealed recently to the significant TGFβ1 inhibitors as therapeutic agents against cancer cells [9]. The issue is that cargo molecules can be lost

or diluted by blood plasma or inside gastrointestinal tract juice, or can be engulfed by immune-system. Furthermore they can cause complications for healthy cells. In this sense, combination of modern therapeutic agents such as TGFβ1 inhibitors with Nano-encapsulation could strengthen their use against cancer cell. In our previous work, many TGFβ1 inhibitors have been encapsulated to block TGFβ1 signaling pathway in different stages. Activin like kinase (ALK1fc) is a ligand trap targeted for ALK1 signaling pathway [10]. LY2157299 (LY), can block signaling through the heteromeric TGFβ receptor complex to reduce levels of active phosphorylated SMAD [11,12]. Interference RNAs, transiently transfected into the cell as siRNAs, or stably incorporated to the DNA with a plasmid the complementary sequence of shDNA inhibit translation of TGFβ1 by interfering with its specific sequence of mRNA. Also, inhibiting peptides, such as P-17 used in this study, bind to either TGFβ1 or its receptors, blocking signal transduction [13].

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