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Understanding TGF β1 signalling pathway is well strategy to use its encapsulated antagonist as nano therapeutic molecules

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Abstract

Transforming growth factors (TGF-β) as a multifunctional cytokine can control proliferation, cellular differentiation, and other functions in most cells. Although many therapeutic strategies had been developed, they are used in limitation related to their complications on healthy cells. Our aim was to encapsulate TGF-β blockers inside moieties of carriers creating finally applicable vehicles can be used for drug delivery system.

Introduction

Integration of cancer chemotherapies inside carrier moieties has become one of the most interesting topic, especially for blockers that can inhibit signaling pathways. Transforming growth factors (TGFβ) has cellular efficiency in case of health and diseases due to their roles in differentiation, growth and cytoskeleton morphology [1]. However, the function of TGF-β may be changed in advanced tumor growth to become an oncogenic factor helping cancer cells to be more invasive and keen to metastasis [2]. Many previous reports were observed the role of TGF-*β* pathway in cancer patients. Observing that the fabrication of therapeutic molecules based on inhibition of TGFβ pathway could be evident. There are many reasons why the inhibition of the TGF-*β* pathway might be a promising target for anticancer therapies. First, TGFβ pathway can effect on tumor cells directly. Secondly, the TGF-*β* pathway has an important role in control endothelial cell behavior and therefore in angiogenesis. Thirdly, TGF-*β* pathway is one of the most potent naturally immune-suppressors [3]. Most of previous studies succeed to pass the preclinical phase (Phase I and II). Although these blockers can inhibit TGFβ pathway, they are used in limitation because their actions can cause major complications on normal cells [4-7]. Additionally, P-glycoprotein acts to repel drugs from the cell, causing a decreased sensitivity and intracellular drugs accumulation [8]. For all of these barriers, it is necessary to develop new and innovative technologies that could help to overcome these complications. In recent work, the integration of chemotherapy among carrier's moieties has emerged as the last development for modern bio-nanotechnology. The micro- and nano-encapsulation is a process that consists of the enveloping of cargo compounds inside polymers assembly, protecting them from the external environment or from the adverse conditions and enabling their controlled release. This condition could improve drug delivery system. Many blockers are recently used in our studies to block TGFβ1 signaling pathways such as Activin like kinase (ALK1), LY2157299 (LY), siRNAs, shDNA, peptide 17. In addition to Bromopyruvic acid (3-BrPA) as glycolytic inhibitor. Initially, our strategy aimed to fabricate and functionalize drug delivery systems starting from a selection of suitable templates until to obtain layered capsule. For this reason, homogenous colloidal calcium carbonate has been fabricated. Diameters and shapes were controlled by biodegradable polymers. Alternate polymers were assembled onto their surface by using Layer-by-Layer (LbL) technique. Finally, layer-by-layer assembled capsules were obtained after core removal. Their quality was closely related to the quality of prepared template [9]. Magnetic nanoparticles (MNPs) were designed by grafting with fluorescent molecule. Then, they were coated by biocompatible and biodegradable polymers. Their hydrogel structures were assembled upon their surface, being used as a good vehicle for encapsulation Activin like kinase (ALK1) targeted ALK1 pathway. Immune assay experiment confirmed inhibition of TGFβ1 signals after incubation HCCs with encapsulated MNPs-ALK1fc [10].

Polymeric micelles optimized by control their chemical composition, exhibit good stability and capacity as drug delivery system. In this study polyacrylic acid and polygalacturonic acid were assembled as spherical layers and they were assembled in one single system by carbonyl group. They are composited as "nano-elastic" vectors having "nano-mechanical" features in acidic and alkaline condition. LY2157299 loaded nano-micelles caused reduction of collagen fibers and change of Golgi apparatus morphology of HCCs [11]. TGFβ1, TGFβR1 and TGFβ1R2 were inhibited after exposure to LY2157299 loaded nano-micelles in animal model of HCC.

Hybrid polymer integrated biological molecules such as lipid or protein were functionalized. These organic carriers made of polymer-protein complexes proven on their ability to encapsulate genetic material

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and peptide. Exhaustive characterization of hybrid protein polymer carriers was performed by means of TEM, AFM, FTIR, fluorescence spectrophotometry and Agarose Gel electrophoresis. They show good stability and were further encapsulated with SHT-DNA, siRNA and P-17. Fluorescence immunoassay showed inhibition of TGFβ1 after its exposure to encapsulated SHT-DNA,siRNA and P-17. Bioactivity of encapsulated P-17 was investigated by using western blot showing degradation of TGFβ1 pathway [12].

Oleic acid (OA) attached chitosan by amide linkages was coated by bovine serum albumin attached to folic acid. This structure is composed of three distinct functional components: i) a hydrophobic polymeric core where chitosan was successfully entrapped inside the core and it was the main place for storage hydrophobic drug ii) BSA-FA shell with targeting delivery purpose and for good liver cells binding; and iii) a lipid monolayer at the interface of the core and the shell that acts as a molecular fence to prevent drug to leak out, thereby enhancing drug encapsulation efficiency, increasing drug loading yield, and controlling drug release. Bromopyruvic acid encapsulated interior hybrid chitosan-lipid carrier was used to treat HCCs. It exhibits rounded and condensed structure with apoptotic morphology [13-14]. The results showed that TGF-β1 was inhibited by those selective inhibitors leading to block the invasion of HCC cells and protect healthy cells from harmful of TGFβ1 inhibitors. It can be concluded that the best way to use cancer chemotherapies is to encapsulate them inside biodegradable and biocompatible polymers, taken in consideration the correct method for polymer- drug attachment [15-17].

According to previous scientific reports, blocking of TGFβ signaling pathways is considered as the most promising therapeutic concepts which are currently under development and mostly are in phase II clinical trials. the drawback of these inhibitors is their effect on healthy cells. Our strategy was to integrate these inhibitors inside moieties of carriers to be more useful and applicable [18].

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Author Contributions

Nemany Abdelhamid Nemany Hanafy designed the paper and wrote the manuscript; Maged El-Kemary revised the manuscript; Stefano Leporatti supervised and revised the manuscript. All authors read and approved the final manuscript version.

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