pharmaceutics

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Efficient Delivery of Therapeutic siRNA by Fe_3O_4 Magnetic Nanoparticles into Oral Cancer Cells

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Received: 22 August 2019; Accepted: 15 November 2019; Published: 17 November 2019

Abstract: The incidence of oral cancer is increasing due to smoking, drinking, and human papillomavirus (HPV) infection, while the current treatments are not satisfactory. Small interfering RNA (siRNA)-based therapy has brought hope, but an efficient delivery system is still needed. Here, polyethyleneimine (PEI)-modified magnetic Fe_3O_4 nanoparticles were prepared for the delivery of therapeutic siRNAs targeting B-cell lymphoma-2 (BCL2) and Baculoviral IAP repeat-containing 5 (BIRC5) into Ca9-22 oral cancer cells. The cationic nanoparticles were characterized by transmission electronic microscopy (TEM), scanning electronic microscopy (SEM), dynamic light scattering (DLS), and vibrating sample magnetometer (VSM). By gel retardation assay, the nanoparticles were found to block siRNA in a concentration-dependent manner. The cellular uptake of the nanoparticle/siRNA complexes under a magnetic field was visualized by Perl's Prussian blue staining and FAM labeling. High gene silencing efficiencies were determined by quantitative real-time PCR and western blotting. Furthermore, the nanoparticle-delivered siRNAs targeting BCL2 and BIRC5 were found to remarkably inhibit the viability and migration of Ca9-22 cells, by cell counting kit-8 assay and transwell assay. In this study, we have developed a novel siRNA-based therapeutic strategy targeting BCL2 and BIRC5 for oral cancer.

Keywords: magnetic nanoparticle; iron oxide; siRNA delivery; BCL2; BIRC5/survivin; oral cancer

1. Introduction

The incidence of oral cancer has increased due to risk factors such as tobacco, alcohol, and human papillomavirus (HPV), resulting in nearly 180 thousand deaths worldwide in 2018 [1,2]. The clinical treatment of oral cancer mainly depends on surgery, radiotherapy, chemotherapy, and several targeted drugs, but the prognosis is poor [3,4]. Therefore, it is necessary to develop novel therapeutic strategies to overcome the limitations of current therapies for oral cancer.

Recent progress in nanotechnology-based gene therapy has brought hopes for cancer treatment [5]. RNA interference (RNAi) is a sequence-specific post-transcriptional gene silencing process in eukaryotes [6]. RNAi could be triggered by microRNA (miRNA) and small interfering RNA (siRNA), which could be designed to target almost any gene [7]. It is exploited by researchers for loss-of-function studies and holds promise for the development of therapeutic gene silencing [8]. The first siRNA drug Onpattro (patisiran) targeting transthyretin (TTR) has been approved by the U.S. Food and Drug Administration (FDA) in 2018, for the treatment of peripheral nerve disease polyneuropathy in adults.