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指示

この博士論文全文の閲覧方法については、以下のサイトをご参照ください。 【担当：薬学部図書室】
Summary of Doctoral Dissertation

Degree requested Doctor of Pharmaceutical Science

Applicant’s name Nour A. K. Shobaki

Title of Doctoral Dissertation

Targeting macrophages in the tumor-microenvironment to enhance their anti-tumorous functions by gene silencing using optimized siRNA-loaded lipid nanoparticles

The tumor-microenvironment is highly infiltrated with tumor-associated macrophages (TAMs) which have an M2 phenotype and pro-tumorous functions [1,2]. Targeting TAMs to educate them and to modify their functions could be novel immunotherapy for cancer. The purpose of this research is to target TAMs and to modify their functions through gene silencing of certain genes responsible for their M2 polarization. This could be achieved using small interfering RNA (siRNA), which is a short sequence of nucleotides that can specifically silence any gene of interest. However, systemic delivery of siRNA can be challenging due to their high molecular weight and hydrophilic and anionic status, which hinder their entry into cells [3]. Furthermore, siRNAs lack stability in the in vivo environments. Therefore, the development of an efficient and optimized siRNA delivery system to target TAMs is significant to realize macrophage-based therapeutics. In this study, a lipid nanoparticle (LNP) formulation with specific lipid composition and size was optimized to target and deliver siRNA to TAMs. The LNP is mainly composed of a novel and a pH-sensitive cationic lipid, referred to as CL4H6 lipid, which has an acid dissociation constant (pKa) value of 6.30 and was used previously in an optimized LNP formulation to target hepatocytes with strong gene silencing efficiency, biodegradability, and safety [4]. In this study, the CL4H6-LNP was used to target another cell population, which is TAMs. The optimized siRNA-loaded CL4H6-LNPs induced strong gene silencing in macrophages, in vitro (in murine bone marrow-derived macrophages (BMDM)) with a superior efficiency than the commercially available Invitrogen™ Lipofectamine™ RNAiMAX transfection reagent, and obtained high and selective uptake and strong gene silencing activity in TAMs in a human tumor xenograft model in mice. Furthermore, a significant anti-tumor therapeutic response was obtained by targeting TAMs using the optimized siRNA-loaded CL4H6-LNPs in the same tumor model. The anti-tumor therapeutic response was obtained through the silencing of two targeted genes responsible for M2 polarization and that resulted in reversing the pro-tumorous functions of TAMs (mainly angiogenesis and tumor cell activation). This research has promising clinical and pharmaceutical applications to realize novel macrophage-based cancer immunotherapy in human patients.

References: