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Treatment of PTEN-positive tumors with small interfering RNA targeting the mammalian target of rapamycin

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Abstract

The mammalian target of rapamycin (mTOR) is a promising target molecule for cancer therapy. The mTOR signaling pathway plays important roles on cell growth and angiogenesis in tumor progression. In the present study, small interfering RNA (siRNA) for mTOR (simTOR) was used for inhibiting this signaling pathway. To achieve knockdown of mTOR *in vivo*, we developed dicetyl phosphate-tetraethylenepentamine (DCP-TEPA)-based polycation liposomes (TEPA-PCL) modified with polyethylene glycol (PEG) and with Ala-Pro-Arg-Pro-Gly (APRPG), a VEGFR-1-targeting probe, as a siRNA vector. APRPG-PEG-modified TEPA-PCL carrying simTOR (APRPG-TEPA-PCL/simTOR) showed high knockdown efficiency toward mTOR and growth inhibition of not only PTEN-null but also PTEN-positive tumor cells which are not susceptible to the treatment with rapamycin. The efficacy of simTOR was different from that of rapamycin because simTOR but not rapamycin inhibited Akt phosphorylation in PTEN-positive cells. In addition, APRPG-TEPA-PCL/simTOR significantly inhibited both the proliferation and tube formation of 2H-11 (PTEN-positive) murine endothelial cells. Potential of APRPG-TEPA-PCL/simTOR *in vivo* was investigated in B16F10 (PTEN-positive) murine melanoma-bearing mice. APRPG-TEPA-PCL/simTOR administered intravenously showed significantly high accumulation in the lungs bearing metastatic B16F10 melanoma compared with non-targeted TEPA-PCL/simTOR. Intravenous administration of APRPG-TEPA-PCL/simTOR significantly suppressed the growth of metastatic B16F10 melanoma compared with other groups such as rapamycin. These findings suggest that inhibition of the mTOR signaling pathway using APRPG-TEPA-PCL/simTOR is a potential strategy for targeted cancer therapy against PTEN-positive tumors.

Biography

Tomohiro Asai got his Ph.D. from University of Shizuoka Graduate School of Pharmaceutical Sciences, Japan. He is currently an Associate Professor of Graduate Division of Pharmaceutical Sciences at University of Shizuoka. He has published more than 65 papers in reputed journals. He received The Pharmaceutical Society of Japan Award for Young Scientists in 2011.