Medical & healthcare, Drug development, Cancer treatment

Improvement of tumor targeting efficiency of nanoparticles in combination with oncolytic reovirus

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Researchmap https://researchmap.jp/read0165081/?lang=en

Abstract

PEGylated liposomes (PEG-liposomes) are a promising drug delivery vehicle for tumor targeting because of their efficient tumor disposition profiles. However, tumor targeting of PEG-liposomes is often disturbed by physical barriers in the tumor, including tumor cells themselves and extracellular matrices. In this study, tumor-bearing mice were injected intravenously with oncolytic reovirus before administration of PEG-liposomes to enhance PEG-liposomes' tumor disposition. Reovirus mediated significant expression of reovirus sigma 3 protein, elevation of apoptosis-related gene expression, and activation of caspase 3 in the tumors, indicating that reovirus efficiently replicated in the tumors and induced apoptosis of tumor cells. The tumor disposition levels of PEG-liposomes were approximately doubled by reovirus pre-administration, compared with a PBS-pretreated group. PEG-liposomes were widely distributed in the tumors of reovirus-pretreated mice, whereas in the PBS-pretreated group, PEG-liposomes were found mainly around or inside the blood vessels in the tumors. Furthermore, pretreatment with reovirus led to the enhancement of PEG-liposome accumulation inside the tumors. Combination treatment with reovirus and paclitaxel-loaded PEG-liposomes (PTX-PEG-liposomes) significantly suppressed the tumor growth. These results provide important information for clinical use of combination therapy of reovirus and nanoparticle-based drug delivery system (DDS).

Background & Results

PEGylated liposomes (PEG-liposomes) are a promising drug delivery nanoparticle for tumor targeting because of their efficient tumor disposition profiles via the enhanced permeability and retention (EPR) effect. However, tumor targeting of PEG-liposomes, particularly their delivery inside the tumors, is often disturbed by physical barriers in the tumor, including tumor cells themselves, extracellular matrices, and interstitial pressures. In this study, tumor-bearing mice were injected intravenously with oncolytic reovirus, which mediates efficient cell lysis activity in not only tumor cells but also cancer-associated fibroblasts, before administration of PEG-liposomes to enhance PEG-liposomes' tumor disposition. Reovirus mediated significant expression of reovirus sigma 3 protein, elevation of apoptosis-related gene expression, and activation of caspase 3 in the tumors, indicating that virus infection and apoptosis were induced inside the tumors. The tumor disposition levels of PEG-liposomes were approximately doubled by reovirus pre-administration, compared with a PBS-pretreated group. PEG-liposomes were widely distributed in the tumors of reovirus-pretreated mice, whereas in the PBS-pretreated group, PEG-liposomes were found mainly around or inside the blood vessels in the tumors. Furthermore, pretreatment with reovirus led to the enhancement of PEG-liposome accumulation inside the tumors. Combination treatment with reovirus and paclitaxel-loaded PEG-liposomes significantly suppressed the tumor growth.

Significance of the research and Future perspective

Oncolytic viruses, including reovirus, are expected to enhance each other's antitumor effects when used in combination with tumor-targeted DDS agents. Various types of tumor-targeted DDS agents have been developed, and further improvement in therapeutic efficacy can be expected when used in combination with novel tumor-targeted DDS technologies in the future.

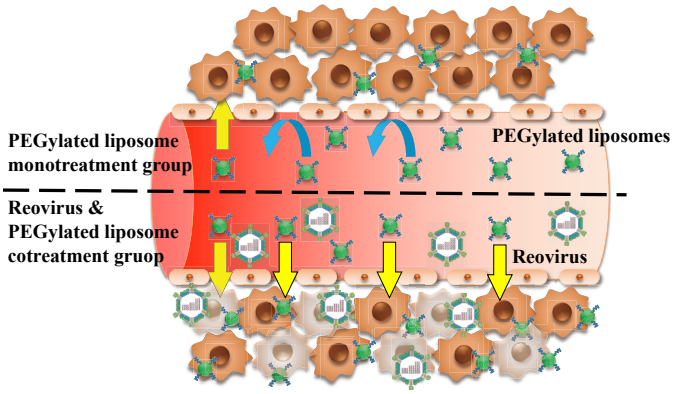

Figure 1. Outline of this study.

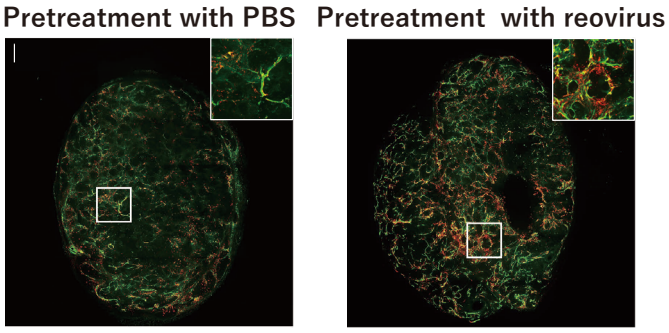

Figure 2. Tumor accumulation of PEGylated liposomes
Red; PEGylated liposome, Green; endothelial cells

Patent
Treatise Eguchi, Maho; Mizuguchi, Hiroyuki; Sakurai, Fuminori. Pre-treatment of oncolytic reovirus improves tumor accumulation and intratumoral distribution of PEG-liposomes. Journal of Controlled Release (2023) 354, 35-44. doi: 10.1016/j.jconrel.2022.12.050
URL
Keyword reovirus, tumor targeting, EPR effect, PEGylated liposome, drug delivery system