A pH-responsive nanoparticle delivery system containing dihydrazidine and doxorubicin-based prodrug for enhancing anti-tumor efficacy

Lianxue Zhang[1], Jianxiang Huang[1], Damiano Buratto[1], Panli Han[2], Zaixing Yang[2], and Ruhong Zhou[1]

[1]Zhejiang University
[2]Soochow University

July 29, 2023

Abstract

The efficacy of nanoparticle (NP)-based drug delivery technology is hampered by aberrant tumor stromal microenvironments (TSMs) that hinder NP transportation. Therefore, the promotion of NP permeation into deep tumor sites via the regulation of tumor microenvironments is of critical importance. Herein, we propose a potential solution using a dihydrazidine (HDZ)-loaded nanoparticle drug delivery system containing a pH-responsive, cyclic RGD peptide-modified prodrug based on doxorubicin (cRGD-Dex-DOX). With a combined experimental and theoretical approach, we find that the designed NP system can recognize the acid tumor environments and precisely release the encapsulated HDZ into tumor tissues. HDZ can notably downregulate the expression levels of hypoxia-inducible factor 1α (HIF1α), α-smooth muscle actin, and fibronectin through the dilation of tumor blood vessels. These changes in the TSMs enhance the enrichment and penetration of NPs and also unexpectedly promote the infiltration of activated T cells into tumors, suggesting that such a system may offer an effective "multifunctional therapy" through both improving the chemotherapeutic effect and enhancing the immune response to tumors. In vivo experiments on 4T1 breast cancer bearing mice indeed validate that this therapy has the most outstanding antitumor effects over all the other tested control regimens, with the lowest side effects as well.

Hosted file

`Dihydazidine nanodrug-Aggregate.docx` available at https://authorea.com/users/644427/articles/657335-a-ph-responsive-nanoparticle-delivery-system-containing-dihydrazidine-and-doxorubicin-based-prodrug-for-enhancing-anti-tumor-efficacy