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Authors: Shu Yang, Huile Gao

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Nanoparticles for modulating tumor microenvironment to improve drug delivery and tumor therapy

Shu Yang, Huile Gao*

Key Laboratory of Drug Targeting and Drug Delivery Systems, West China School of Pharmacy, Sichuan University, Chengdu, China

Corresponding author, E-mail: gaohuile@scu.edu.cn

Abstract:
Tumor microenvironment (TME) plays a critical role in tumorigenesis, tumor invasion and metastasis. TME is composed of stroma, endothelial cells, pericytes, fibroblasts, smooth muscle cells, and immune cells, which is characterized by hypoxia, acidosis, and high interstitial fluid pressure. Due to the important role of TME, we firstly reviewed the composition of TME and discussed the impact of TME on tumor progression, drug and nanoparticle delivery. Next, we reviewed current strategies developed to modulate TME, including modulating tumor vasculature permeability, tumor associated macrophage phenotypes, tumor associated fibroblasts, tumor stroma components, tumor hypoxia, and multiple interventions simultaneously. Also, potential problems and future directions of TME modulation strategy have been discussed.

Keywords: Tumor microenvironment, nanoparticles, drug delivery, tumor associated fibroblasts, tumor-associated macrophages, hypoxia

Introduction

Malignant tumors remain one of the most dreaded killers threatening human life, and effective therapeutic strategies are thus urgently needed. Early on, extensive researches have focused on the studies of tumor cells and host cells, while the critical role of tumor microenvironment (TME) during tumor progression, invasion and metastasis remained largely unexplored. However, with the increasing understanding of tumor progression, TME has been proven critical during tumorigenesis.[1, 2] Studies have focused on developing therapies and relevant delivery systems to target, modulate and even disrupt TME.

Nanoparticles (NPs) have been extensively used as drug delivery systems because NPs could not only increase the drugs' biocompatibility and solubility, but also prolong their blood circulation time. Moreover, specific modification on the surface of NPs could enhance the tumor targeting delivery and the following treatment outcome.[3] Several nanomedicines have been approved by FDA for clinical use, most of which are liposomes, albumin NPs and poly(lactic acid) NPs, such as Doxil and Abraxane. These nanomedicines could passively target tumors owing to enhanced permeability and retention (EPR) effect. However, EPR effect may not always work on various tumors and individuals due to individual differences and the heterogeneity of tumors, which result in the lack of in vitro-in vivo correlation and even the clinical failure of nanomedicines.[4, 5] Thus, modulating TME offers alternative strategies to further improve tumor targeted NPs delivery and consequently the treatment outcome.

Herein, we reviewed TME and its influence on drug delivery, NP delivery, tumor growth,