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Enhancing chemotherapy for pancreatic cancer through efficient and sustained tumor microenvironment remodeling with a fibroblast-targeted nanosystem

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ABSTRACT

Pancreatic cancer (PC) carries a poor prognosis among all malignancies and poses great challenges to clinical drug accessibility due to the severely fibrotic and hypoxic tumor microenvironment (TME). Therein, cancer-associated fibroblasts (CAFs), which are extremely abundant in PC, play a key role in forming the complex PC microenvironment. Therefore, a highly efficient TME reprogramming therapeutic paradigm that can specifically inhibit CAF function is urgently needed. Herein, we successfully developed a novel CAF-tailored nanosystem (Dex-GP-DOCA, DPD) loaded with a potent anti-fibrosis flavonoid compound (Quercetin, QUE), which possesses biological responsiveness to fibroblast activation protein alpha (FAP-α), prolonged TME remodeling and enhancement of clinical chemotherapeutics. Specifically, DPD/QUE allowed for extracellular matrix (ECM) reduction, vessel normalization, hypoxia-induced drug resistance reversal, and blockade of Wnt16 paracrine in CAFs. More importantly, this chemotherapy conducive microenvironment persisted for at least 8 days following treatment with DPD/QUE. It should also be noted that the effective and prolonged microenvironment modulation induced by DPD/QUE significantly improved the chemotherapy sensitivity of Abraxane and gemcitabine, the first-line chemotherapeutic drugs for PC, with inhibition rates increasing from 37.5% and 40.0% to 87.5% and 85.2%, respectively. Overall, our CAFs-targeted nanosystem showed promising prospects for remodeling the TME and facilitating chemotherapy for refractory pancreatic cancer.

1. Introduction

Pancreatic cancer (PC) remains a major threat to human health with rapid onset, progression, and lethality. Over 90% of pancreatic malignancies are classified into pancreatic ductal adenocarcinoma (PDAC) [1,2]. Due to the early metastatic potential pancreatic cancer, the five-year survival rate at the time of diagnosis is often only 5%. Currently, chemotherapy is the only mainstay in clinical treatment [3]. However, PDAC chemotherapy is refractory and often does not prolong survival [4]. As the first-line standard treatment of PDAC, gemcitabine (Gem) has shown a compromised response with a median survival time (MST) of only 4 to 6 months [5]. In recent years, combined chemotherapy has become an optimal clinical strategy in improving the treatment of PDAC, such as FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) and Abraxane (albumin bound paclitaxel nanoparticle)/Gem [6,7]. Although a combination of drugs enhances antitumor responses via synergistic or additive effects against key cellular pathways, a limited improvement in outcome was reported with only a 6 to 9-month improvement in survival [8–10]. Particularly, combination chemotherapy such as FOLFIRINOX displayed increased rates of overall toxicity [11]. Hence, an effective therapeutic paradigm is still urgently needed.

The PC microenvironment is characterized by an extremely fibrotic, hypoxic, and abnormal vasculature, which significantly hinders the efficacy of PADC chemotherapy [12–15]. In specific, an abundant desmoplasia takes up over 90% of the total tumor volume, inducing elevated interstitial fluid pressure (IFP), abnormal neoplastic vasculature, and a complex stromal barrier against drug delivery [16–18]. The

Abbreviations: PC, pancreatic cancer; CAFs, cancer associated fibroblasts; FAP-α, fibroblast activation protein alpha; DPD, Dex-Gly-Pro-DOCA; DGD, Dex-Gly-Gly-DOCA; QUE, quercetin; NPs, nanoparticles; Gem, gemcitabine..

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