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Necrosis of cervical carcinoma by dichloroacetate released from electrospun polylactide mats

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ABSTRACT

It is still a great challenge to apply therapeutic concentration of anti-cancer drugs to the tumor site with low system toxicity. An in situ administration strategy was applied to reverse the aerobic glycolysis of tumor *in vivo* for the first time. Controlled release of therapeutic concentration of dichloroacetate (DCA) from polylactide (PLA) electrospun mats covering the solid tumor locally was designed to suppress the cervical carcinoma *in vivo*. A dramatic decrease in the volume and weight of tumors was observed for 19 days in tumor-bearing mice, and a totally 96% of the tumor suppression degree was obtained even the initial tumor volume was around 200 mm^3. Half of the mice recovered in less than 3 weeks. Necrosis was examined rather than apoptosis on the tumor cells as the main process of cell death induced by the DCA-loaded electrospun mats. A proposed necroptosis mechanism was presented to explain the signal pathways that were induced by the metabolic remodeling of DCA. It provided support for this strategy that target the bio-energy metabolism of the cervical carcinoma locally is a quick and effective pathway to cure the advanced-carcinoma of cervical.

1. Introduction

Therapeutic window is always the bottleneck of the battle on invasive cancer, such as cervical carcinoma [1]. Although many targeting therapeutic strategies have been developed, the management of malignant cervical-cancer still remains clinical challenge because of the difficulty to apply high concentration of anti-cancer drugs to the tumor site [2]. Reprogramming on energy metabolism is an inherent attribute of this aggressive cancer [3]. This important discovery sped up the research on metabolism [4] and mitochondria [5] targeting for cancer therapy, which provides a new cancer targeting therapeutic strategy to sever the bio-energy supply of the malignant proliferation of cancer.

Tumor cells exhibit an altered metabolism which allows them to proliferate at a high rate and resist some cell death signals [4]. Among these metabolic mutations, the best characterized metabolic phenotype observed in tumor cells is the Warburg effect (aerobic glycolysis) [6], an oncological observation that cancer cells tend to “ferment” glucose into lactate even in the presence of sufficient oxygen to support mitochondrial oxidative phosphorylation (OXPHOS) [7]. This bio-energetic feature is a distinctive marker of tumor cells relying mostly on aerobic glycolysis for energy production [8,9] and is thought to be an ideal target for metabolic-targeting therapy [10].

The orally available small molecule dichloroacetate (DCA), which is a metabolic modulator, was found competent to reverse the aforementioned bio-energetic profile of cancer by inhibiting the pyruvate dehydrogenase kinase (PDK) and boosting the flux of pyruvate into the mitochondria [11]. This pyruvate mimetic compound showed remarkable anti-cancer effects by metabolism reversion in preclinical studies [12–14] and has already been tested in clinical trials (NCT00540176, NCT00566410, NCT00703859). Patient data illustrated the improvement in quality life with DCA therapy during the clinical trials [15–18]. However, the adequate dosage to induce the kill of cancer cells is not commonly recommended since there are still some side-effects if high-dose of DCA is spreading out the whole body [19,20]. The low level of the saturated DCA in serum significantly narrowed the therapeutic window of DCA, making it difficult to achieve a better therapeutic effect for tumor by means of oral administration [21].

Instead of the oral administration, the new dosage form for the controlled release of anti-cancer drugs from the biodegradable polymeric electrospun mats in the scale of micrometers and nanometers [22] may meet the requirement of high dosage administration. In our work, DCA was incorporated into the

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