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ACCEPTED MANUSCRIPT

Combination of DESI2 and endostatin gene therapy significantly improves antitumor efficacy by accumulating DNA lesions, inducing apoptosis and inhibiting angiogenesis

Huaying Yan^{a,b1}, Wenhao Guo^{c1}, Ke Li^a, Mei Tang^a, Xinyu Zhao^a, Yi Lei^a, Chun-lai Nie^a and Zhu Yuan^{a,*}

^aState Key Laboratory of Biotherapy /Collaborative Innovation Center of Biotherapy and Cancer Center, West China Hospital, 17# People's South Road, Chengdu, Sichuan University, Chengdu, China, 610041 ^bDepartment of Ultrasound, Women's and Children's Hospital Affiliate to Chengdu Medical College, 290#

Sha Yan West Two Street, Jinyang Road, Wuhou District, Chengdu, 610031

^cDepartment of Abdominal Oncology, Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University

*To whom correspondence should be addressed: Zhu Yuan, State Key Laboratory of Biotherapy Tel: +86-28-85164063; Fax: +86-28-85164060; E-mail: yuanzhu@scu.edu.cn

ABSTRACT

DESI2 is a novel pro-apoptotic gene. We previously reported that DESI2 overexpression induces S phase arrest and apoptosis by activating checkpoint kinases. This work was to test whether the combination of endostatin, an endogenous antiangiogenic inhibitor, with DESI2 could improve the therapy efficacy *in vitro* and *in vivo*. The recombinant plasmid co-expressing DESI2 and endostatin was encapsulated with DOTAP/Cholesterol cationic liposome. Mice bearing CT26 colon carcinoma and LL2 lung cancer were treated with the DNA-liposome complex. We found that, *in vitro*, the combination of DESI2 and endostatin more efficiently inhibited proliferation of CT26, LL2, HCT116 and A549 cancer cells *via* apoptosis, as assessed by MTT assay, colony-formation assays, flow cytometric analysis, hoechst staining and activation of caspase-3, respectively. In addition, DESI2 overexpression caused up-regulation of RPS7, a substrate of DESI2 deubiquitination. Furthermore, siRNA targeting RPS7 partially abrogated, whereas RPS7 overexpression enhanced DESI2-induced inhibition of cell proliferation. Importantly, the combination also caused DNA lesions accumulation, which further promotes apoptosis. Mechanistic rationale suggested

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¹ Those authors contributed equally to this work

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