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Vaginal Delivery of High Fidelity CRISPR/Cas9 Nanoparticle Effectively Reverses Cervical Cancer

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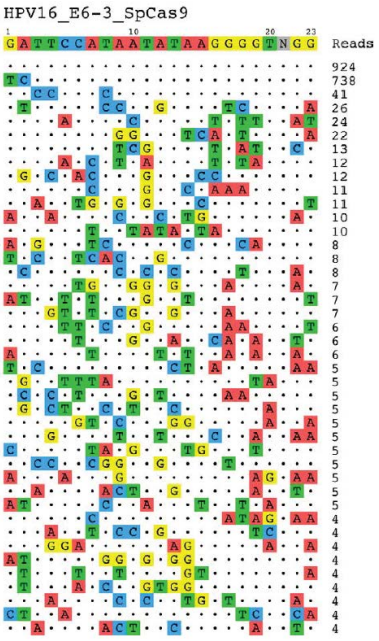
Background and Aims: CRISPR/Cas9-mediated genome editing is a promising antiviral strategy, but its potential off-target effects greatly limit its clinical application. HPV infection is the key etiologic factor of cervical cancer. The aim was to use high specific SpCas9 variant and sgRNAs targeting the HPV 16 E6/E7 to eliminate HPV and reverse cancer.

Methods: We designed and screened efficient sgRNA to target HPV16 E6/E7 by T7E1. Cell apoptosis assay was used to compare the efficiency of inducing HPV type-specific apoptosis of different Cas9s. Moreover, we used GUIDE-seq technology to compare the on-target and off-target of SpCas9 and SpCas9-HF1. Importantly, we evaluated the effect of CRISPR reversing carcinogenesis by vaginal delivery of PBAE/SpCas9-HF1/HPV 16 E6-3 sgRNA nanoparticle targeting HPV16 E6 in K14-HPV transgenic mice.

Results: We identified that HPV 16 E6-3 sgRNA possesses the highest editing efficiency (34%), followed by HPV 16 E7-1 sgRNA (29.3%) when combined with SpCas9. Similar to SpCas9, SpCas9-HF1 can more effectively induce HPV positive cell apoptosis (27.6%) than eSpCas9 (21.3%). The off target of SpCas9-HF1 was significantly lower than SpCas9. Moreover, direct cervical application of PBAE/ SpCas9-HF1 nanoparticle targeting HPV16 E6 effectively is reversing the cervical lesions.

Conclusion: High fidelity CRISPR/Cas9 targeting HPV16 E6 could effectively cleavage HPV and lead to type-specific apoptosis of HPV-positive cells with low off-target effect. Importantly, direct delivery of PBAE/CRISPR nanoparticle targeting HPV16 E6/E7 directly to the cervix via the vagina is a safe and effective strategy for the treatment of HPV-related cervical lesions.



Biography:

Rui Tian is a PhD student of the First Affiliated Hospital, Sun Yat-Sen University. Her work focuses specifically on (i) the mechanisms of HPV integration and its carcinogenic mechanism, and (ii) using different off-target assessment methods to select the most efficient and safe Cas proteins and sgRNAs to eliminate persistent HPV infection both in vitro and in vivo, thus paving the way for their therapeutic potential in the clinic. Her recent publication can be found in carcinogenesis journal.