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Inhibition of DNA replication of human papillomavirus by gene and protein delivered zinc finger based artificial endonucleases

Takashi Sera
Okayama University, Japan

Previously, we reported that artificial zinc-finger proteins (AZPs) inhibited virus DNA replication in planta and in mammalian cells by blocking binding of a viral replication protein to its replication origin. However, the replication mechanisms of viruses of interest need to be disentangled for the application. To develop more widely applicable methods for antiviral therapy, we explored the feasibility of inhibition of HPV-18 replication as a model system by cleaving its viral genome. To this end, we fused a nuclease cleaving DNA as a monomer to an AZP that binds to the viral genome. The resulting artificial endonuclease cleaved its target DNA plasmid efficiently and sequence specifically *in vitro*. Then, we confirmed that transfection with a plasmid expressing the artificial endonuclease inhibited HPV-18 DNA replication in transient replication assays using mammalian cells. Linker mediated PCR analysis revealed that the artificial endonuclease cleaved an HPV-18 ori plasmid around its binding site. Finally, we demonstrated that the protein delivered artificial endonuclease inhibited HPV-18 DNA replication as well and did not show any significant cytotoxicity. Thus, both gene and protein delivered zinc finger based artificial endonucleases efficiently inhibited HPV-18 DNA replication, leading to development of a more universal antiviral therapy for human DNA viruses.

sera@cc.okayama-u.ac.jp

HPV prevalence and cervical cancer screening practices in countries of the former Soviet Union

Rogovskaya S and **Podzolkova N**
Russian Medical Academy of Post-Graduate Education, Russia

The burden of HPV and associated diseases in Russia and Western Countries of the former Soviet Union (Ukraine, Belarus and Moldova), Caucasus region and Central Asia (Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan) is hard. Both cervical cancer incidence and mortality have increased in these countries despite various cancer prevention initiatives. The review available data on HPV prevalence and on national policies of cervical cancer screening and HPV vaccination initiatives is presented. Based on the data published in HPV centre, Monograph 2013 from the 12 countries, high risk HPV (hrHPV) prevalence ranges from 13.4% to 36.2% in women with normal cytology and is highest in younger age groups. The most common hrHPV type was HPV16, followed by HPV56, HPV31, HPV33, HPV18 and HPV45. In ASCUS and low grade lesions hrHPV prevalence varied from 29% to 33% and from 52 to 100%, respectively. HrHPV infection in women with high grade cervical lesions (HSIL) and cervical cancer ranged from 60.0 to 100%. HPV16 was the most prevalent HPV genotype in cervical cancer and HSIL, followed by HPV31, HPV33, HPV18, HPV39, HPV52 and HPV56. As the HPV profile in cervical diseases seems to be similar to that found in Western Europe the implementation of HPV testing in screening programs might be beneficial. Finally, HPV vaccination is currently not widely implemented in most of the twelve countries mainly due to pricing, availability, and limited awareness among public and health care providers. Opportunistic screening programs, the lack of efficient call-recall systems, low coverage, and the absence of quality assured cytology with centralized screening registry are major reasons for low success rates of cervical cancer programs in many of the countries. Country-specific research, organized nationwide screening programs, registries and well defined vaccination policies are continued and being discussed.

srogovskaya@mail.ru