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Okayama University research: Nanotechnology-based approach to cancer virotherapy

(Okayama, 03 February) **Researchers at Okayama University report in *Scientific Reports* a promising method for delivering viral DNA, able to eliminate cancerous cells, to a tumor. The approach, involving encapsulation of the DNA in liposomes, has the potential to enable intravenous delivery of virus-based antitumor agents.**

The principle behind oncolytic virotherapy, an emerging cancer treatment strategy, is to introduce viruses in tumors to infect and kill cancer cells. The targeted delivery of oncolytic viruses to a tumor site is, however, a bottleneck in the development of the therapy — normally, non-specific administering of such viruses leads to their neutralization by the immune system. Inspired by the potential of using nanoparticles for drug-delivery, Professor Toshiyoshi Fujiwara and Associate Professor Hiroshi Tazawa, Assistant Professor Shinji Kuroda from Okayama University have now shown that encapsulating the DNA of a particular type of virus in nano-sized vesicles with a lipid-bilayer shell (so-called liposomes) does not trigger the immune system, while still inhibiting tumor growth.

Liposomes as drug or 'agent' carriers have the advantage of being stable in the bloodstream and can therefore be easily transported. The size of the agent-liposome unit is crucial, however: particles that are too large are usually captured by the reticuloendothelial system (a set of cells forming part of the immune system), whereas too-small particles end up in urine. Professor Fujiwara and colleagues realized that the virus they wanted to use (of a type known as adenovirus, with a diameter of 90 to 100 nm) would result in a too-largeagent-liposome cluster. They therefore encapsulated only the plasmid DNA of the virus — DNA in non-chromosomal form, but still able to replicate.

The scientists first confirmed that their clusters (abbreviated 'Lipo-pTS') display proper cytotoxic activity. In both *in vitro* and *in vivo* settings, exposure of cancer cells to Lipo-pTS indeed led to cancer cell death from the action of the viral DNA. Then, the research team found that Lipo-pTS has a 'stealth effect' on the immune system: the presence or absence of antibodies to the adenovirus providing the DNA used did not influence cytotoxic function. (Previous experiments with the full adenovirus showed that such antibodies, usually present in adult humans as it is the virus causing the common cold, suppress cytotoxic activity.) Importantly, this implies that systemic delivery of Lipo-pTS, i.e. by oral intake or intravenous injection, is possible.

Professor Fujiwara and colleagues point out that, although their study has limitations — they did not perform animal experiments with systemic administration, for example — they

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believe that it “shows the promising potential of liposome-encapsulated oncolytic adenovirus … for cancer therapy” and they are hopeful that it “will serve as a foundation for development of systemically-deliverable oncolytic viral agents”.

Background

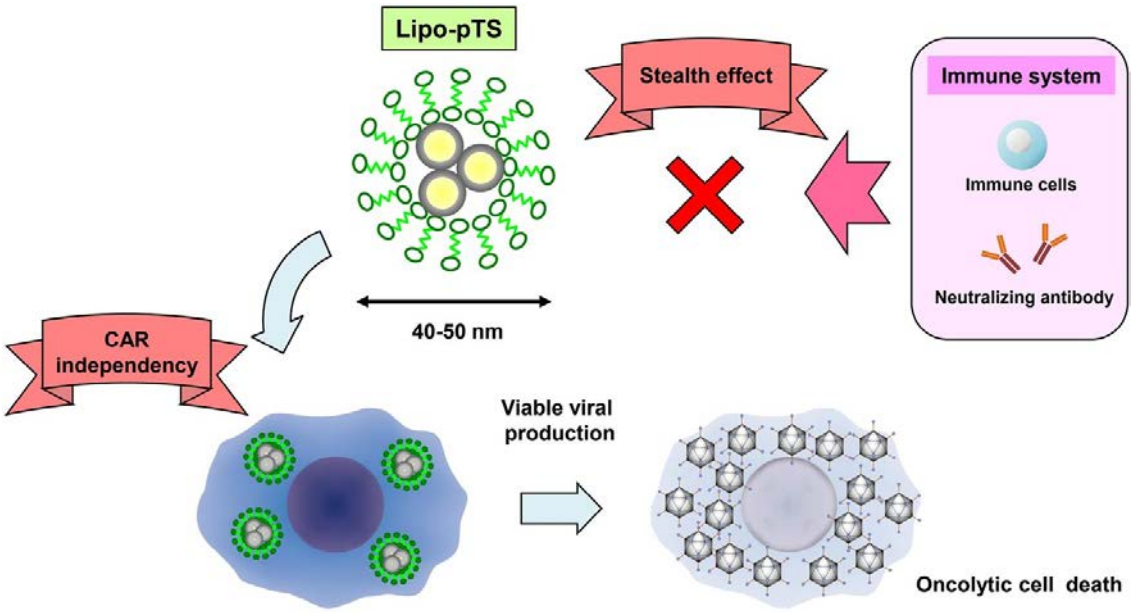
Virotherapy

The idea behind virotherapy is to deploy viruses as agents for treating diseases. In oncolytic virotherapy, the viruses in question target cancerous cells. By now, various oncolytic viruses have been clinically trialed. In 2004, Professor Toshiyoshi Fujiwara from Okayama University and colleagues demonstrated the virotherapeutic activity of so-called telomerase-specific oncolytic adenovirus. Now, Professor Fujiwara and colleagues have shown that taking the DNA of the adenovirus and encapsulating it in liposome results in a deliverable antitumor agent.

Liposomes

Liposomes are spherical particles (vesicles) with a shell composed of a lipid bilayer — two facing layers, consisting of phospholipids, forming a membrane. Liposomes can act as a container for e.g. proteins, peptides and nucleotides, and are easily transportable via the bloodstream. As such, they are common nanoparticles for drug delivery.

The Okayama University researchers have now demonstrated that liposomes can be used for transporting oncolytic viral DNA to a tumor, without triggering the immune system — an important step towards the development of systemic-delivery oncolytic virotherapy methods.



Caption

Viral DNA encapsulated in a liposome can be delivered to a tumor site, resulting in oncolytic cell death, without interference of the immune system.

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Reference
Katsuyuki Aoyama, Shinji Kuroda, Toshiaki Morihiro, Nobuhiko Kanaya, Tetsushi Kubota, Yoshihiko Kakiuchi, Satoru Kikuchi, Masahiko Nishizaki, Shunsuke Kagawa, Hiroshi Tazawa & Toshiyoshi Fujiwara. Liposome-encapsulated plasmid DNA of telomerase-specific oncolytic adenovirus with stealth effect on the immune system. *Scientific Reports*, 7 : 14177, 2017.
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Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Training Place sponsored by the Lord of Okayama and established in 1870. Now with 1,300 faculty and 13,000 students, the University offers courses in specialties ranging from medicine and pharmacy to humanities and physical sciences.

Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.

Website: http://www.okayama-u.ac.jp/index_e.html

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