Okayama University Medical Research Updates （OU-MRU） 2016.08 Vol.28

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Okayama University research: Viral-based therapy for bone cancer

(Okayama, 30 August) Scientists at Okayama University develop a viral-based technique specific to bone cancer that enhances patients' sensitivity to chemotherapy.

Certain cancers, including osteosarcoma (bone cancer), are unresponsive to chemotherapy, making disease prognosis very poor. Osteosarcoma is a rare but severe form of cancer that predominantly affects the growing bones in children and adolescents. The cancerous tissue in osteosarcoma is resistant to chemotherapy, but the precise molecular mechanisms involved are unclear. The search is on to find a way of enhancing the chemo-sensitivity of patients, so that they are more responsive to treatment.

Now, Toshiyoshi Fujiwara and co-workers at Okayama University, Japan, have developed a new combined therapy which uses the properties of a virus to disrupt osteosarcoma cancer cells and enable chemotherapy agents to destroy them. Their findings may transform treatment of bone cancer and other chemo-resistant cancers in future.

One possible target for improving chemo-sensitivity is the BCL2 protein family; these proteins are overexpressed in cancer tissues and aid in the progression of the disease. One such protein is MCL1, whose role is to limit cancer cell death in tumors. The researchers focused on finding a way of downregulating MCL1 in osteosarcoma in the hope that it might encourage chemo-sensitivity.

To do this, Fujiwara's team used their newly-engineered 'telomerase-specific ocolytic adenovirus OBP-301 (telomelysin)', which they had previously shown could reduce the growth of stomach tumors. They created a combined therapy using OBP-301 with chemotherapy agents. The researchers found that OBP-301 activated microRNA-29, which in turn worked to downregulate MCL1. MCL1 knockdown resulted in high levels of cancer cell death in osteosarcoma tumors, weakening the tumors and leaving them open to the effects of chemotherapy.

As the researchers state in their paper in *Nature Scientific Reports*; "Virus-mediated telomerase-specific targeting of MCL1 expression offers a promising strategy to improve the clinical benefits of conventional chemotherapy in osteosarcoma patients."

Background

Adenoviruses

Adenoviruses are common, stable and hardy viruses that have been increasingly used as vectors (or 'carriers') for vaccines and in gene therapy for targeting multiple illnesses. The viruses are capable of infecting multiple cell types, and can therefore be used to target

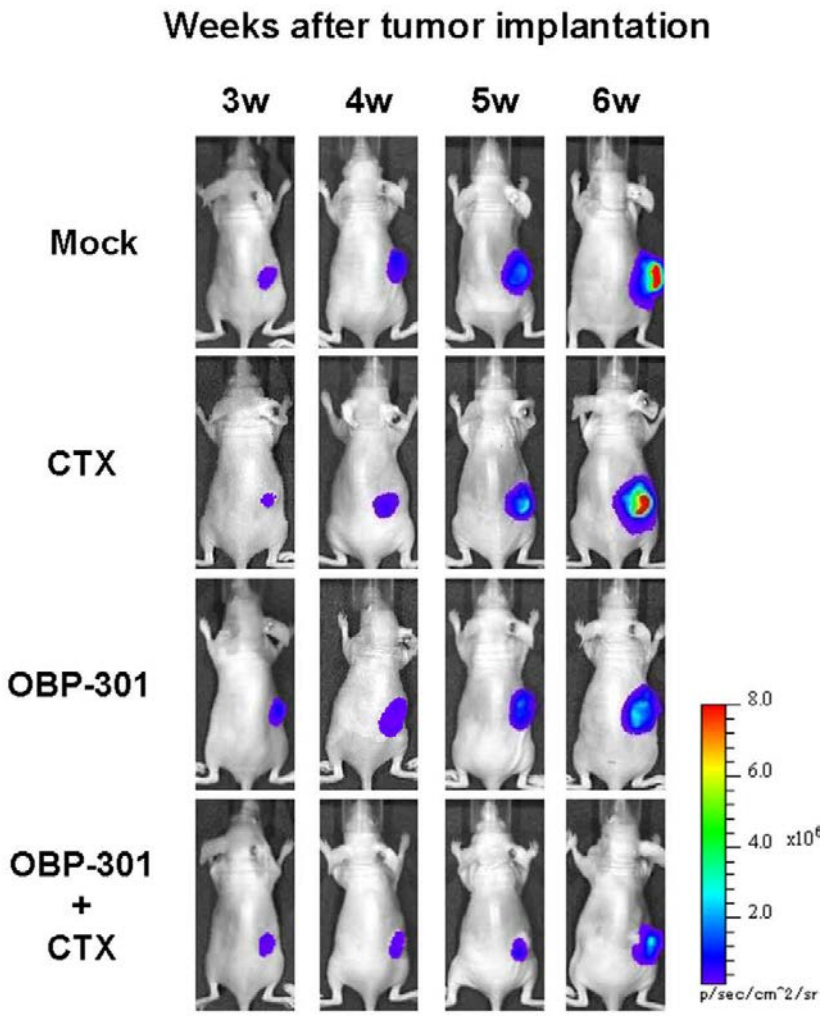
specific diseased cells such as cancerous tissue. The adenoviruses have a relatively simple genome, meaning scientists can modify the genome easily to carry out specific jobs in targeted tissues.

In this study, Toshiyoshi Fujiwara and his team adapted an adenovirus (labelled OBP-301) to target and downregulate the MCL1 protein in osteosarcoma. They created a combined therapy using OBP-301 with chemotherapy agents, which they trialed on both *in vitro* tissue samples and *in vivo* conditions (using a xenograft model). They found that the therapy activated microRNA molecules (including miR-29) which worked to knockdown MCL1, resulting in higher levels of cancer cell death in tumors. This then made the tumors more vulnerable to the effects of chemotherapy.

Crucially, the therapy specifically targets tumors and does not impact on surrounding healthy cells.

Future work

Further investigations are needed into patient tolerance of the combined therapy, and whether or not the treatment is safe, efficient and effective in humans.



Caption

Researchers at Okayama University have developed a combined therapy (OBP-301 plus CTX in image) using an adenovirus and chemotherapy agents to induce chemo-sensitivity in bone cancer tumors. Their success could transform treatment for bone cancer sufferers and other chemo-resistant forms of cancer in future.

Reference

Shuhei Osaki, Hiroshi Tazawa, Joe Hasei, Yasuaki Yamakawa, Toshinori Omori,Kazuhisa Sugiu, Tadashi Komatsubara, Tomohiro Fujiwara, Tsuyoshi Sasaki, Toshiyuki Kunisada, Aki Yoshida, Yasuo Urata, Shunsuke Kagawa, Toshifumi Ozaki, and Toshiyoshi Fujiwara. Ablation of MCL1 expression by virally induced microRNA-29 reverses chemoresistance in human osteosarcomas. *Scientific Reports*, 6, Article number: 28953 (2016)
DOI : 10.1038/srep28953
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Reference (OU-MRU) : Professor Fujiwara's team

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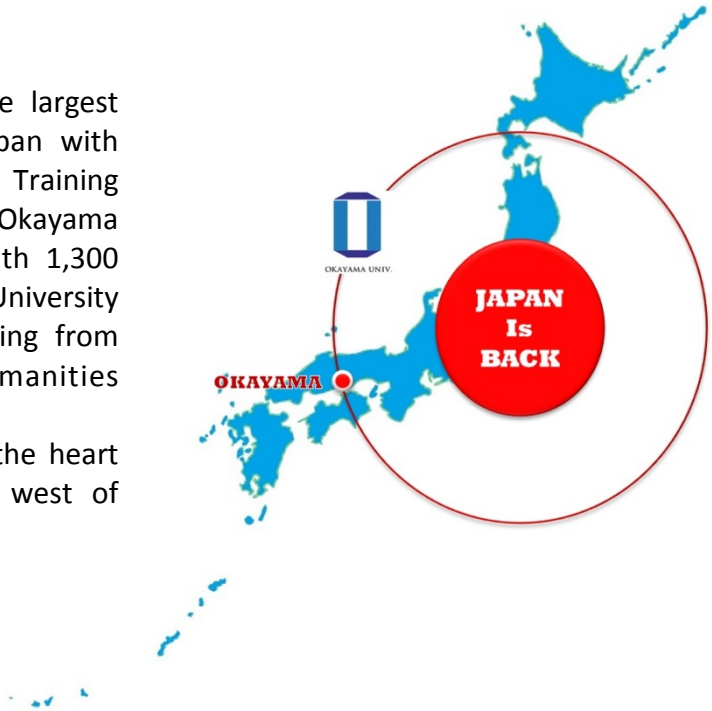
About Okayama University

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 14,000 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.



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