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Okayama University research: Anticancer virus solution provides an alternative to surgery

(Okayama, 25 February) **Researchers at Okayama demonstrate that injection of a virus solution followed by tumour removal can eradicate cancer metastasis in lymph nodes without the need for preventative surgery.**

While early-stage gastrointestinal cancers can be treated non-surgically, once the cancer has invaded to a particular depth preventative – ‘prophylactic’ – surgery is routine. The frequency of lymph node metastasis increases significantly once the cancer has penetrated the submucosal layers, and as there is no way of determining whether the cancer has metastasized in the lymph nodes they will be surgically removed just in case. Now researchers at Okayama University and the University of California in San Diego have demonstrated that injection of a viral solution can eradicate lymph node metastasis making prophylactic surgery unnecessary.

To treat early stage cancers a saline solution is injected creating a fluid cushion, which raises and isolates the tumour. The tumour is then readily removed by equipment through a standard endoscopic viewing tube inserted in the gastrointestinal tract. However if the cancer has already penetrated the submucosal layer it will be prone to relapse in the lymphatic system.

Toshiyoshi Fujiwara and his colleagues adapted the standard endoscopic treatment by injecting a solution of Telomelysin - a virus known to kill epithelial and mesenchymal malignant cells - instead of saline solution. They tested the treatment in a mouse model, injecting green-fluorescent-protein-labelled cancer cells into the submucosal layers of the rectum, which developed lymph node metastasis. Fluorescence imaging showed that cancer cells were successfully eliminated by the treatment with virus solution, in contrast to mice treated with saline solution instead. In addition, treated mice showed no relapse four weeks after the treatment

In their report of the results the researchers conclude, "From a clinical view point, this new, simple, and robust strategy is a more realistic and promising bench-to-bedside translation than prophylactic surgery for ablation of potential lymph node metastases in early gastrointestinal cancer patients."

Background

Submucosal layer cancer invasion

Early stage gastrointestinal cancers are defined by the level of the cancer invasion reaching no further than the submucosa. Endoscopic treatment removes these tumours by dissecting the submucosal layers.

For esophageal gastric and colorectal submucosally invaded cancers the frequency at which the cancer is found to metastasize in the lymph nodes is approximately 10 to 20%. The lymphatic system distributes fluids, proteins, chemicals, cells and drugs. This makes it a major pathway for the spread of metastatic cancers so that cancerous invasion of the lymphatic system is particularly problematic.

It is very difficult to determine whether the cancer has metastases in the lymph nodes. As a result lymph node surgery just in case is routine when treating esophageal gastric and colorectal submucosal cancers, even though in many cases it may not have been necessary.

Anticancer viruses

Previous research has demonstrated that certain viruses replicate in cancer cells and break them down, and may be developed for cancer treatments. The researchers further exploited the role of the lymph system in mediating proteins and fluids, a function which makes it more prone to exposure to a virus injected in the surrounding area.

The researchers experimented with Telomelysin – a telomerase-dependent, tumor-killing replicating adenoviral agent (OBP-301). The virus is known to kill epithelial and mesenchymal malignant cells.

Exploiting lymphatic functions with the virus

The researchers first tested the virus on green-fluorescent-protein-labelled colorectal cancer cell lines with. Using fluorescence imaging they observed rapid cell death in response to injection with the virus while there was no such response in cell lines treated with mutant strains of the virus that had replication deficiencies.

The researchers demonstrated how their treatment exploited the lymph node function using mouse models injected with red-fluorescent-protein-labelled lymph node metastasized cancer cells. After six days the virus labelled with green fluorescent protein was injected and fluorescence images showed the position of the virus coincided with the metastatic foci in the lymph nodes.

Reference

Kikuchi S, Kishimoto H, Tazawa H, Hashimoto Y, Kuroda S, Nishizaki M, Nagasaka T, Shirakawa Y, Kagawa S, Urata Y, Hoffman RM, Fujiwara T: Biological Ablation of Sentinel Lymph Node Metastasis in Submucosally Invaded Early Gastrointestinal Cancer. *Mol Ther.* 2014 Dec 19.

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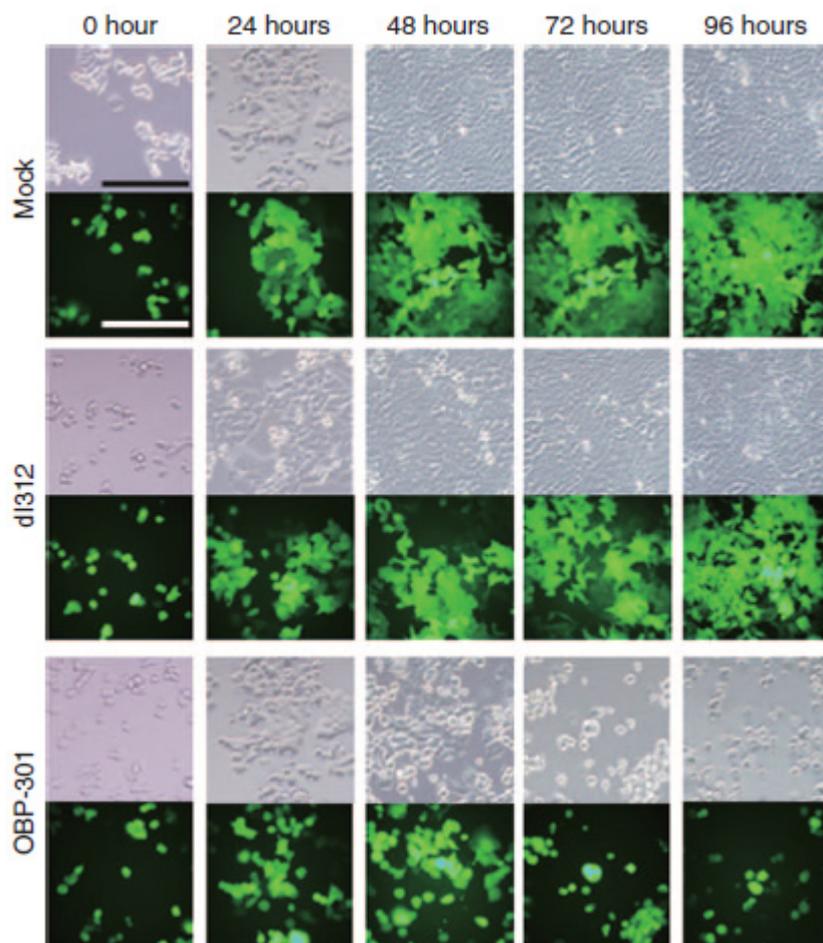


Figure caption

Cytopathic effect of the virus (OBP-301) on human colorectal cancer cell lines. (a) Green-fluorescent-protein (GFP)-labelled colorectal cancer cells were infected with replication-deficient adenovirus (dl1312) or the treatment virus (OBP-301) at a multiplicity of injection (MOI) of 10. Cell morphology and GFP expression were evaluated at the indicated time

points by phase-contrast (top panels) and fluorescence (bottom panels) microscopy, respectively. Magnification: $\times 200$. Scale bar, 200 μm .

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