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Okayama University research: Diabetes drug helps towards immunity against cancer

(Okayama, 23 March) **Studies reveal how a diabetes drug helps towards the rejection of tumours by supporting immune cells.**

A 30-40% decrease in the risk of cancer has been observed in patients using the drug metformin to treat diabetes 2. This characteristic is in striking contrast with insulin-based diabetes treatments, which are linked to increases in cancer, however the mechanism behind metformin's anticancer effects has so far not been well understood. Now Heiichiro Uono and colleagues at Okayama University and Kawasaki University in Japan explain these anticancer responses in a report investigating the drug's effects on the immune system's T cells.

The researchers tested the effects of dissolving metformin in the drinking water of mice injected with leukaemia cells and confirmed complete rejection of the tumours. When the mice were subsequently re-injected with twice the amount of cancer cells, no tumours formed suggesting an immunologic memory response. Renal and skin cancers also responded to the treatment and low doses similar to diabetes prescription concentrations were still effective for tumour rejection. Further experiments with mice lacking certain cell types showed that the influence of metformin on CD8⁺ T cells in particular was responsible for the anticancer effects.

During chronic diseases including cancer, CD8⁺ T cells undergo a process called 'immune exhaustion', where after repeated antigen (Ag) stimulation the cells can no longer secrete chemicals crucial for the immune system to function. 'Apoptosis' or cell death of these exhausted T cells ensues. The researchers incubated isolated T cells and found that CD8⁺ T cells from metformin-treated mice still produced immune response chemicals.

Further comparisons revealed specific memory characteristics and protein producing abilities in the T cells of metformin treated mice. “These findings provide novel insights into anticancer immunity,” conclude the researchers in a report of their results. Further work is needed to study the effects on different types of tumours and to clarify the specific cellular and molecular mechanisms involved.

Background

About metformin

Metformin is antihyperglycemic, and so counters insulin resistance. Early use has been shown to increase survival in patients either suffering from obesity-involved type 2 diabetes or cardiovascular disease or both.

The observed anticancer effects triggered further epidemiological studies that confirmed a 30-40% reduction in cancer risk for patients treated with metformin. It was further shown to reduce cancer in a breast cancer mouse model and to increase life expectancy. However while the mechanism seemed to stem from destruction of cancer initiating cells, until now the mechanism was unclear.

Immune exhaustion

White blood cells in the immune system help protect the body against disease. T cells are a particular type of white blood cell that fight infection by activating cells to release cytotoxic cytokines – small proteins - and signalling chemicals instead of involving antibodies.

CD8⁺ are cytotoxic T cells that destroy virus cells and cancer tumours. However as cancer cells and pathogens repeatedly stimulate CD8⁺, they eventually lose their ability to secrete the signalling chemicals that cause cell death and regulate the immune system such as interleukin 2 (IL-2), tumour necrosis factor alpha (TNF α) and interferon gamma (IFN γ). These chemicals continued to be produced by T cells isolated from metformin-treated mice.

In addition CD8⁺ cells in diseased organisms undergo phenotypic changes to express exhaustion markers causing the cell death processes of apoptosis to ensue. Blocking these markers has been studied as a means to tumour rejection and further studies are underway to investigate T-cell exhaustion management in tumour immunotherapy.

Memory T cells

T cells that have encountered a disease or cancer can respond more quickly when faced with the same pathogen a second time. This improved 'memory response' on second encounter was observed in the metformin study.

Although these 'memory T cells' are not yet well understood, a classification model has been proposed on the basis of acute viral studies. The model includes two types: central memory (TCMs) and effector memory (TEMs). The researchers studied the proportions of TEMs and TCMs in tumour infiltrating white blood cells with and without metformin. They found that TEM cells played a more significant role in tumour rejection.

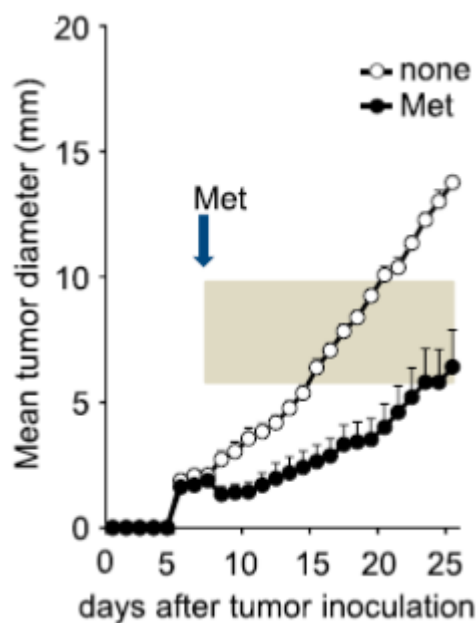


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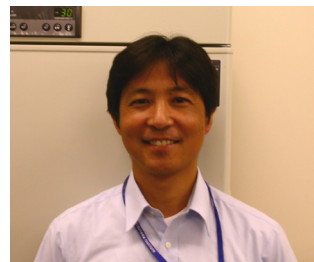
Metformin improves the multifunctionality of antigen-specific CD8⁺ T cells in vivo. Mice inoculated with 2×10^5 melanoma cells were treated with or without metformin from day 7, as indicated by the shadowed rectangle, and tumour growth was monitored. The results are representative of two independent experiments. n = 5 per group.

Reference

Shingo Eikawa, Mikako Nishida, Shusaku Mizukami, Chihiro Yamazaki, Eiichi Nakayama, and Heiichiro Udon, Immune-mediated antitumor effect by type 2 diabetes drug, metformin, *PNAS*, 112(6), pp.1809-1814, 2015. DOI: 10.1073/pnas.1417636112
<http://www.pnas.org/content/112/6/1809.abstract>

Correspondence to

Professor Heiichiro Udonon, M.D., Ph.D.
Department of Immunology, Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, Okayama University,
Shikata-cho 2-5-1, Okayama city, Okayama 700-8558, Japan
E-mail: udono@cc.okayama-u.ac.jp



Further information

Okayama University

1-1-1 Tsushima-naka , Kita-ku , Okayama 700-8530, Japan

Planning and Public Information Division, Okayama University

E-mail: www-adm@adm.okayama-u.ac.jp

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

Okayama Univ. e-Bulletin: <http://www.okayama-u.ac.jp/user/kouhou/ebulletin/>

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