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For immediate release

An international joint research group has discovered the mechanism of how microbial exopolysaccharide (EPS) produced by OLL1073R-1, one of the Meiji proprietary *Lactobacillus* strains, enhances the therapeutic effect of immune checkpoint inhibitors for the treatment of cancer
- Published in *Cancer Discovery*,
the journal of the American Association for Cancer Research -

An international joint research group has discovered that microbial exopolysaccharide (EPS) produced by OLL1073R-1, one of the Meiji proprietary *Lactobacillus* strains, enhances the therapeutic effect of immune checkpoint inhibitors*1 for the treatment of cancer and revealed its mechanism of action. The group is comprised of researchers from Japan, France, and Australia, including Juntendo University (President, Hajime Arai), Meiji Holdings Co., Ltd. (CEO, President and Representative Director, Kazuo Kawamura), The University of Tokyo (President, Teruo Fujii), and the Institut Pasteur (President, Stewart Cole). These results were published in online version of *Cancer Discovery* on February 18 (U.S. Eastern time), the journal of the American Association for Cancer Research, one of the most respected journals worldwide.

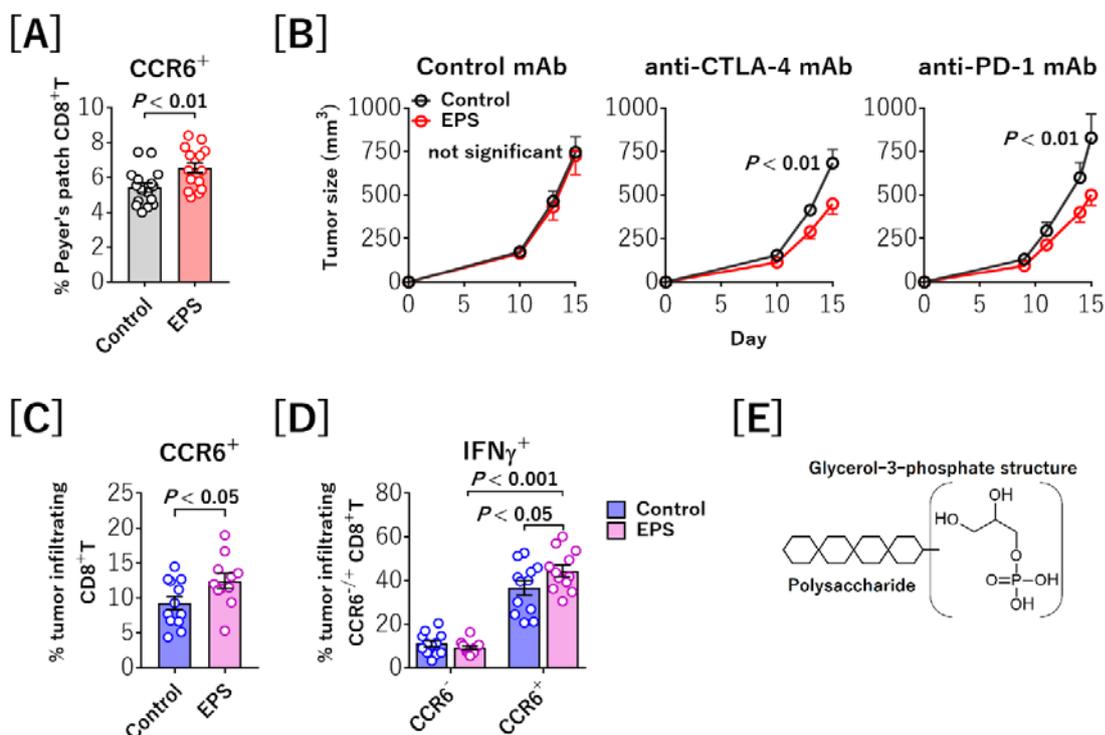
Under our slogan, Now ideas for wellness, Meiji Holdings fuses food and pharmaceuticals researches in the Co-Creation Center, opened in April 2019, while promoting open innovation with domestic and international research institutions. This international joint research is part of that. Meiji Holdings will work on creating health value unique to the Meiji Group which leads to extend healthy life expectancy.

■Background of the study

Immune checkpoint inhibitors, such as the anti-PD-1 antibody, are effective therapeutic drugs against numerous types of cancers. However, it is reported that these inhibitors provide insufficient therapeutic effects in some cases. Recent studies revealed that intestinal flora and/or metabolites produced by commensal bacteria in patients with cancer are correlated to therapeutic effect. Based on this knowledge, researches have been conducted to enhance the therapeutic effect by altering the intestinal flora or through probiotics consumption. Since EPS produced by the *Lactobacillus* strain OLL1073R-1 has been reported to show various immunomodulating effects, we studied whether the EPS enhances the efficacy of immune checkpoint inhibitors against cancers.

■ Research results overview

The research group first identified that oral ingestion of the EPS increased CCR6⁺2-expressing CD8⁺T cells in the Peyer's patches³ (Figure A), further demonstrating the possibility of systemic migration of these cells from the intestines. Then, using a tumor type that produces CCL20, which binds with CCR6, we observed that no change in tumor size through oral ingestion of the EPS alone. However, combination of the EPS and an immune checkpoint inhibitor resulted in statistically significant reduction in tumor size (Figure B). A detailed analysis of these tumor tissues indicated that the oral ingestion of the EPS resulted in the infiltration of a greater number of CCR6-expressing CD8⁺T cells (Figure C), which produced IFN γ ⁴ (Figure D), and resulted in the infiltration of a greater number of activated T cells. Furthermore, it was suggested that the unique glycerol-3-phosphate structure (Figure E) in the EPS was the functional component of these reactions.



■ Significance of the study and future developments

This study demonstrated that the oral ingestion of the EPS enhances therapeutic effect of immune checkpoint inhibitors as intended. It is thus considered that certain immune cells increase in the small intestine and these immune cells infiltrate into the tumor, thereby modulate the tumor microenvironment that promotes anti-tumor immune response.

Thus far, little has been known about the mechanism of how the intestinal flora and/or probiotics impact the therapeutic effect of immune checkpoint inhibitors. This study revealed that CCR6-expressing CD8⁺T cells were identified as one of the links between the intestine and tumor. There is potential for dramatic advances in these researches and their clinical applications, and Meiji Holdings continue to advance applied research related to the EPS in human patients with cancer.

■Terminology

*1 Immune checkpoint inhibitor: Immune responses that eliminate cancer tend to be impeded by various immune escape mechanisms. Therapeutic drugs such as the anti-PD-1 antibody help stimulate immune responses by constraining the functions of the immune escape. This, in turn, promotes remission of the cancer. In some cases, however, the immune escape mechanisms are multiple in number and complex, which can result in poor therapeutic effect.

*2 CCR6: One of the roughly 20 types of chemokine receptors. CCR6-expressing immune cells are specifically stimulated by the chemokine known as CCL20 and are known to migrate towards tumor tissue that produces CCL20.

*3 Peyer's patch: One of the immune organs found throughout the small intestine. The Peyer's patch has a vast number of lymphocytes, such as CD8+T cells, and works to control the immune response of antigens in the intestinal flora.

*4 IFN γ : An highly important cytokine known to activate cell-mediated immunity, which works to eliminate tumor cells and virus-infected cells.

■Original article

Cancer Discovery (online version)

Dietary *Lactobacillus*-derived exopolysaccharide enhances immune checkpoint blockade therapy

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