

Morinaga Milk has the world's top share in the production of "lactoferrin" \*1.

## **Morinaga Milk confirmed that lactoferrin activates dendritic cells (pDCs) that play important roles in the initiation of immune response.**

Morinaga Milk confirmed that **lactoferrin activates plasmacytoid dendritic cells (pDCs)** that play important roles in the initiation of viral immune response. This research was mainly conducted with the Wakayama Medical University, Japan. We reported these results at the 15<sup>th</sup> International Conference of Lactoferrin held on 6–10th December, 2021 in Beijing, China.

\*1 Absolute Reports (2021 edition), the production share of lactoferrin in our subsidiary, MILEI GmbH.

### **1. The International Conference on Lactoferrin**

The International Conference on Lactoferrin has been held every two years since 1992 for the development of lactoferrin research. Morinaga Milk joined this conference and has been reporting its research achievements since the 1<sup>st</sup> conference. At the 15<sup>th</sup> conference, over 200 attendees from 28 countries joined, and more than 70 oral reports about the various aspects of lactoferrin, including the protective effects against infection and the results of clinical trials, were provided.

URL: <https://15thlactoferrin.com/>

### **2. Our research reports**

#### **1) Summary**

Plasmacytoid dendritic cells (pDCs) are immune cells that play important roles in the initiation of viral immune response. We confirmed that lactoferrin activated pDCs using cell assays. This finding may explain one aspect of the mechanism by which lactoferrin widely modulates the immune system.

#### **2) Background and Objective**

From clinical trial reports to date, we confirmed that ingestion of lactoferrin alleviates subjective symptoms including respiratory and gastrointestinal symptoms in daily life. Concerning the mechanism of these effects, lactoferrin is thought to activate various immune cells such as NK cells, T cells, and B cells. The pDCs are immune cells that are low in number in the blood, and are known to activate a variety of immune cells, as listed above. Therefore, lactoferrin has a possibility to activate pDCs and consequently, pDCs activate these immune cells. However, the number of pDCs is small compared with that of other immune cells, and little is known about the effects of lactoferrin on pDCs. In this study, we focused on pDCs and examined the effects of lactoferrin on pDCs in the peripheral blood using cell assays.

#### **3) Titles of our reports**

1. Effects of bovine lactoferrin on plasmacytoid dendritic cells in peripheral blood ex vivo.
2. Effects of bovine lactoferrin on the production of type I IFNs from plasmacytoid dendritic cells.

#### 4) Research overview

After obtaining approval from the institutional review board and informed consent for the collection of peripheral blood from healthy adults, peripheral blood was collected, and peripheral blood mononuclear cells (PBMCs) were prepared. PBMCs comprise various immune cells, including pDCs. The effects of lactoferrin on the activity of pDCs in PBMCs were examined in the absence or presence of virus-derived genetic material. The activity of pDCs was evaluated using three parameters (CD86, HLA-DR, and IFN- $\alpha$ ). In the absence of virus-derived genetic material, only CD86 was significantly upregulated by lactoferrin, but the other two parameters did not change (Figure 1).

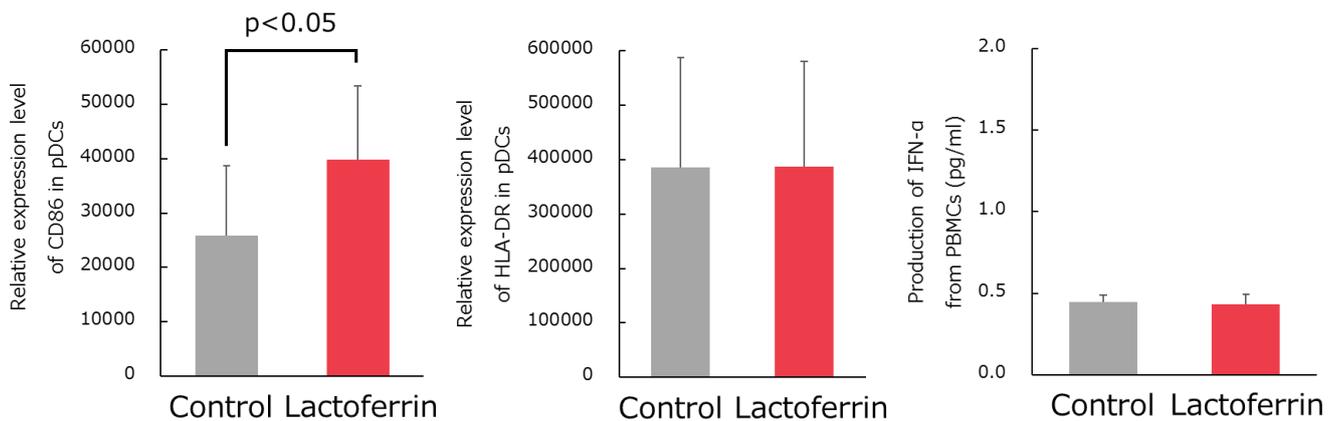


Figure 1 Activation of pDCs in PBMCs in the absence of virus-derived genetic material.

In the presence of virus-derived genetic material, all three parameters were significantly upregulated by lactoferrin (Figure 2).

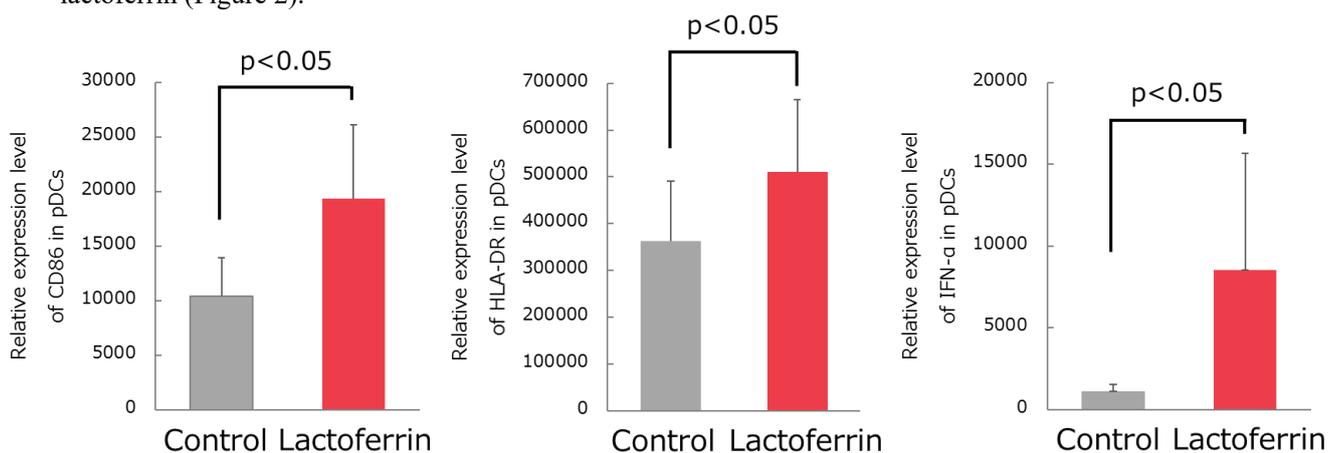


Figure 2 Activation of pDCs in PBMCs in the presence of virus-derived genetic material.

Next, to exclude the influence of other immune cells, pDCs isolated from PBMCs were used for the experiments. The effects of lactoferrin on the activity of pDCs were examined in the presence of virus-derived genetic material. The activity of pDCs was evaluated using two parameters (IFN- $\alpha$  and IFN- $\beta$ ). Both parameters were significantly upregulated by lactoferrin (Figure 3).

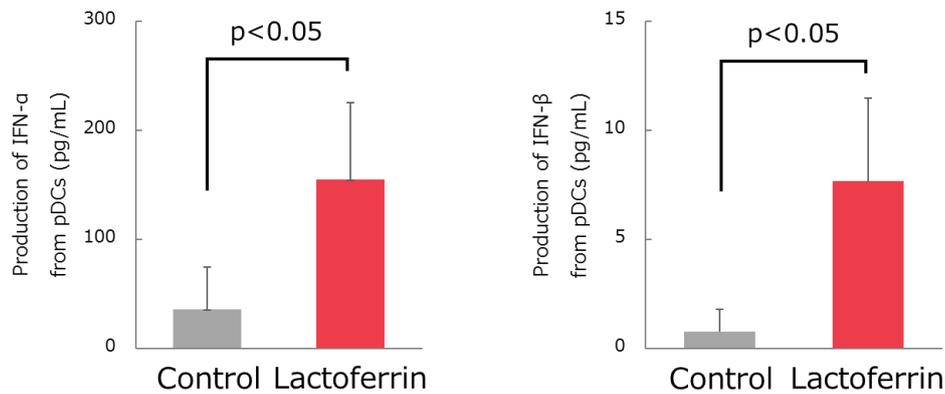


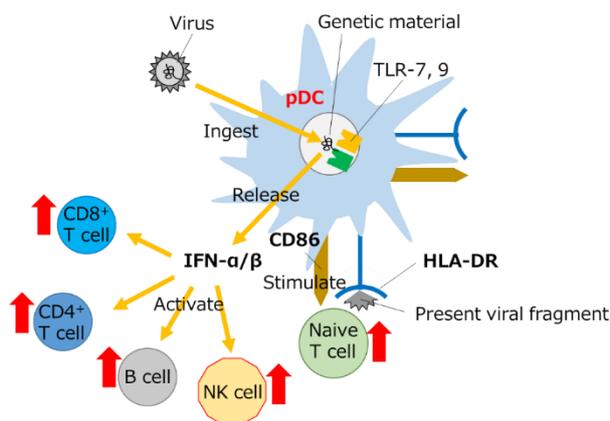
Figure 3 Activation of pDCs in the presence of virus-derived genetic material.

## 5) Conclusion

From the results above, we confirmed that **lactoferrin activates pDCs** in cell assays. Therefore, lactoferrin has a possibility to activate pDCs and consequently activate a variety of immune cells. The activation occurs especially in the presence of virus-derived genetic material. This suggests that lactoferrin modulates the immune system via the activation of pDCs, particularly when they recognize viruses in the environment, thus preventing viral infection. We will continue to investigate the mechanisms through which lactoferrin modulates the human immune system.

### <What are plasmacytoid dendritic cells (pDCs)? >

pDCs are a type of immune cells that comprise a minor population (0.2–0.5 %) in the PBMCs. pDCs have sensors for pathogen-derived genetic material, toll-like receptor (TLR)-7 and TLR-9, which recognize virus-derived genetic material and produce a massive amount of immune substances, such as type I interferon (IFN- $\alpha/\beta$ ), which activate NK cells, T cells, and B cells. Activated pDCs also upregulate the expression of HLA-DR (MHC class II molecules) and CD86 (co-stimulatory molecules) on the cell surface and activate naive T cells. Therefore, pDCs activate a variety of immune cells of the innate and adaptive immune systems (see the illustration below).



### Reference:

Lande R et al. Ann N Y Acad Sci. 2010;1183:89-103.

### **<Morinaga Milk and lactoferrin>**

Morinaga Milk has a long history of lactoferrin research (approximately 60 years), lactoferrin production (over 30 years), and delivering products that contain lactoferrin (35 years). Morinaga Milk has published the most research papers on lactoferrin among companies in the world \*2. In addition to these facts, considering our high quality, production volume, and strict compliance with food safety regulations, our lactoferrin is preferred by customers from around the world. As a leading lactoferrin company, further efforts will be made to enhance the value of lactoferrin and the contribution to human health.

\*2 Database: Search “lactoferrin” in Scopus by Elsevier (search at Nov. 2021)

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