Studies on the mechanism of immune exhaustion and development of novel therapeutic strategies for chronic infections in cattle

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Abstract

With the recent scaling up of farms, the control of infectious diseases has become one of the most important issues in the management of livestock farms. In contrast to acute infections, which can be controlled with vaccines and antibiotics, chronic infections lack effective prevention and treatment methods in cattle, causing enormous economic damage on domestic farms. In fact, in 2022, there were 6,188 cases of bovine infectious diseases surveyed under the law in Japan, of which 70% (4,334 cases) were bovine leukemia and 19% (1,147 cases) were Johne's disease, both of which are chronic infectious diseases.

In chronic infections, the pathogen persistently infects cattle and causes clinical signs after long latent periods. These pathogens have evasion mechanism of host immune response, and it was difficult to develop effective vaccines or treatments. In fact, there are no measures other than selective culling. Therefore, we focused on the immune dysfunction called "T-cell exhaustion" in cattle, and worked on the development of antibody drugs for the treatment of the chronic infections in cattle.

Previously, it was reported that T cells overexpress immunoinhibitory receptors (PD-1, LAG-3, and TIM-3) in mouse models of chronic infections, which induces T cell exhaustion by suppressing T cell activation signals. Therefore, we analyzed bovine lymphoma virus (BLV)-infected cattle and found that the expression levels of immunoinhibitory receptors (PD-1, LAG-3, and TIM-3) on T cells increased with disease progression, leading to an increase in exhausted T cells with reduced cytokine production. In other chronic infections of cattle such as Johne's disease and anaplasmosis, overexpression of PD-1 and LAG-3 promoted T-cell exhaustion and clinical signs.

Then, we developed antibody drugs including anti-bovine PD-1 antibody and anti-bovine PD-L1 antibody that inhibit the binding of immunoinhibitory receptors to their ligands in cattle. Clinical studies in cattle showed that administration of anti-PD-1 and anti-PD-L1 antibodies restored T-cell responses and exerted antiviral effects. These results indicate that antibody drugs targeting immunoinhibitory receptors can be a novel treatment for chronic infections in cattle.

Taken together, we have been working on the clinical application of antibody drugs from various perspectives inspired by problems in clinical practice. We are also examining the efficacy of antibody drugs in combination with vaccines and other drugs to find the optimal use of these antibody drugs. Furthermore, we are currently collaborating with pharmaceutical companies to develop antibody drugs for veterinary use and to study mass production methods. Based on this research, it is expected that antibody drugs will be clinically applied as a method to control various chronic infections in cattle.