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of the sporozoite surface molecule, p67, which plays an essential role in parasite invasion into host cells, and the biological properties of parasites.

Hereafter, we must examine the utilities of

genes obtained in this study for controlling *T. sergenti* infection. And the information of genome structure and karyotype make possible to analyze the generation mechanism of genetic polymorphism via a sexual stage.

### Interacting host immune responses affecting on the disease progression in animals experimentally infected with bovine leukemia virus

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Only a few animals infected with bovine leukemia virus (BLV) develop leukemia after long latent period for 7–8 years. This observation shows that BLV has some mechanisms to modulate host immune systems and that several interactions between BLV and hosts determine the course of disease progression. Several studies have been carried out to determine the factors which have effects on the disease progression of BLV infection, including major histocompatibility complex (MHC) haplotypes, cell-mediated immune responses (CMI), changes in cytokine profiles, and mutations in the p53 gene. In this study, to develop the therapy to prevent the disease progression of BLV infection, the following were examined; 1) Development of a peptide vaccine which can induce CMI against BLV, 2) Relationship between the changes in cytokine responses during the early phase of infection and the susceptibility to BLV-infection, and 3) Mechanisms to modulate the host immune systems by BLV.

1) Development of a peptide vaccine which can induce CMI against BLV

Epitope peptides derived from the BLV envelope (BLVEnv) induced specific CMI in some of immunized sheep, and these sheep were prevented from the viral expressions. Neutra-

lizing antibodies to BLV were detected even in sheep in which virus replicated, suggesting that CMI rather than humoral immunity play an important role in the prevention of BLV replication. However, it was also shown that some sheep immunized with the peptide did not show immune responses against BLV, suggesting the restricted effectiveness of the peptide vaccine.

In addition, the mannan-coated liposome has also been developed as a candidate for the effective delivery system of the peptide antigen. BALB/c mice immunized with a peptide (BLVEnv 98–117) encapsulated in the mannan-coated liposome developed peptide-specific Th 1 immune-responses.

2. Relationship between the changes in cytokine responses during the early phase of infection and the susceptibility to BLV-infection

The mRNA expressions of the interferon- $\gamma$  (IFN $\gamma$ ), interleukin- (IL-) 2,4,6 and 10 genes were suppressed in the peripheral blood mononuclear cells (PBMC) from all of the sheep at two weeks after the BLV-challenge. Tumor necrosis factor  $\alpha$  (TNF  $\alpha$ ) mRNA expression was enhanced in all of the sheep which were prevented from the BLV replication, whereas reduced in the sheep which showed BLV expansion. Some of sheep with enhanced expression of TNF  $\alpha$

showed low CMI responses specific to BLV antigens, but were protected from BLV expansion. These results indicate that, during the early phase of BLV infection, as non-specific immune responses, inflammatory cytokines, *e.g.* TNF  $\alpha$ , produced by macrophage can effectively eliminate the BLV-infected cells though T-cell functions were temporally suppressed. The TNF  $\alpha$  gene is located in the MHC class III region, and the level of TNF  $\alpha$  expression is thought to be linked to MHC haplotypes. Thus, it was suggested that the class III region which regulates the TNF  $\alpha$  production, as well as the class II region, could define the MHC haplotype, and could be one of the genetic factors associated with the susceptibility to the disease.

### 3) Mechanisms to modulate the host immune systems of BLV

Some of the sheep which were immunized with the recombinant BLVEnv protein produced antibodies showing no neutralizing activities, and CMI against BLV antigens were suppressed in those sheep. This indicates that BLVEnv protein can induce suppression of the immune responses in host animals, and can provide the antibody-dependent enhancement of the viral infectivity.

It was also shown that two peptides (peptide 61, CKS-17/BLV) derived from BLVEnv modulated the lymphocyte functions in BALB/c mice. CKS-17, a peptide whose amino acid sequence is relatively conserved among retroviruses, is known to induce immunosuppression, and the BLV homologue of CKS-17 (CKS-17/BLV) also induce immunosuppression. On the other hand,

peptide 61 suppressed the lipopolysaccharide (LPS)-driven responses though enhanced concanavalin A (Con A)-driven responses involving the promotion of IL-2 production and sensitivity. Furthermore, peptide 61 activated the CD8-positive and type 2 cytokine producing cell population which is reported to contribute to immunosuppression. These results suggest that BLVEnv contains several molecules which modulate the host immune functions and thus contribute to the disease progression in the course of BLV infection

Effective anti-BLV therapy should be designed to prevent the disease progression in the BLV-infected animals although not completely protect animals from the infection. The results shown here concerning the importance of induction of Th 1 immunity and TNF  $\alpha$  expression for the prevention of disease progression will contribute to the development of the ideal anti-BLV therapy. In the future, the detailed analysis of the changes in the expressions of TNF  $\alpha$ -related molecules, such as TNF  $\alpha$  and TNF  $\alpha$  receptor, p55 and p75, in the BLV-infected animals should be important to understand the pathogenesis of BLV-infection. CMI and cytokine responses which are closely associated with BLV pathogenesis are known to be regulated by the genetic factor, MHC haplotype. Therefore, genetic analysis focusing on the genetic factors related to the disease progression of BLV infection should be further progressed for the purpose of controlling the pathogenesis of BLV in the infected animals.