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The goal of the research in this laboratory is prevention and control of important infectious diseases of animals and man. For this purpose, the ecology of pathogens is thoroughly studied at the levels of their host animal populations, indivisuals, tissues, cells and molecules. The research efforts thus focus on 1) the origin, evolution and perpetuation mechanism of pathogens in nature, 2) host range, route of transmission, pathogenesis and immunology of the infections, through *in vivo* and *in vitro* analyses of the host-parasite interactions and 3) development of strategies for prevention and control of infections. The results hitherto obtained from these studies contribute not only to the fields of veterinary medicine, but also to public health, the ecology of wildlifes and life sciences.

The main ongoing research projects by the staff, graduate and undergraduate students, and visiting researchers in international collaboration with other laboratories are as follows :

1. Origin, evolution and perpetuation mechanism of influenza viruses in nature ; Prediction of emerging pandemic strains : Influenza viruses were isolated from fecal samples of ducks and water samples of the lakes where they nest in central Alaska. Even in autumn when most of the ducks had left for migration to the south, viruses were still isolated from the lake water. The results support the notion that influenza viruses are maintained in waterfowl population by water-borne transmission and revealed the mechanism of year-by-year perpetuation of the viruses in the frozen lake water in winter[1]. Futher studies are being conducted in Siberia where ducks migrating to Southern China, an epicenter of influenza, nest.

At least one strain of each subtypes of avian influenza viruses replicated in pigs and the pigs coinfected with a swine virus generated reasortants. The results indicate that avian viruses of any subtypes can contribute genes in the generation of reasortants and that pigs play an important role in emerging pandemic strains[2]. Attempts to define the viruses among pig population are currently in progress.

2. Structure and function of the glycoproteins of herpes-, paramyxo-, orthomyxo- and filoviruses : Glycoproteins of the envelope virus are responsible for initiation of infection such as adsorption and penetration. We demonstrated that bovine herpesvirus 1 glycoprotein gC functions as a major virus attachment protein through binding to a heparin-like moiety on the host cells[3] and that the amino acid sequence between residues 172 and 323 contains the functional domain of the glycoprotein for heparin-binding[4]. Ebora virus glycoproteins were incorporated into vesicular stomatitis virus particles. Studies in which the recombinant system is utilized are under way to define specific receptor for Ebora virus. Efforts continue in this laboratory to define the mechanisms of membrane fusion which are involved in penetration of the envelope virus into their host cells.

3. Factors involved in the pathogenesis of ortho- and paramyxoviruses : To clarify the mechanisms by which the virus causes diseases, we direct our attention not only to the pathogen but also to the host factors. Survey of the hemagglutinin cleavage site sequence of H5 and H7 avian influenza viruses were carried out and amino acid sequence at the cleavage site is regarded as a marker of pathogenicity potential[5]. Recently we found that soluble factor extracted from the chicken cells infected with influenza virus causes disseminated intravascular coagulation syndrome in the birds. Purification of the factor is now ongoing to further characterize the

entity.

4. Structure and function of the immediate-early and early proteins of herpesviruses and the polymerase complex of influenza viruses: Immediate-early and early proteins take important parts in transcriptional regulation of herpesvirus genes. We mapped these proteins of pseudorabies virus to define the transregulatory domains[6,7]. Attempts to generate transgenic animals resistant to infection with the virus by administration of the gene encoding the regulatory domain are currently in progress.

Influenza virus RNA polymerase complex consists of PB1, PB2 and PA proteins. We made panels of monoclonal antibodies against these proteins. Antigenical and functional mapping is under way using these panels.

5. Mucosal immunity, development of nasal and oral peptide and DNA vaccines: We have developed a strategy for making synthetic peptide vaccines, in which a peptide derived from hemagglutinin of H3 influenza virus is introduced into MHC-binding motif of C57BL/B10 mouse. Intranasal administration to mice with the peptide vaccine loaded in multilamellar liposomes confered protective immunity to the animals against infection not only with H3 homologous virus but also with H3 variant virus. The results indicate that our peptide vaccine may become the basis for a new strategy to prepare effective vaccines that will overcome the ineffectiveness of classical vaccines due to antigenic drift of influenza viruses[8]. Attempts to apply this strategy to other animals are currently in progress. The possibility of subunit and DNA vaccines against herpesvirus infections are also being investigated[9].

References

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