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Conclusions and recommendations for future research

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Introduction

The European Society for Veterinary Virology (ESVV) first organized a symposium on ruminant pestiviruses in Hannover, Germany in 1990; the proceedings were published in a special issue of *Archives of Virology* (Suppl. 3, 1991). The second symposium, jointly organized by the ESVV and the Merieux Foundation, was held at the Merieux Foundation conference centre in Annecy, France, from 1st to 3rd October 1992. The proceedings are in press (to be published by Foundation Mérieux, Lyon, France). The scope of this second meeting was broadened to include comparative aspects of hog cholera and hepatitis C viruses in addition to the dominant theme of ruminant pestiviruses. Representatives were gathered from most of the major pestivirus research teams, both European and worldwide.

Major topics addressed were: structure and organization of the genome, genome products, pathogenesis of pestivirus infections, epidemiology, diagnosis, and control. At the conclusions of the meeting, a group of experts was invited by the organizers to draw up conclusions and recommendations for future research. These are presented below.

Impressive progress has been made in the area of genome structure and expression although the functions of the gene products need further clarification. Looking to the future we expect to see significant progress in this area and in our understanding of the immunology of the infection, which is at present poorly defined. The recent reclassification of pestiviruses opens up the field of comparative virology within the *Flaviviridae*, while for pragmatic reasons attention should be given to the taxonomy and definition of virus species within the pestivirus genus. Thus it would seem appropriate that a third symposium should be convened to review progress after a further three years, and the Executive Council of the ESVV should give this matter their consideration.

Recommendations

Comparative Aspects

(i) Whilst pestiviruses are of foremost interest within the scope of the ESVV, studies on the comparative aspects of members of the *Flaviviridae* namely pestiviruses, flaviviruses,

and hepatitis C virus should be encouraged.

(ii) To avoid confusion the abbreviation HCV should be adopted for hog cholera virus and HepCV for hepatitis C virus.

(iii) A common nomenclature should be found for the structural proteins of the 3 genera in the family *Flaviviridae*. This should be taken forward to the ICTV.

Structure

(i) Understanding of the structure and function of ruminant pestiviruses has benefited greatly from studies with HCV and vice versa. The complete genome sequences of 2 HCV strains, 2 cytopathogenic (CP) BVDV strains, and a noncytopathogenic (NCP) BVDV strain are now available. Priority viruses for generating further genome sequence data are a border disease (BD) virus (?Moredun), pairs of CP and NCP BVD viruses from the same animal, and a virulent BVDV strain such as that causing haemorrhagic syndrome.

(ii) Consideration should be given to establishing a central register of gene sequence information.

(iii) Generation of an infectious clone would help to advance biological studies.

(iv) While the gene products are known, many processing pathways require elucidation.

(v) The functional role of NS p 20/23, which appears unique to pestiviruses, needs to be determined.

(vi) Of the 4 structural proteins p 14 is the capsid protein and gp 53/55 the major envelope protein. There is evidence that of the other two envelope glycoproteins gp 44/48 is a surface protein and gp 25/33 a transmembrane protein but the inter-relationship of these envelope glycoproteins and their roles in induction of immunity requires further work.

(vii) The position of the C-terminus of the gp 53/55 needs to be determined and more work is needed on identifying the conserved and hypervariable domains including neutralisation epitopes in this protein.

(viii) Among the nonstructural proteins the cleavage products of p 125 are of great interest. The p 80 serine proteinase, which also possesses RNA-stimulated NTPase activity is of major importance since over-expression of this protein is associated with cytopathogenicity of BVDV isolates from cases of mucosal disease.

(ix) Explanations for the apparent multiple mechanisms by which NCP viruses become CP are awaited, and how p 80 exerts its cytotoxic effect has also yet to be determined.

Pathogenesis and Immunity

(i) The cell tropism of NCP and CP strains of pestiviruses needs to be further elucidated in the fetus, acutely infected and persistently infected (PI) animals.

(ii) The pathogenetic potential of pestivirus isolates requires monitoring and reasons for the emergence of virulent strains such as that causing haemorrhagic disease in calves need to be investigated.

(iii) Mechanisms of immunity in acute pestivirus infections are poorly understood. Both B and T cell epitopes require identification, and antigenic variation among BVD and BD viruses needs elucidation to enable sensible vaccine development.

(iv) The apparent highly specific tolerance to pestivirus antigens in persistently infected animals is an intriguing feature of the biology of pestiviruses which requires explanation.

Epidemiology

(i) While the prevalence of ruminant pestiviruses is known to be high, there is little information on the extent of disease and economic losses they cause. Further information is required and the approach by mathematical modelling is to be encouraged.

(ii) Persistently infected cattle and sheep are the principal spreaders of infection. The identification of other potential sources of virus including wild animal reservoirs should be reported. The ability of the virus to circulate in herds or flocks in the absence of PI animals should be investigated.

(iii) The ability of pestiviruses to replicate in non-artiodactyl hosts *in vitro* and *in vivo* requires substantiation.

Diagnosis

(i) ELISAs are now used commonly for the serological diagnosis of pestivirus infections, and ELISAs for antigen detection have been developed widely. Inter-laboratory comparisons of these tests using reference reagents should be encouraged.

(ii) The exquisitely sensitive nucleic acid detection systems based on PCR appear suited to screen serum, cells and vaccines for the presence of pestivirus contaminants. Such systems should be evaluated.

Control

(i) Control methods without vaccination will vary from herd to herd depending on the husbandry methods used. Basically though, control will be based on the identification and removal to slaughter of PI animals. Such schemes are currently being tried in Germany, Norway, Sweden, and The Netherlands. Should such schemes prove successful their wider adoption should be encouraged.

(ii) There is a need for an effective vaccine to prevent *in utero* infection. Development of recombinant vaccines should include the strategy of being able to distinguish serologically between vaccine and field virus antibody.

(iii) Cost-benefit analyses of various schemes for the control of ruminant pestiviruses should be re-examined as new information becomes available and new vaccines are developed.

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