

providing a direct link between E5 viroporin activity and the processes involved during oncogenic change. Development of potent E5 inhibitors could therefore provide a means of targeting both HPV infection and also potentially the proliferation tumours.

9.5 Viroporins of Animal Viruses

Antiviral prophylaxis is not generally employed in agriculture owing to prohibitive costs and the effectiveness of culling programmes. However, the ambiguity and uncertainty surrounding the question of vaccination against many agricultural pathogens continue in many areas, with foot and mouth disease virus (FMDV) being the prime exemplar. Unfortunately, FMDV 2B proteins are dissimilar to those of enteroviruses and are not likely to possess viroporin activity, yet a number of animal viruses with significant agricultural impact are likely to encode viroporins by analogy with their mammalian counterparts. Antiviral therapy, if rendered cost-effective, could provide an alternative to ring vaccination strategies in the event of disease outbreaks.

Concerns surrounding the zoonotic transfer of resistant viruses may be a relevant concern if antiviral strategies were adopted, yet effectively suppressing virus replication in some animal reservoirs may represent a means to limit the jumping of viruses from animals into humans. Of note, reports of the use of amantadine in commercial poultry farms in Southeast Asia were linked by the WHO to acquisition of drug resistance by highly pathogenic H5N1 strains in the early part of the century (http://www.who.int/foodsafety/micro/avian_antiviral/en/index.html). Clearly, sub-optimal dosing of a weak-potency monotherapy is highly likely to drive the selection of resistance in such variable viruses. Nevertheless, more effective therapies may be productive in this regard.

Pestiviruses are an example of an agricultural pathogen where viroporin function has been documented. These express a p7 protein^{328,329} with very limited sequence homology (<10%) to that of HCV, yet BVDV p7 has been shown to form oligomers and to promote surface transport of influenza HA, implying proton conductance.⁷¹ BVDV was also the surrogate system used to demonstrate cell culture efficacy of BIT225,⁸⁷ providing proof of principle that viroporin inhibitors are able to reduce the spread of infection. A recent investigation of the related classical swine fever virus (CSFV) p7 protein demonstrated its importance for virus replication in swine,⁴¹ and also confirming channel-forming activity *in vitro*. Interestingly, unlike HCV p7, peptides corresponding to the CSFV p7 C-terminus also displayed channel-forming activity, which, combined with the presence of a highly conserved His47 residue, supported the view that the C-terminal helix forms the channel lumen in these proteins. The activity of full-length peptides was sensitive to high concentrations of amantadine ($EC_{50} \approx 2$ mM), and also to lower concentrations ($EC_{50} \approx 200$ μ M) of the phenylalkylamine calcium channel inhibitor, verapamil. In addition, both drugs significantly reduced ($\sim 2\log_{10}$ reduction for 500 μ M amantadine and 17 μ M verapamil) in virus titre when applied during the initial infection process. This may suggest a role for CSFV p7 during entry, although