progressive multifocal leuko-encephalopathy (JC virus), but also contain simian vacuolating virus 40 (SV40), which was used as the first viral tool to demonstrate nuclear localisation signals. Recently, two polyomavirus proteins were shown to demonstrate viroporin activity. The first, VP4, is a late-acting protein containing a central hydrophobic core and a nuclear localisation domain. These target the protein to the nuclear envelope at late times of infection in order to mediate membrane disruption and so enable release of assembled virions from the nucleus. VP4 forms defined integral membrane pores of $\sim$3 nm diameter and its activity is abrogated by mutation of the hydrophobic domain.[320]

The second polyomavirus protein to display viroporin activity is the agnoprotein of JC virus.[44] This small accessory protein of 71 amino acids also possesses a central hydrophobic TM domain which, along with an N-terminal region, is required for ER/plasma membrane localisation and membrane integration. Agnoprotein expression increases plasma membrane permeability and elevates cytosolic calcium, resulting in enhanced virion release. As such, agnoprotein appears functionally reminiscent of picornaviral 2B and rotavirus NSP4. No structural information exists for either VP4 or agnoprotein, although the lack of treatments for polyomavirus associated disease may drive further investigation into these potential drug targets.

9.4.2 The E5 Protein of Human Papillomavirus 16 (HPV16) is an Oncogenic Viroporin

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection worldwide and high-risk viruses, such as HPV16, are the major cause of cervical cancer, which kills over 275 000 women per year. HPV also causes a growing number of anal, penile and head and neck carcinomas in both sexes. Recently introduced vaccines will take decades to affect cancer incidences, are not available to men and cannot aid many millions of currently infected women. HPV-associated carcinomas are virus-driven tumours and persist as a result of viral oncogene expression. In addition to the well-characterised E6 and E7 proteins, HPV encodes a third oncogenic protein, E5.[321,322] The role of E5 during the virus life cycle is not clear, although its oncogenic properties appear strongly linked to its ability to up-regulate growth factor signalling *via* the perturbation of endosomal pH.[323–327]

HPV16 E5 is a highly hydrophobic 9 kDa protein with three predicted TM domains. This was recently demonstrated to form hexameric complexes in membrane-mimetic detergents by native PAGE and EM studies of E5 fusion proteins.[45] E5 complexes were active in liposome dye release assays with sensitivity to relatively high concentrations of rimantadine. As for HCV p7, *de novo* modelling of E5 complexes was successfully employed in the development of a novel, bespoke E5 inhibitor, MV6, with a markedly improved *in vitro* IC_{50} compared with rimantadine. Importantly, both MV6 and rimantadine were able to repress E5-mediated enhancement of EGFR signalling in culture,