argument for a role for Cyps in the replication of vaccinia virus (VV) was provided by the demonstration that cyclosporine analogs with strong binding affinity for CypA were potent inhibitors of VV replication whereas analogs with weak affinity for CypA lost antiviral activity.[84] Subsequent studies revealed an incorporation of CypA into VV virions as an essential event for successful maturation.[85] A similar incorporation of CypA into viral particles has been reported for vesicular stomatitis virus[86] and SARS coronavirus;[87] however, in each case additional functions of CypA have been proposed.

A novel activity of a Cyp in viral entry was described for human papillomavirus type 16 involving a cell-surface fraction of CypB which, following attachment, serves to effect a conformational change in capsid proteins L1 and L2 leading to efficient infection.[88]

Incorporation of CypB into virions of measles virus (MV) has been shown to be an important requirement for expanding the tropism of the virus to include epithelial and neuronal cells.[89] Neutralizing antibodies directed at CD147/EMMPRIN, a member of the Ig superfamily and a functional receptor for CypA and CypB, served to limit infection of epithelial cells by MV.[89] Inhibition of MV infection was also demonstrated by treatment with CsA and has led to the proposal that MV incorporates CypB, but not CypA, into mature virions and that this CypB serves to allow effective infection of CD147/EMMPRIN expressing epithelial cells.[89]

A role for Cyps in the replication of herpes simplex virus has been suggested by the finding that CsA inhibits virus production *in vitro*;[90] however, the immunosuppressive properties of CsA need to be taken into consideration when assessing such results.

While Cyps play a supportive function in the replication of numerous viruses, some evidence of Cyps being restrictive towards viral replication has been reported. CypA was shown to bind to the M1 protein of influenza A and to restrict viral replication by inducing ubiquitin/proteosome-dependent degradation of the M1 protein.[91] Notably, a PPIase-deficient CypA protein could still bind M1 and inhibit viral replication while depletion of CypA was found to enhance the replication of influenza A virus *in vitro*.[91] A similar finding was reported by Wu and co-workers[92] as a result of studies on the effect of CypA on rotavirus replication. Silencing CypA resulted in a decrease in interferon-β production and an increase in viral replication, with both effects being reported to be independent of the PPIase activity of CypA.[92]

A role for Cyps in signaling pathways that are activated following viral infection was first suggested by the demonstration that CypB is involved in regulation of IRF-3.[93] Knockdown of CypB was found to suppress virus (Newcastle disease virus) induced phosphorylation of IRF-3 which blocked IRF-3 dimerization and inhibited the production of interferon-β. A recent report from Hopkins *et al.*[81] described a novel induction of type I and III interferons in HCV-infected patients following treatment with a non-immunosuppressive Cyp inhibitor, SCY-635. These results point to a possible new activity for Cyps in virus-induced blocks on innate immune responses that