S U M M A R Y

Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are two human herpesviruses which both can cause mononucleosis. This clinical syndrome appears to be the main one associated with EBV, whereas CMV affects a number of organ systems and thus gives rise to a wider spectrum of clinical symptoms. In this thesis, early interactions of EBV and CMV with cells have been studied. Attempts were also made to characterize possible target cells for these viruses in blood.

It is shown that EBV-receptors are present on both B-lymphocytes and nonB-nonT-lymphocytes. Only B-lymphocytes expressed EBV antigens and could be transformed by the virus. Presence of EBV receptors correlated with presence of complement (C3)-receptors on both B-lymphocytes and nonB- nonT-lymphocytes, whereas C3-receptor carrying T-lymphocytes were not shown to adsorb the virus. In our attempts to identify cells with C3-receptors, we found that these receptors adsorbed both cleaved and native C3.

After infection of B-lymphocytes with EBV, the cells start dividing. This cell division continues indefinitely and the cells are thus immortalized. The EBV-determined nuclear antigen (EBNA) is invariably present in EBV immortalized cells. EBNA has been implicated as a possible T-antigen. T-antigens are induced in many DNA tumor virus systems, and are probably responsible for transformation of the cells. It was therefore essential to determine if EBNA induction precedes transformation of the cells. We found that EBNA does indeed precede the induction of DNA-synthesis in the infected cells, by approximately 20 hours. No sign of blast transformation could be seen before EBNA-induction. The ability of EBNA to infect already activated B-lymphocytes was also studied. We found that EBV could infect mitogen-stimulated cells, but that susceptibility to infection decreased with time after exposure to the mitogen.

The target cell for CMV in CMV mononucleosis is not known. Neither is it known which cells harbour CMV latently. We found that almost all cells studied adsorbed CMV to some extent, although the adsorptive capacity was highly variable. Most cells could also support an abortive infection with induction of CMV early antigens (EA). A full replicative cycle was observed only in human lung fibroblasts. CMV thus has a broad range of target cells in vitro, in contrast to EBV. This is a situation similar to that found in vivo. CMV was not found to share its cellular receptors with other human herpesviruses (HSV-1, HSV-2 or VZV).

After adsorption, CMV was rapidly transported to the cell nucleus. This was the case even in cells with a relatively low susceptibility to induction of EA. There thus seems to be an intra-cellular block to EA-induction. A block to induction of late antigens (LA) appears to exist in some abortively infected cells with a high susceptibility to EA-induction. Also in permissive lung fibroblasts, EA was often induced without subsequent LA-induction. LA was eventually induced also in these cells due to superinfection from adjacent foci, which shows that LA-defectiveness is not due to lack of permissiveness of the cells. LA-defective particles could not be separated from other infectious particles on a density gradient, which might indicate that LA-defectiveness is not a virion property. We found that the intensity of EA-fluorescence varied with the viral dose, whereas LA-fluorescence was constant, and always detected in fewer cells than EA. This indicates a threshold effect, where LA is induced only after a certain amount of EA has been produced.

Human blood cells appeared to be almost refractory to CMV infection. This was surprising, since CMV can cause mononucleosis, can be transferred with blood and furthermore has been isolated from leukocytes.

Leukocytes produced interferon after exposure to CMV, as well as EBV, but this does not account for the inability to demonstrate CMV antigens, since CMV-infection in the presence of anti-interferon antibodies did not alter this. The picture was different when we changed from an established laboratory strain (Ad.169, established in 1956 and presently the most widely used CMV-strain in the world), to CMV isolates, passaged only 1-10 times in vitro. After exposure to the isolates, EA was readily induced in infected leukocytes. The majority of the EA-producing cells were monocytes. A small fraction appeared to be polymorphonuclear cells or lymphocytes. We did not detect signs of virus production in the infected blood cells. If possible, elimination of the CMV-carrying cell from transfusion blood could reduce the risk of serious CMV-infections in immunocompromised hosts.