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# APP, APOE, complement receptor 1, clusterin and PICALM and their involvement in the herpes simplex life cycle

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ABSTRACT

The major Alzheimer's disease susceptibility genes (APOE, clusterin, complement receptor 1 (CR1) and phosphatidylinositol binding clathrin assembly protein, PICALM) can be implicated directly (APOE, CR1) or indirectly (clusterin and PICALM) in the herpes simplex life cycle. The virus binds to proteoliposomes containing APOE or APOA1 and also to CR1, and both clusterin and PICALM are related to a mannose-6-phosphate receptor used by the virus for cellular entry and intracellular transport. PICALM also binds to a nuclear exportin used by the virus for nuclear egress. Clusterin and complement receptor 1 are both related to the complement pathways and play a general role in pathogen defence. In addition, the amyloid precursor protein APP is involved in herpes viral transport and gamma-secretase cleaves a number of receptors used by the virus for cellular entry. APOE, APOA1 and clusterin, or alpha 2-macroglobulin, insulysin and caspase 3, which also bind to the virus, are involved in beta-amyloid clearance or degradation, as are the viral binding complement components, C3 and CR1. There are multiple ways in which the products of key susceptibility genes might be able to modify the viral life cycle and in turn the virus interacts with key proteins involved in APP and beta-amyloid processing. These interactions support a role for the herpes simplex virus in Alzheimer's disease pathology and suggest that antiviral agents or vaccination might be considered as viable therapeutic strategies in Alzheimer's disease.



Alzheimer's disease is a devastating condition characterised by beta-amyloid deposition in amyloid-containing plaques, an accumulation of the phosphorylated microtubule protein tau in neurofibrillary tangles and by massive cortical and hippocampal cell loss [53,43]. A number of susceptibility genes and environmental risk factors, the latter including infection with herpes simplex and other pathogens (*Chlamydia pneumoniae*, *Helicobacter pylori*, *inter alia)* [18] have been implicated in the disease. Herpes simplex infection in mice also induces neuronal degeneration in the entorhinal cortex and hippocampus, as well as memory deficits, all features of Alzheimer's disease [2] and *C. pneumoniae* infection can also provoke cerebral beta-amyloid deposition in mice [36]. It is likely that both environmental and genetic influences play a role in the disease, and that genes and environment may act together to influence its incidence and pathology. For example, many cholesterol and lipoprotein related genes are implicated in Alzheimer's disease and dietary factors that influence Alzheimer's disease risk and progression can clearly be related to cholesterol homoeostasis [11,47]. As discussed below, the herpes simplex virus can also be related to a number of Alzheimer's disease susceptibility genes and pathological processes.

Two genome-wide association studies (GWAS) have identified apolipoprotein E, (APOE) clusterin (CLU), complement receptor 1 (CR1) and the phosphatidylinositol binding clathrin assembly protein, PICALM, as major susceptibility genes in Alzheimer's disease. The authors pointed out areas of convergence between these genes; for example, both APOE and clusterin are involved in lipoprotein and cholesterol function and both CR1 and CLU are members of the complement pathways involved in pathogen defence [15,30]. There is a further common feature. These genes, and several others, can all be related to the herpes simplex virus, which, via this association, can be related to a number of APP and beta-amyloid processing pathways. These and other interactions are summarised in a database at http://www.polygenicpathways.co.uk/herpalz.htm (Table 1).

The herpes simplex virus binds to artificial proteoliposomes containing APOE or APOA1, as well as to all classes of serum lipoprotein in man (very low density, low density and high density lipoprotein) [19]. The herpes simplex and influenza virus also bind to complement receptor 1 on erythrocytes [44] HSV-1 infection has been implicated as a risk factor in Alzheimer's disease, acting in synergy with APOE4 [35]. Viral DNA is found in Alzheimer's disease amyloid plaques, and HSV-1 infection also results in beta-amyloid (Aβ) deposition and *tau* phosphorylation, the key hallmarks of Alzheimer's disease, in mice or neuroblastoma cells [61,62,60]. Possession of the human APOE4

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**Table 1**
A glossary of the abbreviations used in the text.

| | | | |
|---|---|---|---|
| Amyloid precursor protein related | | Complement related | |
| APP | Amyloid precursor protein: beta- and gamma-secretase cleavage generate beta-amyloid | CR1 | Complement receptor 1; Complement inhibitor |
| Appican | Chondroitin sulphate proteoglycan form of APP | C3 | Complement components C3 and C4 |
| | | C4 | |
| CASP3 | Caspase 3: degrades Abeta | CD59 | Complement inhibitor |
| IDE | Insulin-degrading enzyme: degrades Abeta | MAC | Complement membrane attack complex: assembly inhibited by clusterin and CD59 |
| Cholesterol/lipoprotein related | | Herpes simplex receptors | |
| ABCA1 | Cholesterol/lipoprotein transporter | CSPG | Chondroitin sulphate proteoglycan |
| A2M | Alpha-2-macroglobulin: Binds to ABeta and lipoprotein receptors | HSPG | Heparan sulphate proteoglycan |
| APOA1, APOE | Apolipoproteins | M6PR | Mannose-6-phosphate receptor |
| CLU | Clusterin/apolipoprotein J | PVRL1 | Poliovirus receptor-related 1 (herpes virus entry mediator C) |
| LRP1 | Lipoprotein receptors | SDC1 | Syndecans 1 and 2 |
| | | SDC2 | (Heparan sulphate proteoglycans) |
| LRP2 (Megalin) | | Miscellaneous | |
| LRP8 (Apoer2) | | Crm1 XPO1 | Nuclear exportin |
| | | PICALM | Phosphatidylinositol binding clathrin assembly protein |

allele in mice also favours cerebral infection by the herpes virus [10].

The herpes simplex viral glycoprotein C acts as a CR1 mimic and, like CR1, binds to complement C3 components, blocking complement pathways and preventing the formation of the membrane attack complex (MAC) [20] (Fig. 1). This forms a channel that inserts into pathogen cell membranes, killing them by lysis. This complex is activated by the immune network in response to pathogen invasion and can also target the host cells which contain the pathogen [38]. This complex is present in dystrophic neurites and in the neuronal cytoplasm in Alzheimer's disease, suggesting a role in neuronal cell death [22,39]. Clusterin inhibits formation of this complex by binding to several of its components (C7, C8, C9) [54]. In addition a herpes simplex virion component, CD59 [37] prevents MAC complex formation via binding to C8 and C9 [41] (Fig. 1). Clusterin, CR1 and herpes simplex all prevent formation of this complex, which could pave the way for other infectious agents implicated as Alzheimer's disease risk factors (e.g. *C. pneumoniae* and *H. pylori*) [18]. Interestingly *H. pylori* eradication in infected Alzheimer's disease patients has been shown to improve cognitive function [26].

Although other receptors are the principal routes of entry, the mannose-6-phosphate receptor (M6PR) is used by herpes simplex in certain cells [9]. This receptor is also involved in the routing of the virus to endosomes [8] and the viral glycoprotein D blocks the entry of lysosomal enzymes to the endosomal compartment by binding to M6PR; one of several ways by which the virus blocks apoptosis [63] (Fig. 1). The mannose-6-phosphate receptor binds to clusterin [32] and its traffic through the endosomal compartments is controlled by PICALM, whose overexpression reduces M6PR localisation in endosomes, suggesting blockade of its transport from the plasma membrane or the trans-Golgi network [52]. The herpes simplex virus also uses exportin (Crm1) dependent pathways for nuclear egress [58]. PICALM and other endocytic-regulatory proteins bind to Crm1 [56]. Although there have been no studies specifically addressing the roles of PICALM or clusterin in viral traffic, both of these clearly influence endosomal routing pathways that are used by herpes simplex.APOE, clusterin and complement receptor 1 play key roles in beta-amyloid clearance as do two further viral binding proteins APOA1 [19], and alpha-2-macroglobulin (A2M) [1]. This is primarily mediated via lipoprotein receptors. A2M, or APOE-bound Aβ are cleared by LRP1 (low density lipoprotein receptor-related protein 1) while LRP2 (megalin) clears clusterin-bound Aβ [21,4]. Apoer2 (LRP8) is a receptor for both APOE and clusterin [23] APOA1 is also involved in beta-amyloid clearance via its transporter ABCA1 [25]. The Varicella Zoster and herpes simplex glycoprotein E binding protein, insulin-degrading enzyme [34] is also involved in beta-amyloid degradation [29] as is caspase 3 [51] which is activated by the viral US3 kinase [6] .The HSV-1 binding protein, complement C3 is also a ligand for LRP1 and LRP8, both of which play a role in C3 cellular uptake [40]. Beta-amyloid in the bloodstream is processed by its binding to complement C3, which subsequently binds to complement receptor 1 on erythrocytes [45]. As plasma levels of beta-amyloid may influence cerebral beta-amyloid efflux [14] this could impact on the cerebral load of beta-amyloid.

Interestingly, the lipoprotein and complement pathways may also be linked via clusterin, as the formation of the MAC attack complex is increased in kidney subepithelial cells by antibodies to the clusterin receptor megalin (LRP2). Impaired clusterin import via LRP2 reduces its inhibitory effects on MAC complex formation [46]. It is not known whether this is relevant to cerebral clusterin/LRP2/MAC interactions. However LRP2 and clusterin are expressed in the brain and the MAC complex has been detected in Alzheimer's disease dystrophic neurites and neuronal cytoplasm [22,39] and links between the lipoprotein and complement compartments may be relevant to complement related lysis.

In addition to these effects, APP is involved in anterograde herpes simplex transport in squid axons [48]. A 15 amino acid APP C-terminus peptide is important for general anterograde transport in this system [49]. The APP binding protein APPBP2 (beta-amyloid precursor protein (cytoplasmic tail) binding protein 2 or pat-1) also plays a role in anterograde APP and viral transport in mammalian