

**Seminar 1**

**The role of apolipoprotein E**

**in Alzheimer's disease**

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**Abstract**

Apolipoprotein E (apoE) is the major lipid transporter in the brain that is encoded by gene variants ε2, ε3, and ε4 in the human genome. ε4 is the most significant risk factor for sporadic Alzheimer's disease (AD), increasing disease prevalence in homozygous carriers 12-fold as compared to carriers of the common ε3 variant. Many hypotheses have been advanced indicating allele-specific effects of APOE on neurodegeneration including effects on neuroinflammation, tau hyperphosphorylation, Aβ aggregation and clearance. Most suggested functions of apoE involve its interaction with receptors that facilitate the cellular intake of this ligand. sortilin has been identified as a novel apoE receptor in neurons. Sortilin-dependent uptake of lipidated apoE promotes conversion of polyunsaturated fatty acids (PUFA) into endocannabinoids (eCBs) that act through nuclear receptors to sustain neuroprotective gene expression in the brain. This sortilin function is disrupted by binding of apoE4, increasing pro-inflammatory markers.

**Keywords**: apoE4, Sortilin, Neuroprotective gene expression