**Supplementary material**

**Supplementary Table 1**: Overview of proposed mechanisms of cholesterol on APP processing including selected publications. Cholesterol has been shown to increase amyloidogenic and to decrease non-amyloidogenic APP processing leading to an enhanced A production by pleiotropic mechanisms further accelerating AD pathology by affecting A toxicity, aggregation and clearance. Epidemiological studies or clinical trials are not summarized here but are reviewed e.g. in [1-2] or [3].

Supplementary Table 1:

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| **Effect of cholesterol on A production :** | | |
| **Mechanism of action / key findings** | **Experimental approach** | **Selected literature** |
| ↓ A production | cholesterol depletion in hippocampal neurons | [4] |
| ↑ A deposition, ↑ AD pathology | hypercholesterolemia in transgenic mouse model | [5] |
| ↓ A peptides, ↓ A load | cholesterol-lowering drug BM15.766 in transgenic AD mouse model | [6] |
| ↓ A | cholesterol depletion by simvastatin treatment of guinea pigs and cell culture experiments | [7] |
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| **Effect of cholesterol on - and -secretase activity:** | | |
| **Mechanism of action / key findings** | **Experimental approach** | **Selected literature** |
| ↓ - & -secretase activity | cholesterol depletion by statins and cyclodextrin (CDX) in SH-SY5Y cells | [8] |
| ↑ - &  -secretase activity | addition of cholesterol on human AD samples and N2A cells | [9] |
| ↓ -secretase activity | measurement of -secretase activity of recombinant full length BACE1 in reconstituted vesicles supplemented with cholesterol | [10] |
| positive correlations of -secretase activity and cholesterol at higher membrane cholesterol levels | membrane -secretase activity in the presence of a range of membrane cholesterol levels in SH-SY5Y human neuroblastoma cells after cholesterol addition | [11] |
| ↓  -secretase activity | measurement of  -secretase activity in buoyant membrane fractions containing presenilin 1 after cholesterol depletion | [12] |
| **Effect of cholesterol on BACE1:** | | |
| **Mechanism of action / key findings** | **Experimental approach** | **Selected literature** |
| ↓ APP/BACE proximity | FRET based proximity measurement of APP and BACE1 after cellular cholesterol depletion | [13] |
| ↓ BACE dimerization | statins added in cell culture experiments | [14] |
| ↑ BACE level, | feeding rabbits with 1% cholesterol for 7 months | [15] |
| **Effect of cholesterol on non amyloidogenic processing:** | | |
| **Mechanism of action / key findings** | **Experimental approach** | **Selected literature** |
| ↓ sAPP | cholesterol addition to HEK293 cells transfected with APP695 | [16] |
| ↑ non-amyloidogenic pathway,  ↑ expression of ADAM10 | reduction of cholesterol in peripheral and neuronal cell lines by treatment with CDX or statins | [17] |
| ↓ sAPP, ↑detergent soluble A | high cholesterol diet in transgenic mice for 6 weeks | [18] |
| **Effect of cholesterol on gene expression of genes involved in amyloidogenic processing:** | | |
| **Mechanism of action / key findings** | **Experimental approach** | **Selected literature** |
| ↑ PS1 and PS2 expression | cells exposed to cholesterol | [19] |
| **Effect of cholesterol on A aggregation and clearance:** | | |
| **Mechanism of action / key findings** | **Experimental approach** | **Selected literature** | |
| cholesterol acts as a promoter for Aβ-membrane interactions facilitating Aβ aggregation | effect of cholesterol levels on interaction of Aβ(1-42) monomer with 1-palmitoyl-2-oleoylphosphatidylcholine bilayer using all-atom molecular dynamics simulations | [20] | |
| cholesterol alters membrane-Aβ interactions via fine tuning of glycosphingolipid conformation | molecular modeling simulations and surface pressure measurements of membranes | [21] | |
| Aβ-cell surface interactions are mediated by cellular cholesterol levels | fluorescence microscopy studies of PC-12 and SH-SY5Y,  situ scanning probe microscopy, fluorescence anisotropy, and electron microscopy to investigate within brain lipid bilayers | [22] | |
| Aβ(1-42) preferentially binds to cholesterol-rich domains of cell membranes and forms amyloidosis | interaction of native Aβ(1-42) with PC12 cells was visualized using Congo red | [23] | |
| derivates of cholesterol induce Aβ aggregation, generation of reactive oxygen species and cytotoxicity | addition of cholesterol derivates to murine GT1-7 hypothalamic neurons | [24] | |
| ↓ insoluble Aβ, Aβ-oligomers from AD brains associate with raft membrane fraction in a cholesterol-dependent manner | cholesterol depletion in neuronal cells, analysis of human *post mortem* AD samples | [25] | |
| **Effect of cholesterol on Aβ & ROS:** | | |
| **Mechanism of action / key findings** | **Experimental approach** | **Selected literature** |
| Aβ promotes oxidative stress directly by catalytically producing H2O2 from cholesterol | effect of high cholesterol on neuroblastoma cells in A-mediated neurotoxicity | [26] |

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| **Effect of cholesterol distributions / Lessons from NPC models:** | | |
| **Mechanism of action / key findings** | **Experimental approach** | **Selected literature** |
| ↑ β-CTF, ↑ γ-secretase activity, ↑Aabnormal distribution of PS1 in the endosomal system | mouse model of Niemann-Pick type C disease; in these mouse brains, cholesterol accumulates in late endosomes/ lysosomes | [27] |
| ↑ -secretase activity on APP C-terminal fragments, ↑Aβ40&Aβ42, PS1 and PS2 accumulation in Rab7-positive vesicular organelles | addition of cholesterol transport-inhibiting agents in neuronal and CHO cells and analysis of NPC1 deficient cells | [28] |
| ↑ Aβ accumulation in late endosomes | Niemann-Pick type C (NPC) model cells and NPC mutant cells, showing aberrant cholesterol trafficking, & NPC mouse brain | [29] |
| ↓ expression of APP at the cell surface and ↑ processing of APP through the β-secretase pathway resulting in ↑ -CTF, sAPPβ and intracellular Aβ40 levels | analysis of NPC1 deficient cells | [30] |
| shift in fl-APP/CTF compartmentalization into lipid raft fractions | raft fractions of CHO NPC1(-/-) cells (NPC cells) and parental CHOwt cells were analyzed | [31] |
| **Effect of cholesterolesthers and ACAT:** | | | |
| **Mechanism of action / key findings** | **Experimental approach** | **Selected literature** |
| cholesteryl-ester levels directly correlate with Aβ production | genetic, biochemical and metabolic approaches altering the choleterolesthers in different cells | [32] |
| ↓ cognitive deficits, ↓ APP and APP proteolytic fragments | analysis of ACAT1 gene ablation in triple transgenic AD mice | [33] |