FONDAZIONE S.I.S.A.
Per la promozione della ricerca sulle malattie da arteriosclerosi

Borsa di Studio «Andrea Mezzetti» 2019

Role of PCSK9 in Alzheimer's Disease: focus on inflammation and lipid metabolism

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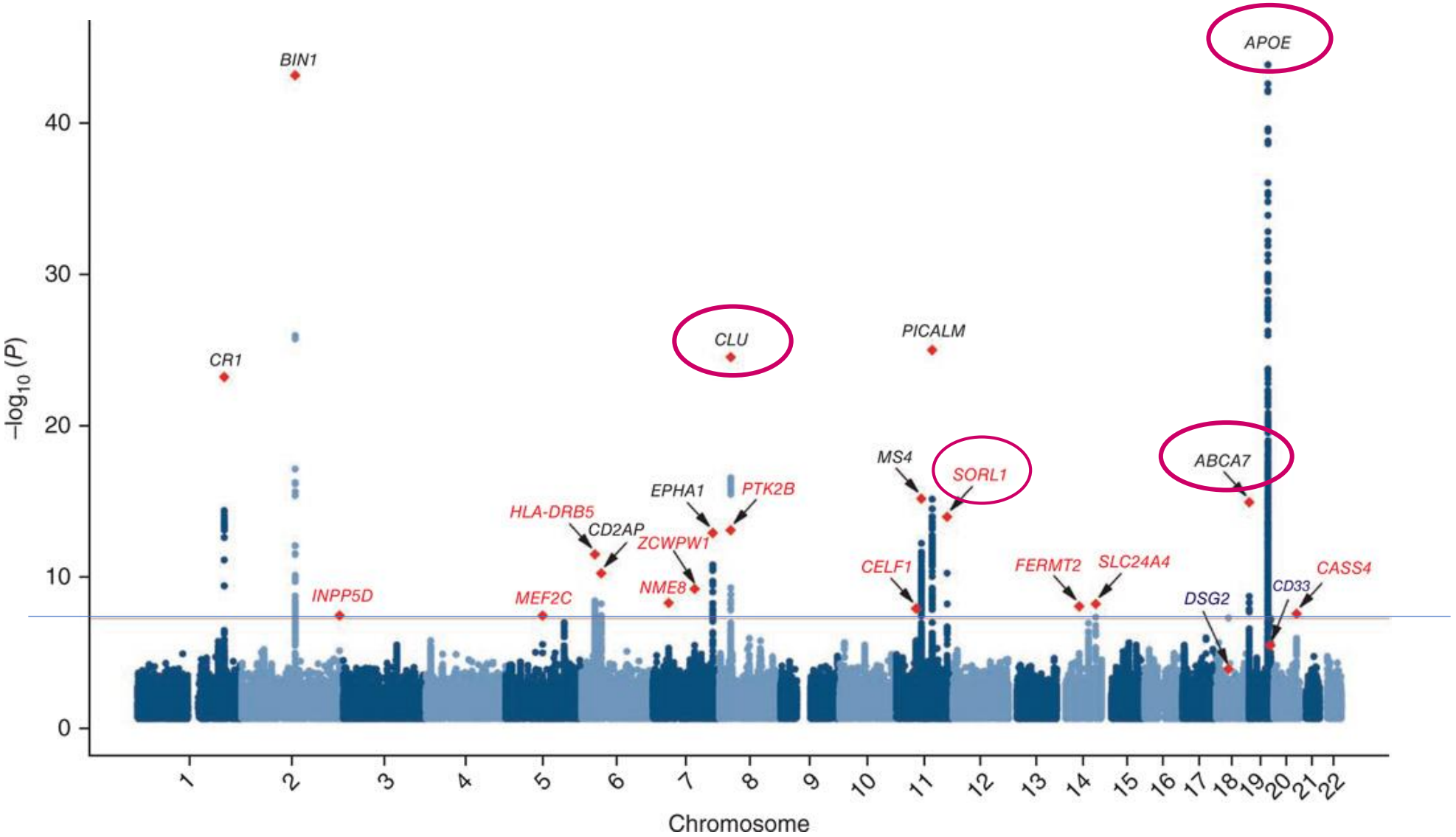
Università di Parma

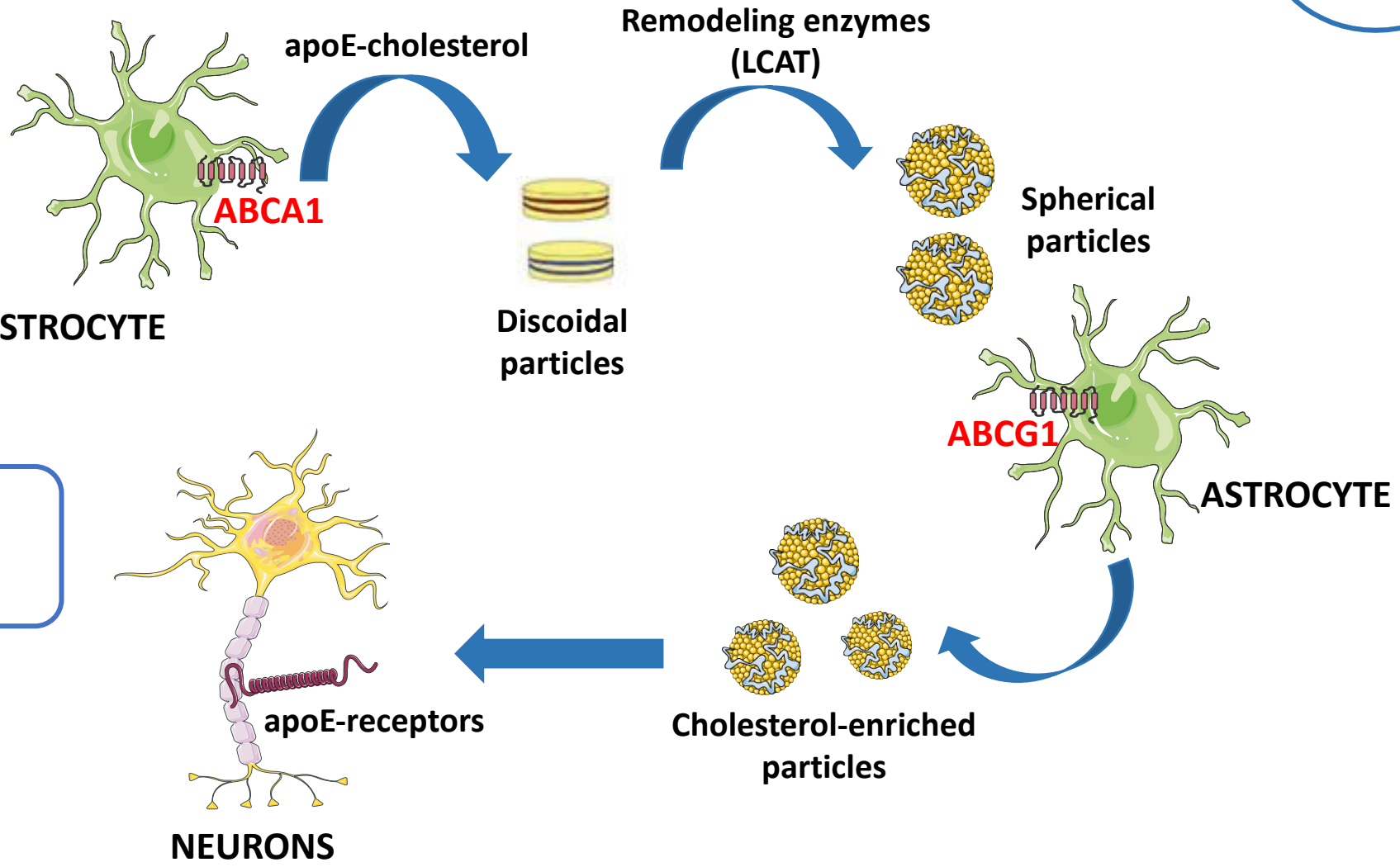
GENES INVOLVED IN CHOLESTEROL AND LIPID METABOLISM AMONG THE ALZHEIMER'S DISEASE SUSCETIBLE LOCI



Cholesterol in the brain

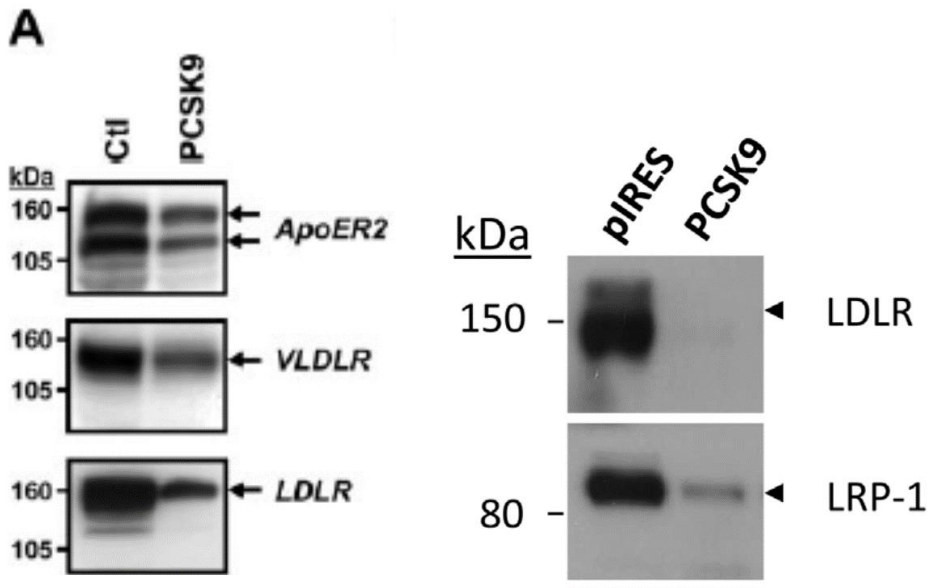
- Brain contains approximately 30% of total body cholesterol;
- Cholesterol in central nervous system plays crucial roles: important component of myelin, neuronal development, synaptogenesis, maintenance and repair of damaged membranes;
- Brain cholesterol is mainly synthetized in situ and provided by de novo synthesis. Peripheral cholesterol can not cross the blood-brain barrier;
- Neurons progressively loose their capacity to synthetize cholesterol during adulthood.

Brain cholesterol transport from astrocytes to neurons



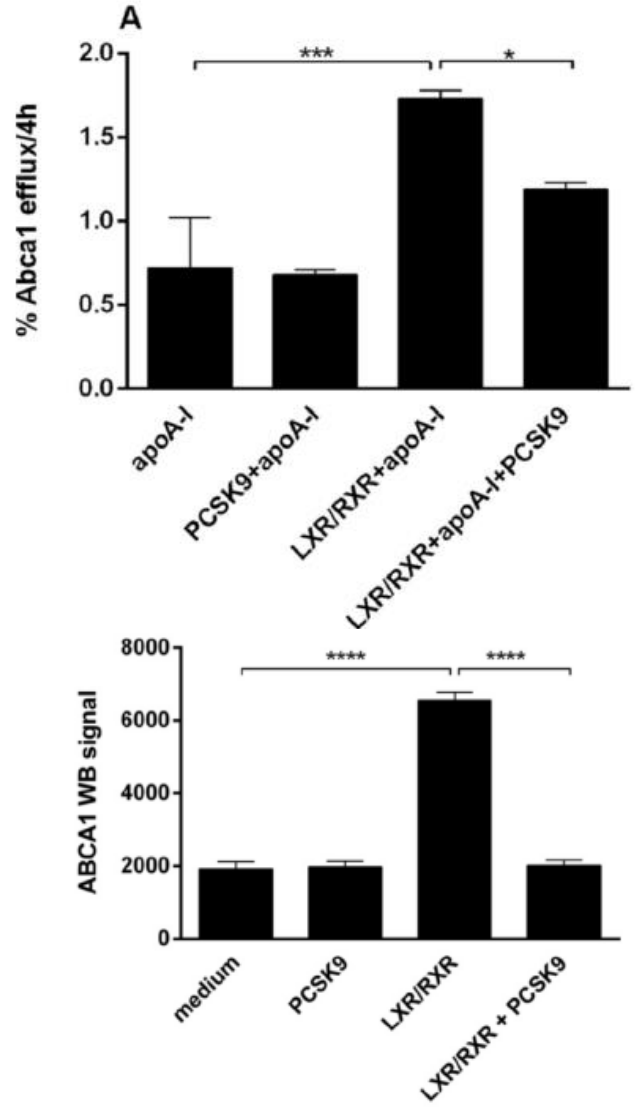
- Synaptogenesis
- Axonal and dendritic growth
- Neuronal repair

PCSK9 and CEREBRAL LIPID METABOLISM

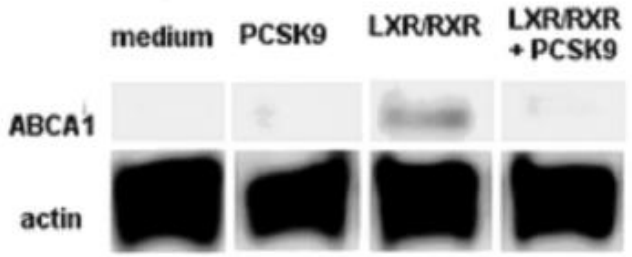


PCSK9 induces the degradation of apoE neuronal receptors implicated in neuronal cholesterol internalization

PCSK9 and MACROPHAGE LIPID METABOLISM



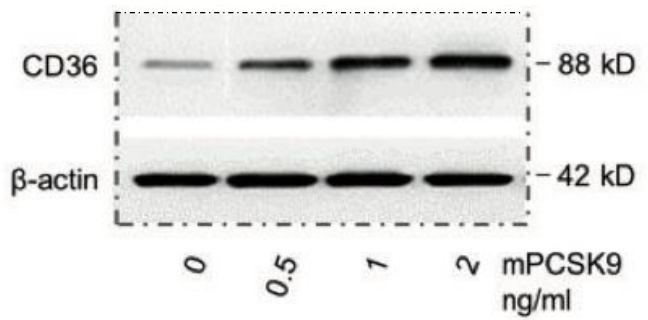
PCSK9 plays a direct role on Abca1-mediated cholesterol efflux through a downregulation of Abca1 gene and Abca1 protein expression



Adorni MP et al., Atherosclerosis 2017;

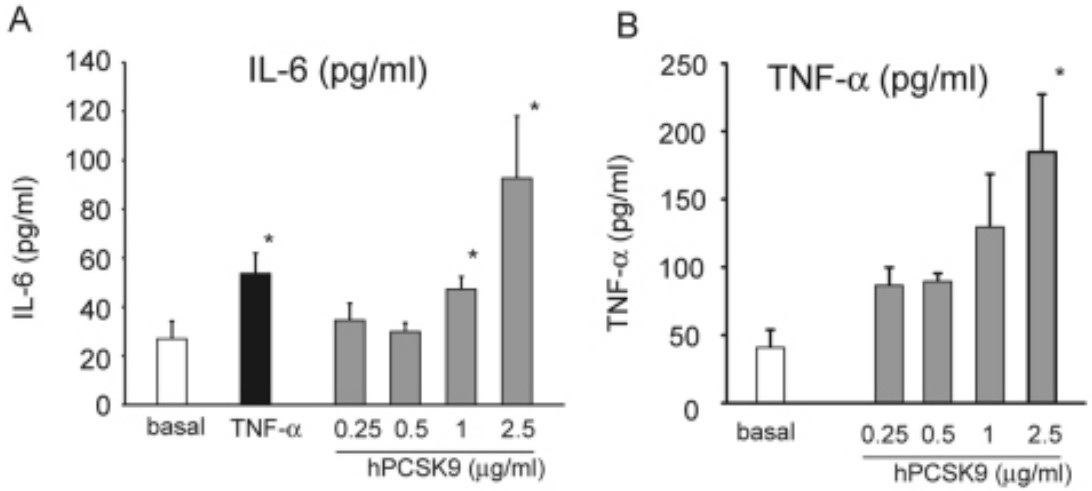
PCSK9 and MACROPHAGE INFLAMMATION

1.

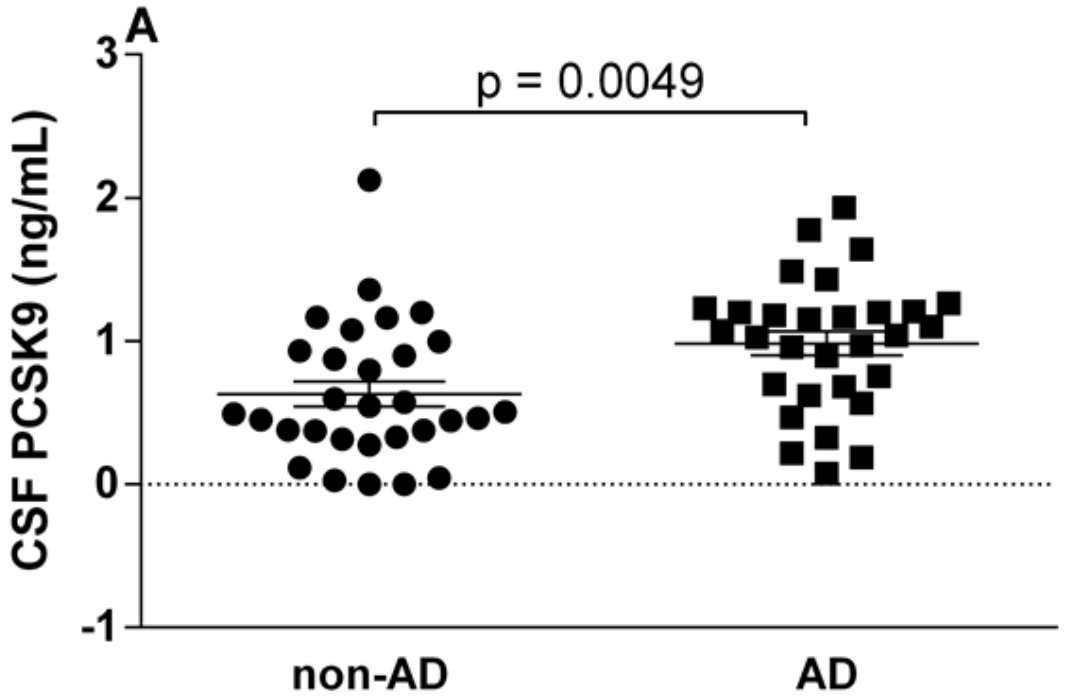


1. PCSK9 increases the expression of CD36 in macrophages, microglial-like cells;
2. PCSK9 drives an inflammatory response on macrophages by inducing the pro-inflammatory cytokines

2.



PCSK9 CSF levels are increased in AD patients



AIM of THE PROJECT

To investigate the molecular mechanisms by which PCSK9 may exert a pathogenetic role and a deleterious effect on brain cells by negatively modulating **cholesterol homeostasis** or **neuroinflammation** through *in vitro* studies

HYPOTHESES:

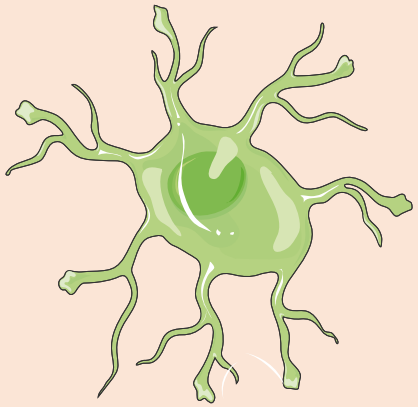
1. **PCSK9 degrades apoE neuronal receptors relevant for the cholesterol internalization and therefore neuronal functions;**

2. **PCSK9 reduces ABCA1 expression in astrocytes, preventing apoE lipidation and consequent generation of HDL-like particles;**

3. **PCSK9 modulates CD36 expression in microglia, resulting in amplified Aβ-dependent neuroinflammation.**

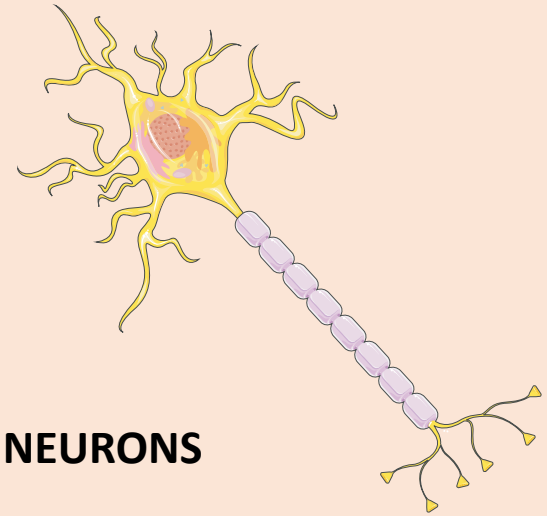
Cellular models:

***In vitro* studies**



ASTROCYTES

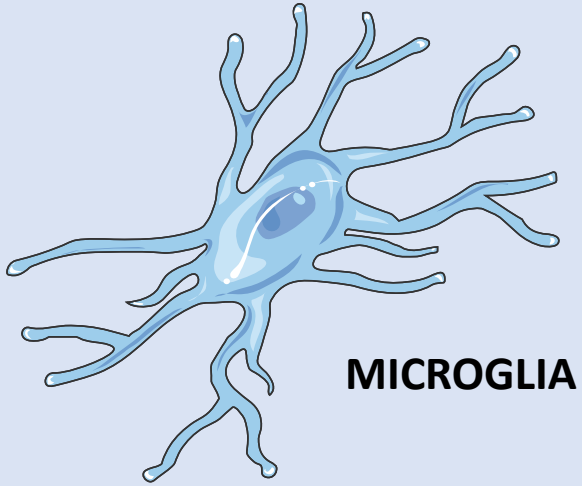
U373
±
Human recombinant PCSK9



NEURONS

- **SH-SY5Y ± Human recombinant PCSK9**
- **SH-SY5Y control and overexpressing PCSK9**

CHOLESTEROL METABOLISM



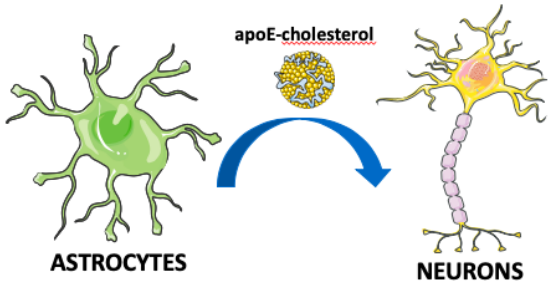
MICROGLIA

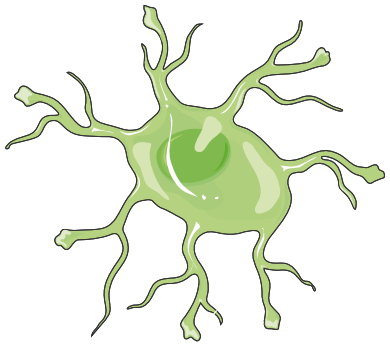
HMC3 ± Aβ
±
Human recombinant PCSK9

NEUROINFLAMMATION

In vitro studies

IMPACT OF PCSK9 ON CHOLESTEROL METABOLISM:



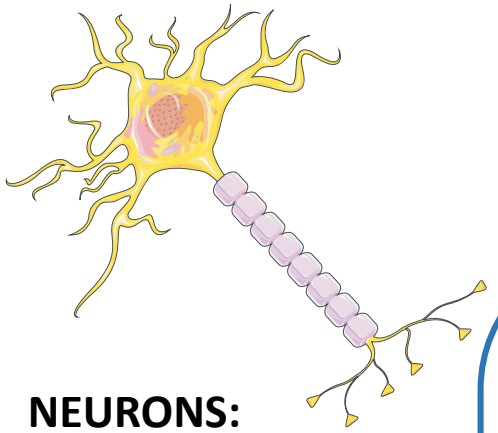


ASTROCYTES:

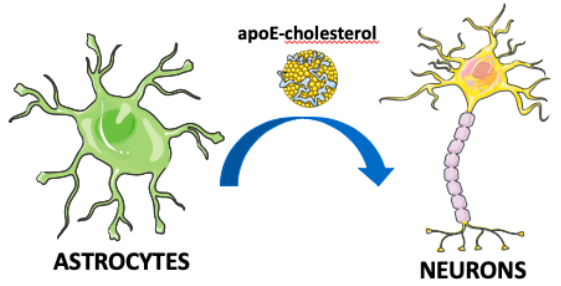
- Cholesterol efflux
- Expression of receptors involved in brain cholesterol efflux: i.e. ABCA1 and ABCG1
- Endogenous cholesterol synthesis
- Membrane cholesterol distribution

IMPACT OF PCSK9 ON CHOLESTEROL METABOLISM:

***In vitro* studies**



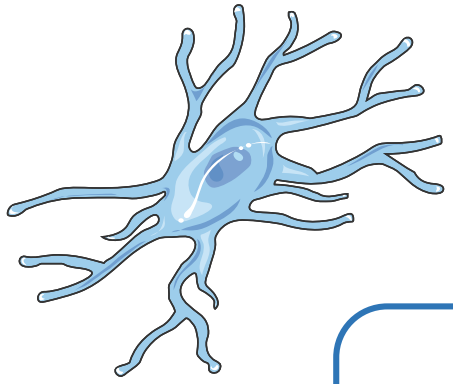
NEURONS:



- Cholesterol uptake
- Expression of receptors involved in cholesterol uptake: i.e. ApoER2, LDLr, LRP-1
- Endogenous cholesterol synthesis
- Membrane cholesterol distribution
- Consequences of PCSK9-induced alteration of lipid metabolism on:
  1) apoptosis (caspase 3 levels)
  2) Aβ production

IMPACT OF PCSK9 ON NEUROINFLAMMATION:

***In vitro* studies**



MICROGLIA:

- Inflammatory response to Aβ: levels of IL-6, IL-1β and TNF-α
- Expression of CD36

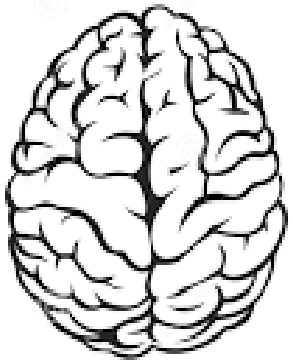
EXPECTED OUTCOMES:

Provide new perspectives for understanding the connection between PCSK9, brain cholesterol metabolism and neuroinflammation

Fill the existing knowledge gap on PCSK9 potential involvement in Alzheimer's Disease

Identify PCSK9 as a novel player and potential therapeutic target for future pharmacological strategies

ACKNOWLEDGMENTS:



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