UNIVERSITÀ DEGLI STUDI
DI MILANO

Studio di TREM2 nell'evoluzione della malattia di Alzheimer

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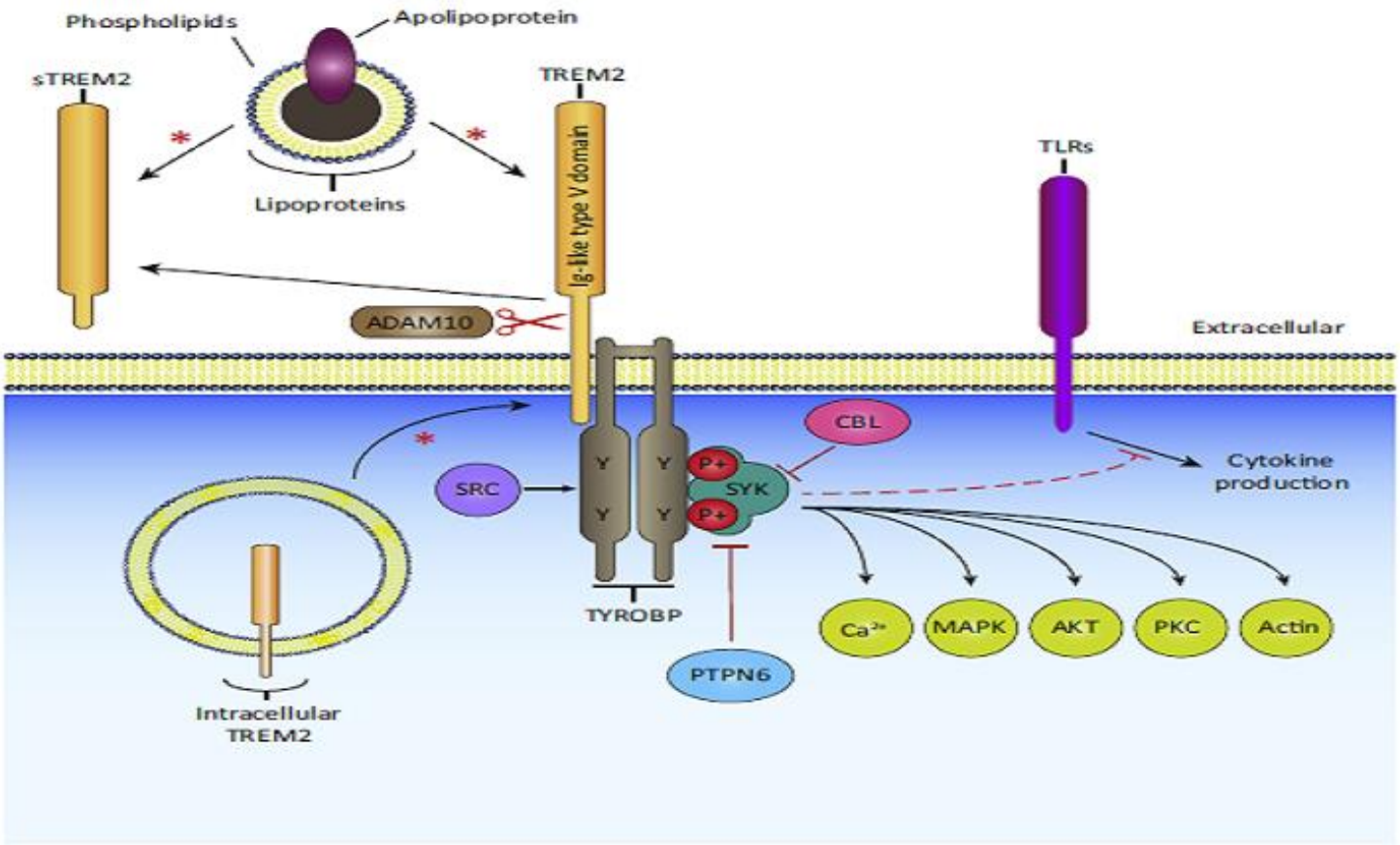

Trends in Molecular Medicine

Figure 1. Regulation of TREM2 Signaling. TREM2 binds to phospholipids, apolipoproteins, and lipoproteins through its immunoglobulin (Ig)-like V-type domain. Surface levels of TREM2 can be regulated by shedding (cleavage by ADAM10 to produce soluble sTREM2) or through trafficking from intracellular stores of TREM2. Upon ligand binding, SRC family tyrosine-protein kinases phosphorylate the tyrosine residues within the ITAM domain of TYROBP (a disulfide-linked homodimer). Spleen tyrosine kinase (SYK) is then recruited, initiating a host of downstream signaling events such as Ca^{2+}, MAPK, RAC serine/threonine-protein kinase (AKT), protein kinase C (PKC), and actin mobilization. SYK signaling can be negatively regulated through PTPN6, which dephosphorylates the ITAM domain of TYROBP, and also by CBL, an E3-ubiquitin ligase. TREM2–TYROBP signaling attenuates the production of proinflammatory cytokines in response to activation of Toll-like receptors (TLRs). Asterisks denote processes affected by disease-associated TREM2 variants.

Yeh FL et al, Trends in Molecular Medicine, 2017

Neurobiology of Aging xxx (2017) 1e1–1.e9

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Contribution to Alzheimer's disease risk of rare variants in *TREM2*, *SORL1*, and *ABCA7* in 1779 cases and 1273 controls

Céline Bellenguez[a,b,c,1], Camille Charbonnier[d,1], Benjamin Grenier-Boley[a,b,c,2]

LETTERS

nature genetics

Sims R et al. Nat Genet. 2017

Rare coding variants in *PLCG2*, *ABI3*, and *TREM2* implicate microglial-mediated innate immunity in Alzheimer's disease

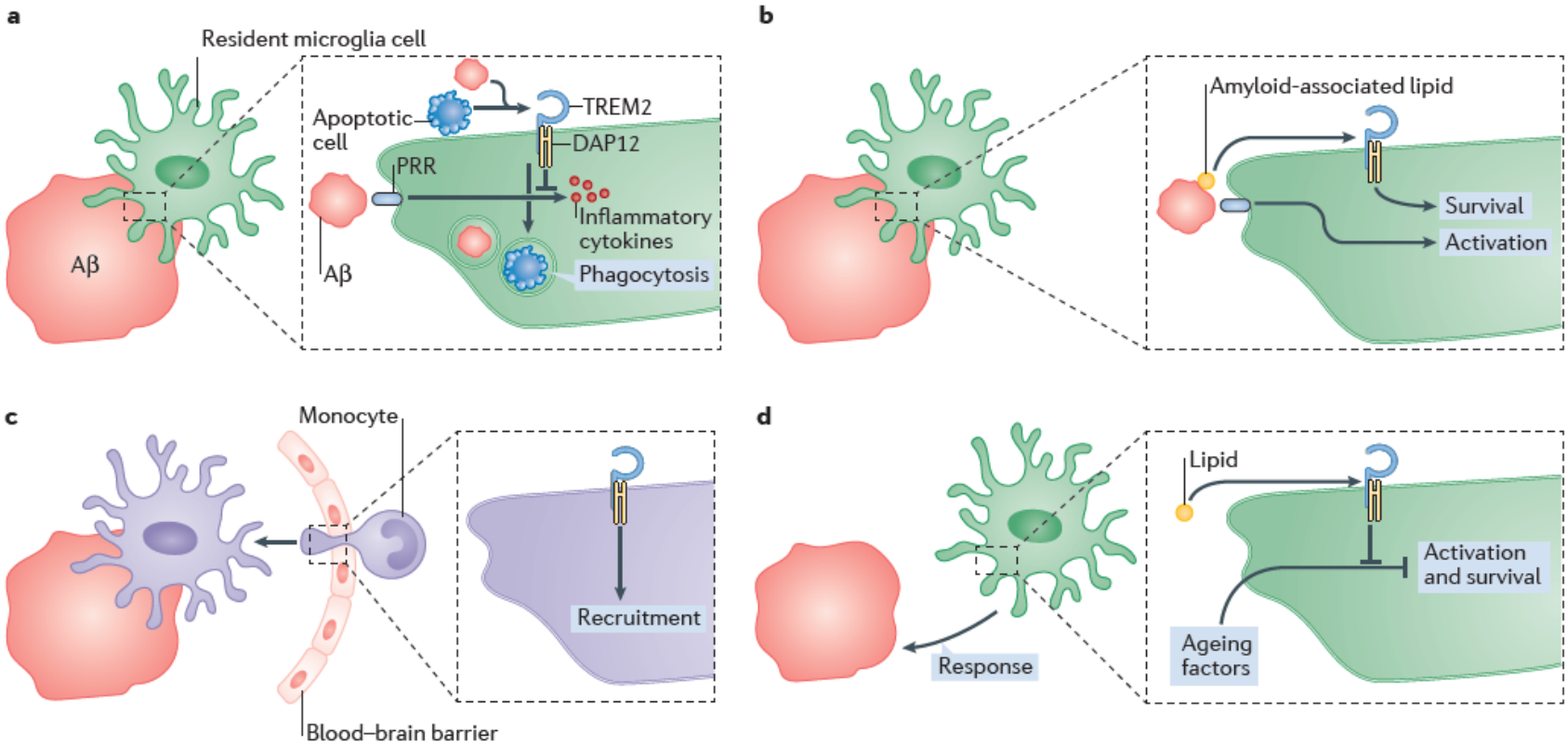


Figure 2 | **Potential models of TREM2 function in microglial response to Alzheimer disease. a** | According to one model, triggering receptor expressed on myeloid cells 2 (TREM2) in resident microglia promotes the phagocytosis and removal of apoptotic cells and amyloid-β (Aβ). Moreover, this model suggests that TREM2 limits inflammation by interfering with pro-inflammatory signals, which could be transmitted by pattern recognition receptors (PRRs) upon amyloid recognition. **b** | A second model suggests that TREM2 signals sustain the long-term survival of microglia in response to lipids that may become exposed during Alzheimer disease (AD) owing to cell death, myelin degradation and the generation of Aβ complexes with phospholipids. By promoting microglial survival, TREM2 would therefore enable and sustain the activation of microglia by PRRs or other receptors that sense Aβ deposition. **c** | A third model suggests that TREM2 expression on peripheral monocytes promotes their recruitment through the blood–brain barrier to the Aβ plaque. **d** | Finally, a fourth model suggests that upon sensing brain lipid components, TREM2 delivers a tonic signal that delays ageing and deactivation of microglia by suppressing the effects of as-yet-undefined ageing risk factors.

Colonna M et Wang Y, Nature Reviews/Neuroscience, 2016

Obiettivo

Studio, in soggetti affetti da Mild Cognitive Impairment (MCI), dell'espressione di TREM2 in cellule mononucleate periferiche del sangue (PBMC) allo scopo di:

- ✓ **identificare un nuovo pathway coinvolto nell'evoluzione della malattia**
- ✓ **identificare un marker periferico di neuroinfiammazione**

Disegno dello Studio

- 57 pazienti MCI (età media 78.5 ± 0.8 anni; MMSE 26 ± 0.4)
  (Petersen RC, Journal of Internal Medicine, 2004)

- 50 pazienti Alzheimer (AD) (età media 78.6 ± 0.6; MMSE 22 ± 0.6)
  (Dubois HH et al, Lancet Neurol, 2007; McKhann G et al, Neurology, 1984)

- 42 soggetti controllo (età media 78.9 ± 0.7 anni; MMSE 29 ± 0.2)

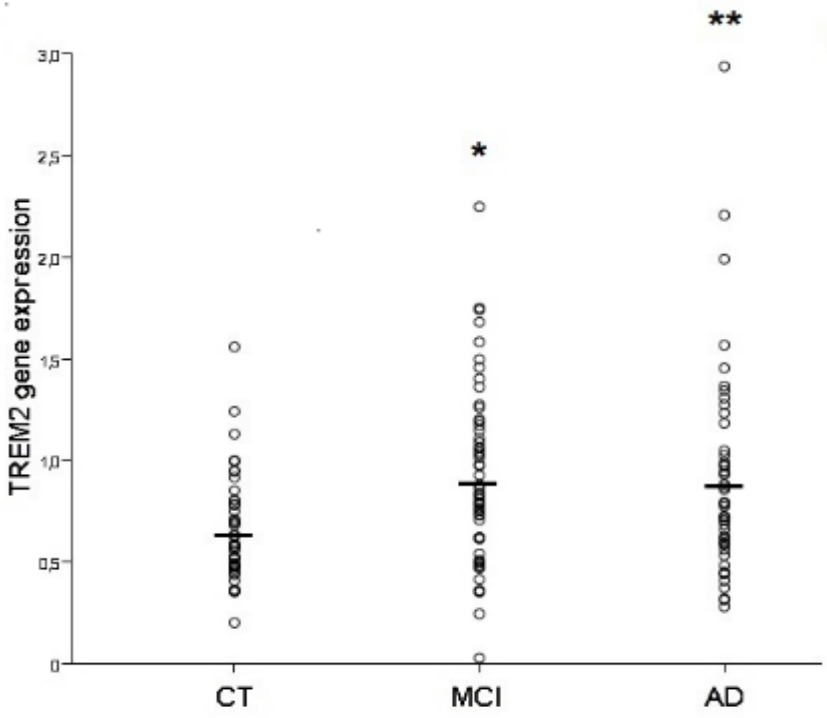
Dopo un follow-up di due anni i pazienti MCI sono stati suddivisi in:

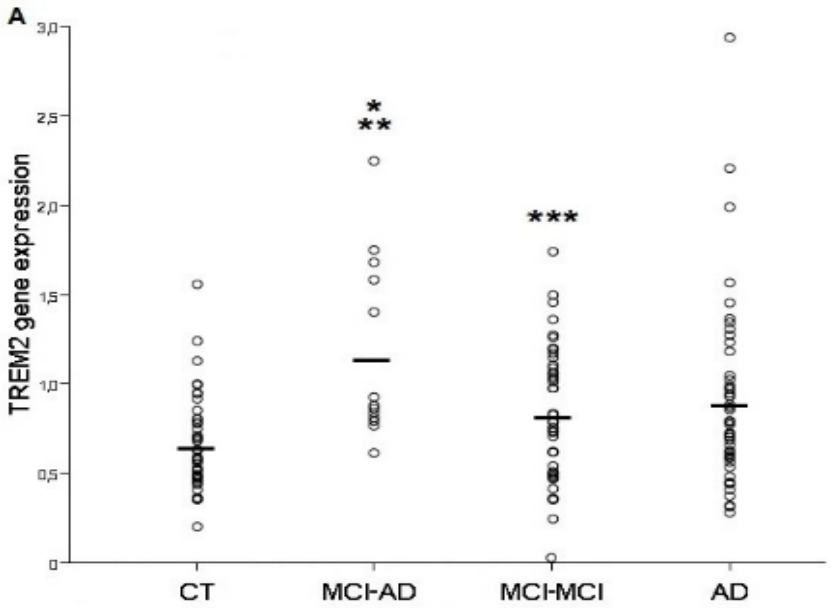
- 13 MCI evoluti (MCI-AD) (età media 75.1 ± 0.7 anni; MMSE 22 ± 1.5)
- 44 MCI stabili (MCI-MCI) (età media 79.4 ± 0.7 anni; MMSE 25 ± 0.6)

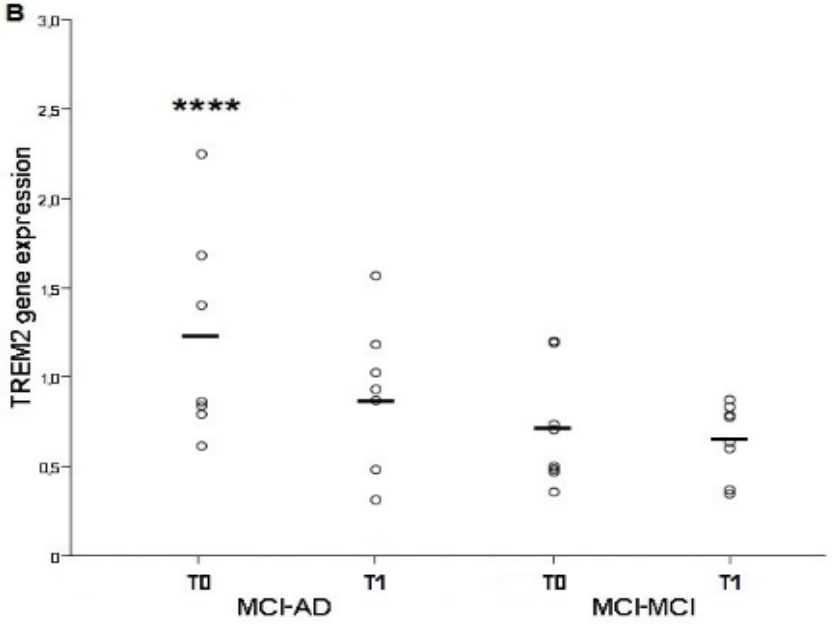
Metodi

- Estrazione RNA da PBMC
- Espressione genica di TREM2 mediante real-time PCR e calcolo del $2^{-\Delta\Delta Ct}$
- Estrazione DNA mediante salting-out
- Genotipo ApoE mediante PCR-RFLP (Esone 4: ε2, ε3 e ε4)
- Dosaggio proteico plasmatico di sTREM2 mediante Human TREM2 ELISA Kit (Sigma-Aldrich)
- Analisi statistica utilizzando il programma SPSS versione 24 (Kruskal-Wallis e test U di Mann-Whitney)

Risultati

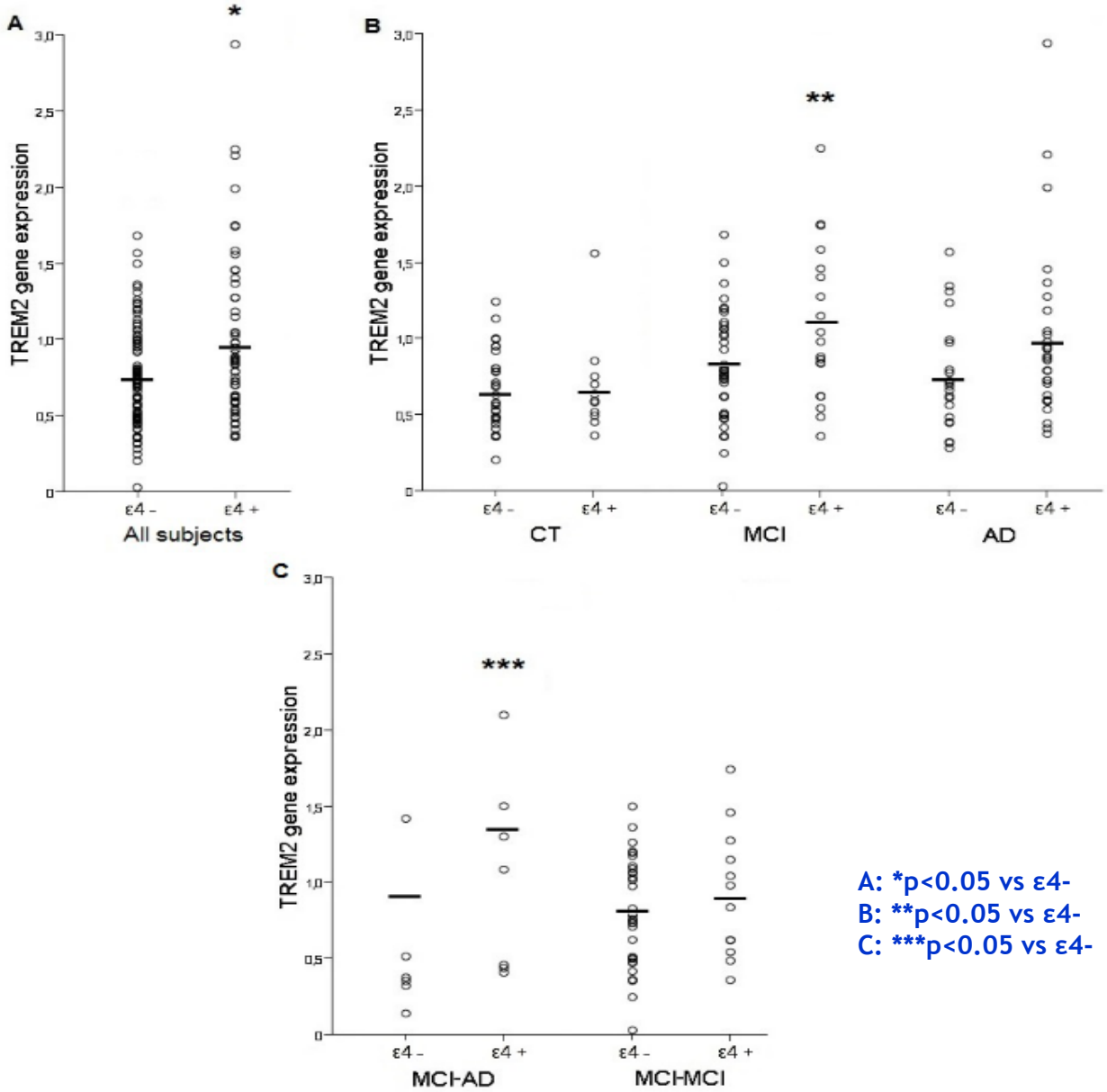






*p<0.001 vs CT; **p<0.05 vs CT
A: *p<0.001 vs CT; **p<0.05 vs MCI-MCI and AD; ***p<0.05 vs CT
B: ****p<0.05 vs T1 MCI-AD

Risultati



A: *p<0.05 vs ε4-
B: **p<0.05 vs ε4-
C: ***p<0.05 vs ε4-

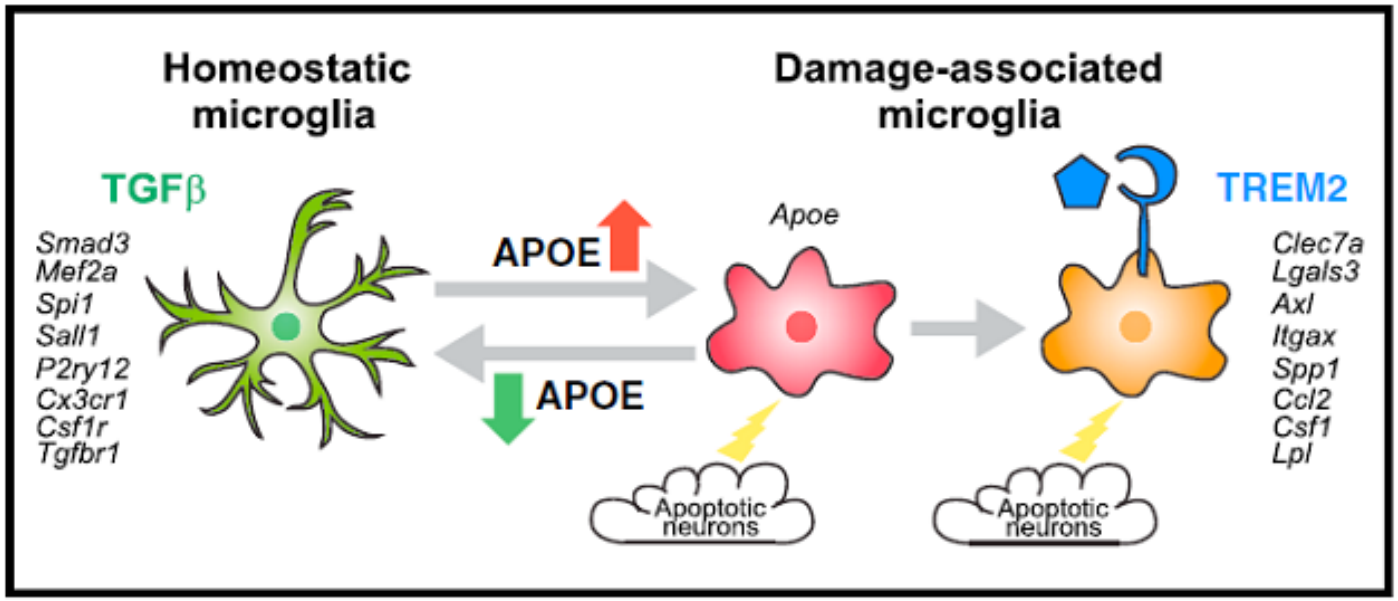


Figure 1. The Transition between Homeostatic and Damage-Associated Phenotypes of Microglia Is Regulated by APOE and TREM2

Pimenova et al, Immunity, 2017

The TREM2-APOE Pathway Drives the Transcriptional Phenotype of Dysfunctional Microglia in Neurodegenerative Diseases

Susanne Krasemann,[1,2,17] Charlotte Madore,[1,17] Ron Cialic,[1] Caroline Baufeld,[1] Narghes Calcagno,[1] Rachid El Fatimy,[1] Lien Beckers,[1] Elaine O'Loughlin,[1] Yang Xu,[3] Zain Fanek,[1] David J. Greco,[1] Scott T. Smith,[1] George Tweet,[1]

Krasemann et al, *Immunity, 2017*

Conclusioni

I nostri dati:

- ✓ **mostrano un coinvolgimento di TREM2 nelle fasi precliniche dell'AD ed in particolar modo in quei soggetti con scadimento cognitivo che poi svilupperanno AD**

- ✓ **confermano l'esistenza di un possibile sinergismo tra TREM2 e ApoE**

- ✓ **sembrerebbero indicare la possibilità di utilizzare TREM2 come biomarcatore precoce dell'AD.**