Iron exacerbates ferroptosis by downregulating GPX4 via the Alzheimer's disease-associated TREM2 R47H

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Abstract

Genome-wide association studies (GWAS) have identified the R47H allele of triggering receptor expressed on myeloid cells 2 (TREM2) R47H as one of the most significant genetic risk factors for Alzheimer's disease (AD). However, the mechanism by which it contributes to AD remains largely unknown.

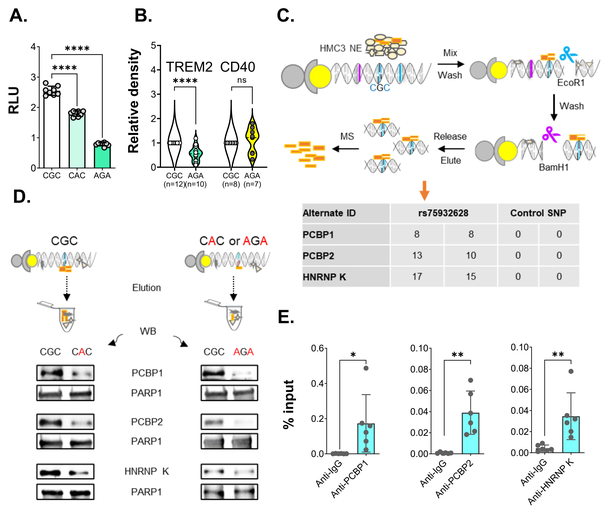
Ferroptosis is a programmed cell death caused by the abnormal increase in iron-dependent lipid peroxidation. Increasing evidence suggests that ferroptosis could be one of the mechanisms involved in the development of AD, but, so far, no genetic evidence has been discovered.

Here, we report that rs75932628, an exonic SNP encoding TREM2 R47H, is also part of a cis-regulatory element that modulates TREM2 expression by recruiting at least two iron chaperones, namely Poly(rC) Binding Protein 1 (PCBP1) and PCBP2. Further analysis revealed that iron suppresses TREM2 expression by disrupting the binding of these proteins to rs75932628, and that downregulation of TREM2 by iron, as well as other heavy metals, inhibits the expression of glutathione peroxidase 4 (GPX4). Decreased GPX4, an enzyme capable of converting lipid peroxide to lipid alcohol, results in ferroptosis, due to the accumulation of lipid peroxide.

Thus, our results reveal how iron, the most abundant heavy metal in nature, can regulate ferroptosis by interacting with the AD-associated TREM2 R47H allele. These data provide human genetic evidence supporting the ferroptosis hypothesis of AD pathogenesis.

Results

Figure 1. Identification and validation of rs75932628 as part of a cis-RE binding to PCBP1, PCBP2 and HNRNP K



Alternate ID	rs75932628		Control SNP	
PCBP1	8	8	0	0
PCBP2	13	10	0	0
HNRNP K	17	15	0	0

Figure 2. PCBP1, PCBP2, and HNRNP K bind to rs75932628 and regulate TREM2 expression

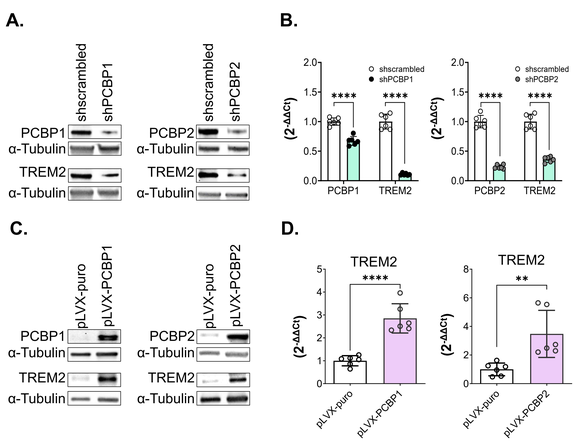
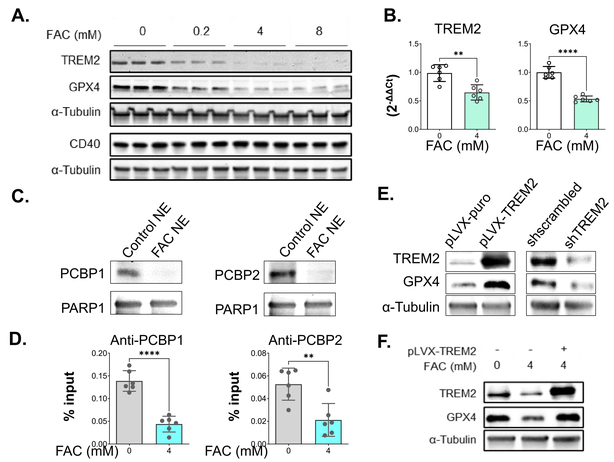


Figure 3. Iron suppresses the GPX4 by inhibiting TREM2 expression via disrupting the binding of PCBP1 and PCBP2 to rs75932628



Conclusions

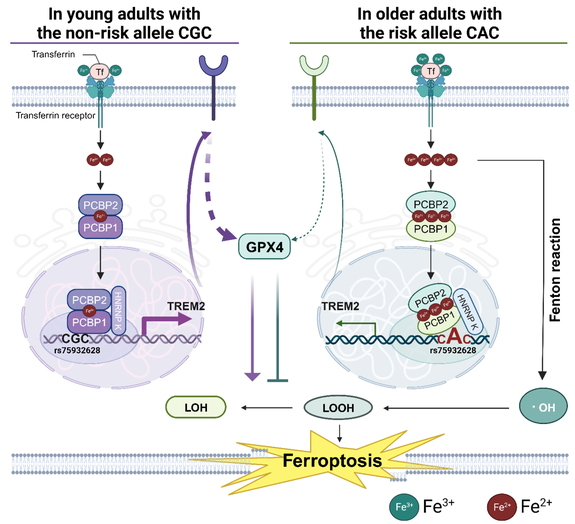
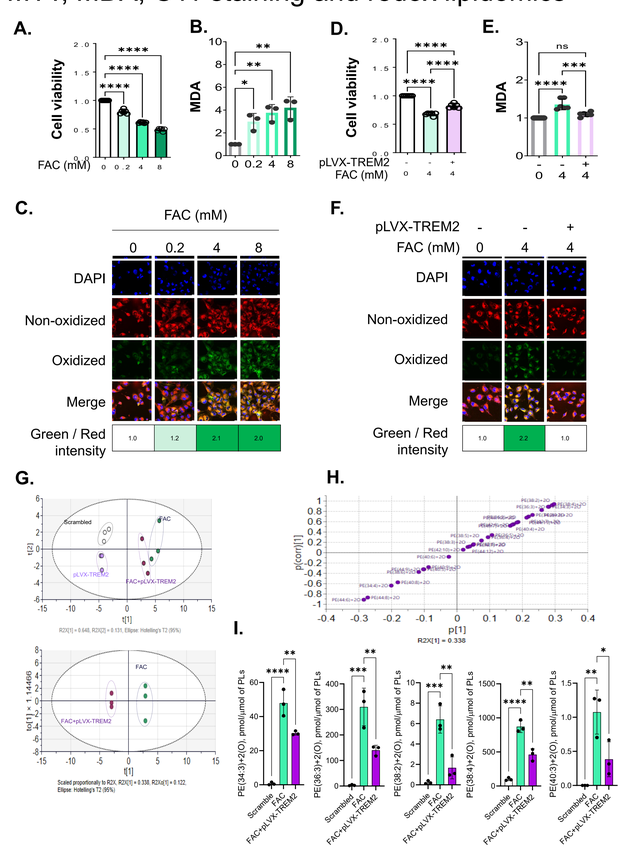


Figure 4. TREM2 overexpression blocks ferroptosis induced by iron as measured by MTT, MDA, C11 staining and redox lipidomics



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