Unraveling the Immunological Nexus: The Role of Complement Factor I and Cub and Sushi Domains in Schizophrenia Pathogenesis

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Introduction

- The complement system, an effector of innate immunity, also plays a role in synaptic pruning & plasticity, osonizing synapses for elimination via microglial activation.
- In GWAS, genes linked to the complement system, including Cub and sushi multiple domains (CSMD1), have emerged as Schizophrenia (SCZ) risk genes.
- CSMD1 and its cofactors Complement Factor I (CFI) and Factor H (FH) negatively regulate complement activity. SCZ patients display alterations in serum levels of complement inhibitors.

Little is known of the mechanisms by which these regulators influence SCZ risk and synaptic pathogenesis in humans.

Results: Effects of Diagnosis

CSMD1, CFI and FH mRNA expression is unaltered across groups.

Effect of Confounders: CFI expression correlates with PPI (r=-0.02), pH (r=0.01) and RIN (r=0.001). FH correlates with pH (r=-0.07) and RIN (r<0.001). CSMD1 was not significantly correlated with any of the above. Sex, smoking at time of death, age at onset and duration of illness did not impact gene expression.

In psychiatric subjects, CFI expression correlates with lifetime antipsychotic dose (p=0.045).

Materials and Methods

- Sample: SCZ (33), BD (32) and control (34) post-mortem brain samples of prefrontal cortex.
- Procedures: mRNA expression was quantified by qPCR. Normalization was performed by geometric averaging of reference genes (ACTB, GADPH, TBP). Pre-synaptic marker SNAP-25 was quantified by ELISA.
- Statistical Analysis: Between-group differences were investigated using ANCOVA, with diagnoses as contrasts. Potential confounders were evaluated with Spearman’s correlations.

Results: Effects of Suicide

CSMD1 expression is lower in psychiatric patients who did not die by suicide relative to CON (p=0.046).

Results: Synaptic Markers

CSMD1 (r=-0.252, p=0.015) and CFI (r=-0.206, p=0.047) are significantly correlated with SNAP-25 levels.

Conclusions and Future Steps

- CSMD1 expression is altered in psychiatric disorders.
- CSMD1 and CFI correlate with synaptic density.
- CSMD1, CFI and FH protein expression will be quantified. Expression will be correlated with other markers of synaptic density and complement activation.

References

[1] Vreuls et al. 2022 PMID: 35600020

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