Global transcriptional network reveals that tocopherols rescue TREM2-driven microglial dysfunction in vivo

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Data-driven formulation of novel biological hypothesis is the most challenging and the most rewarding avenue for the re-usage of publicly available transcriptional data. While previous approaches rely heavily on the curated portion of the database, we developed GeneQuery, novel geneset-based phenotype search engine that can be applied across all available public transcriptional data independent of the curation status. GeneQuery revealed an unexpected connection between transcriptional signatures of Trem2-deficient microglia and a portion of the aging-associated signature consisting of genes responsive to α/γ-tocopherol treatment. We thus utilized two mouse models of TREM2-associated deficiency – 5xFADxTrem2 mice (partly Trem2-dependent model of Alzheimer's Disease) and Cuprizone treatment (fully Trem2-dependent model of Nasu-Hakola Disease). We demonstrate that α/γ-tocopherol treatment rescued clinical pahtogenesis in the context of Cuprizone model but not in the 5xFAD mice. In fact, α/γ-tocopherol treatment led to complete recovery of myelination following cuprizone-induced injury in Trem2-deficient mice. These results validate a powerful new computational approach, highlight the critical role of TREM2 in microglial function and suggest new therapeutic approaches for treating TREM2-associated neurodegeneration.