

Aberrant autophagy and skewed inflammatory and tolerogenic functions in STAT1 gain-of-function dendritic cells

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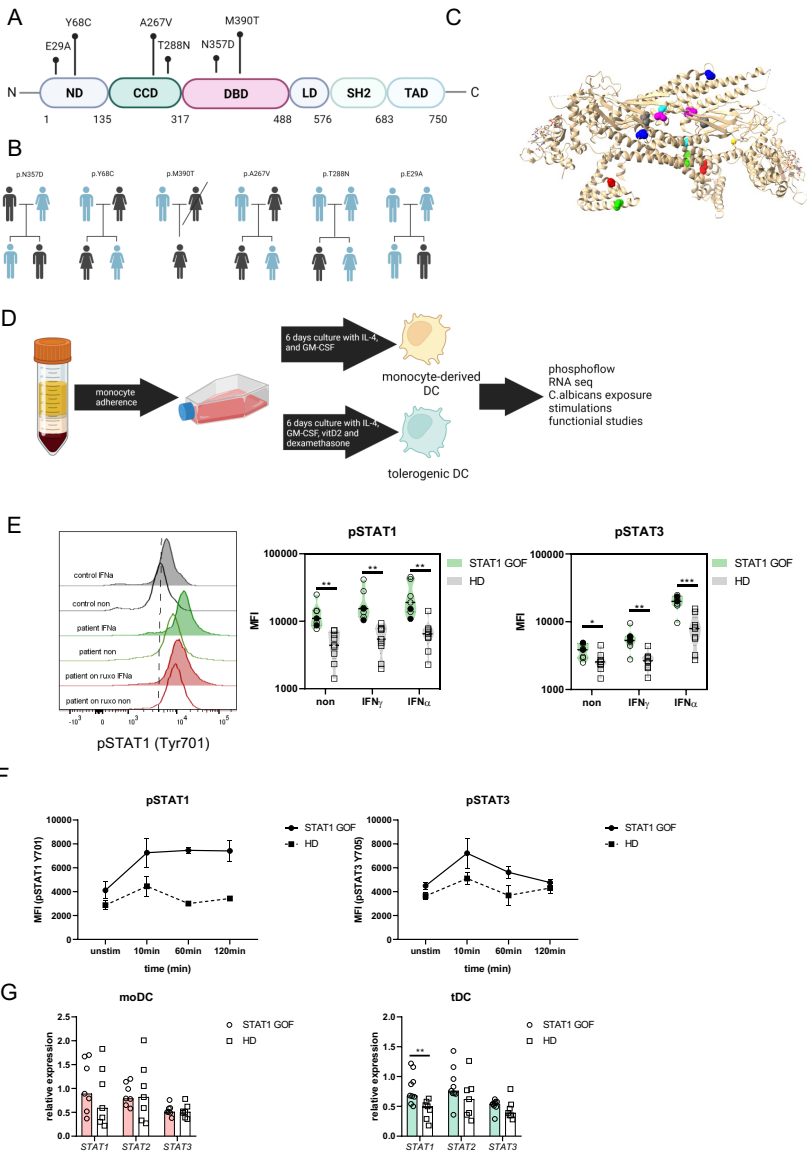
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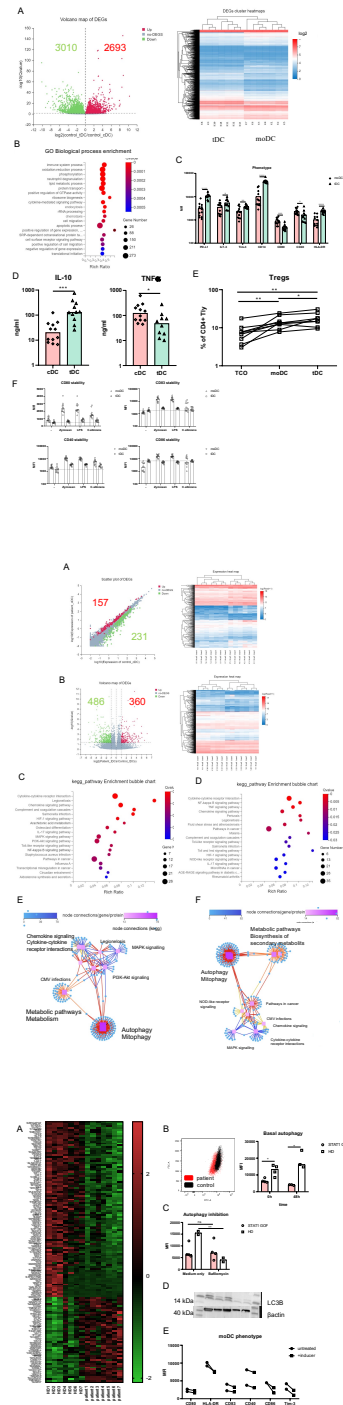
Abstract

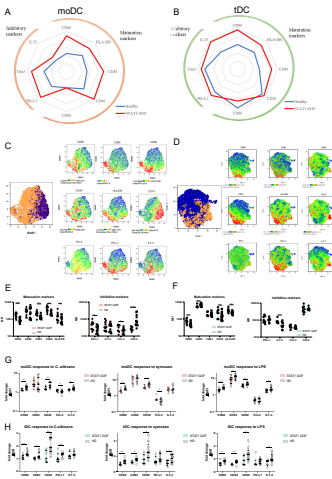
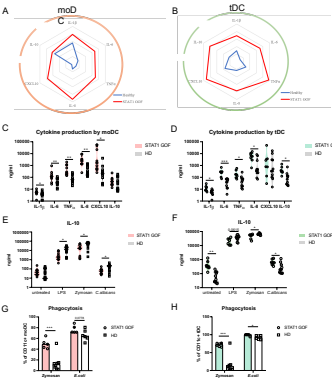
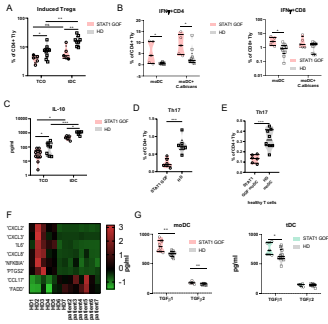
Signal transducer and activator of transcription 1 (STAT1) gain-of-function (GOF) mutations underlie an inborn error of immunity called chronic mucocutaneous candidiasis. Beyond the fungal susceptibility, attributed to Th17 failure, over half of the reported patients suffer from autoimmune manifestations, the mechanism of which has not been explained yet. Dendritic cells (DCs) have been implicated in the pathogenesis of various autoimmune disorders, however, to date they have not been studied in STAT1 GOF CMC. We hypothesized that the STAT1 mutations would affect DCs' properties and alter their inflammatory and tolerogenic functions. To test the hypothesis, we generated monocyte-derived DCs (moDCs) and tolerogenic DCs (tDCs) from freshly isolated STAT1 GOF patients' monocytes cultivated in the presence of IL-4 and GM-CSF (moDCs), and tolerogenic factors vitamin D2 and dexamethasone (tDCs). Functional and signaling studies, co-culture experiments and RNA sequencing demonstrated that STAT1 GOF DCs were profoundly altered in their phenotype and functions, characterized by defective autophagy, proinflammatory skew and loss of tolerogenic functions. The results suggested that DCs play an important role in the immune dysregulation in STAT1 GOF CMC and may contribute to the disease-associated autoimmune manifestations via alteration in various cellular mechanism, including autophagic processes.

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