

Aberrant tolerogenic functions and proinflammatory skew of dendritic cells may contribute to autoimmunity in STAT1 gain-of-function patients

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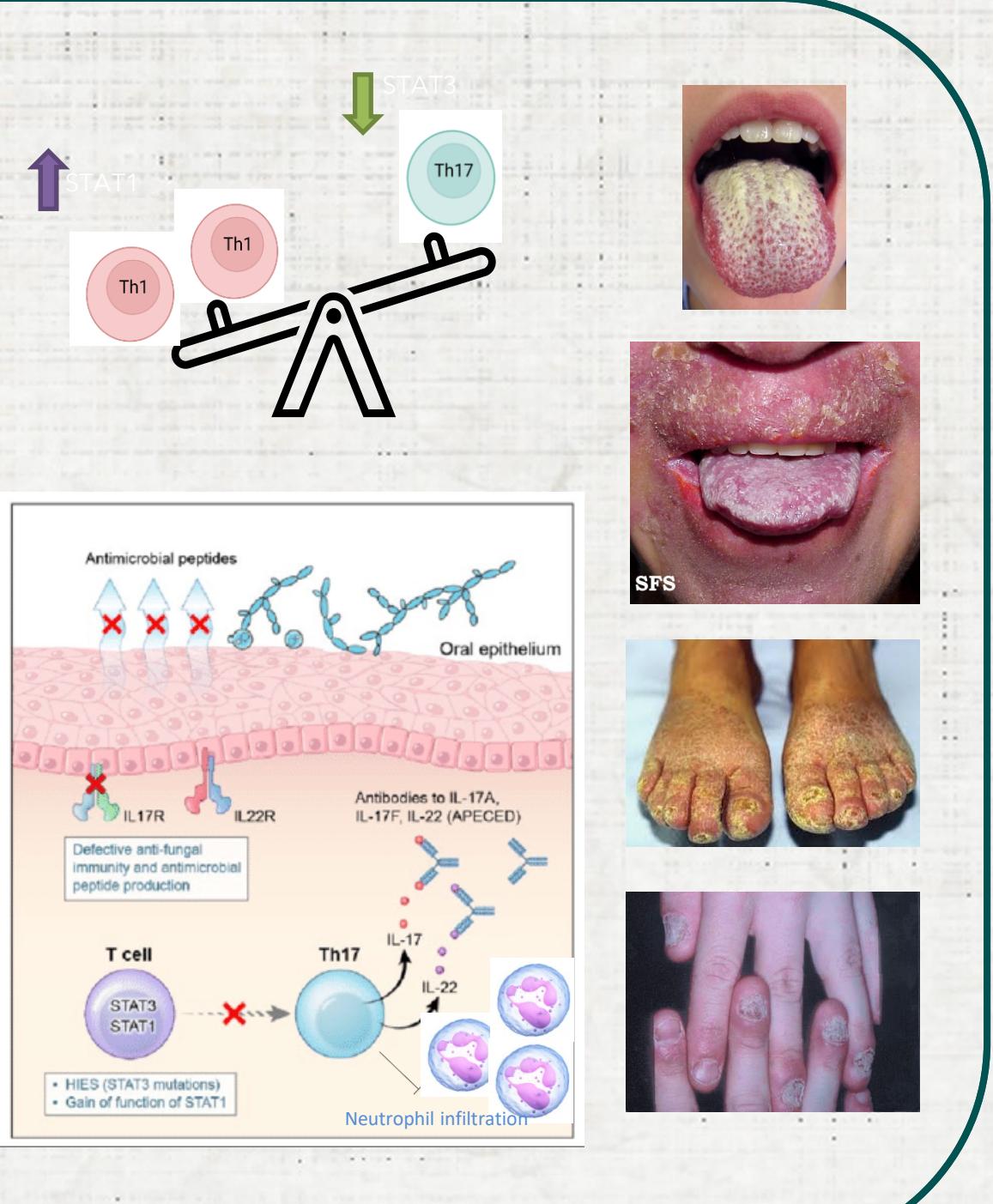


Introduction

STAT1 gain-of-function: when balance is everything

STAT1 GOF

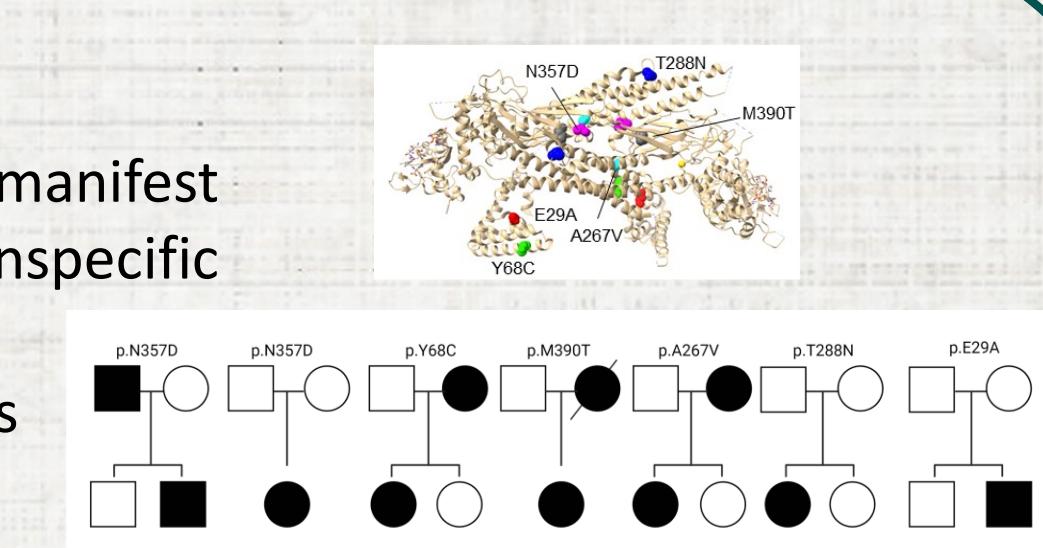
- is an inborn error of immunity hallmarked by chronic mucocutaneous candidiasis (CMC) – recurrent or persistent infections with *Candida albicans* affecting the nails, skin, oral and genital mucosae via Th17-mediated immune failure
- also underlies a variety of autoimmune features with are not explained yet but herald poor outcome
- the skewing of STAT1 and STAT3 signalling results in the dysbalance between Th1 and Th17 cells, which are essential components in mucosal immunity



Patients and Methods

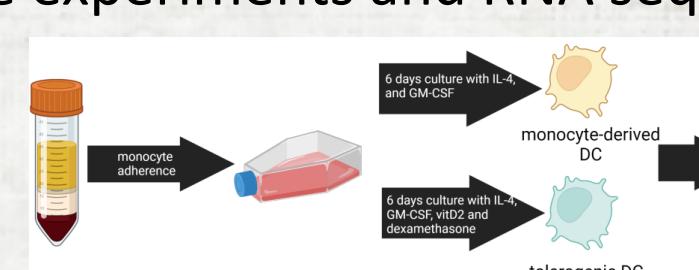
Patient cohort:

- 3 males, 7 females; CMC of various severity, three had clinically manifest autoimmunity and six had autoantibodies against organ-nonspecific antigens
- increased IFN α - and/or IFN γ -induced STAT1 signalling in CD3+ T cells
- low counts of peripheral CD4+ Th17 cells



Methods:

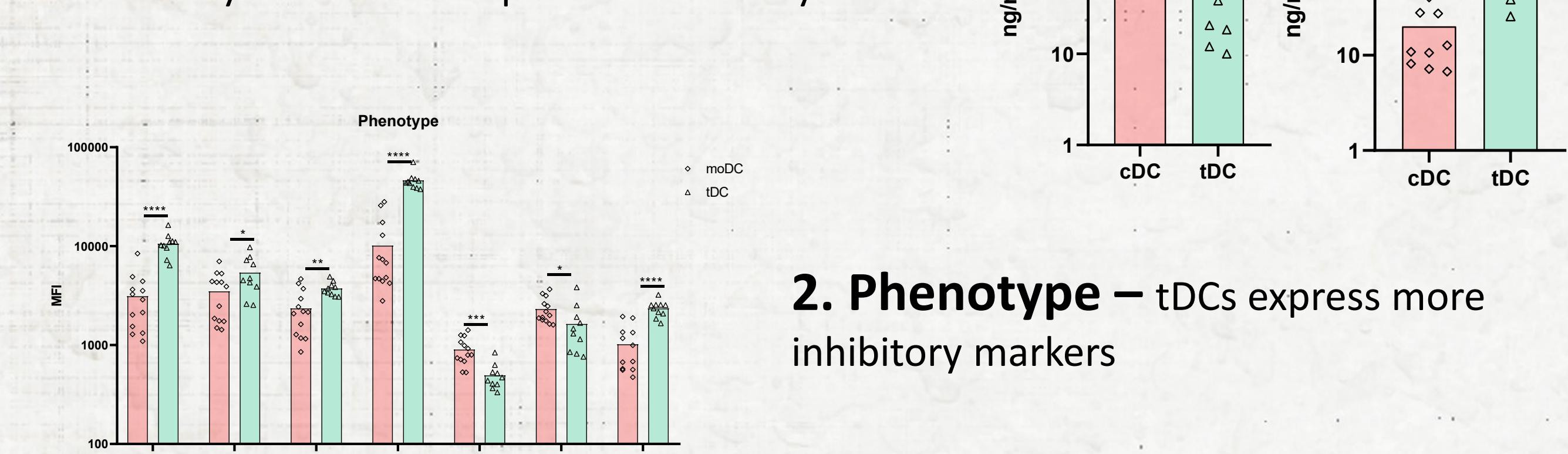
- monocyte-derived DCs (moDCs) and tolerogenic DCs (tDCs) were generated from freshly isolated patients' and healthy donors' monocytes cultivated in the presence of IL-4 and GM-CSF (moDCs), and tolerogenic factors vitamin D2 and dexamethasone (tDCs). Functional and signalling studies, co-culture experiments and RNA sequencing were performed.



Results

Generation and validation of tolerogenic dendritic cells model (tDCs)

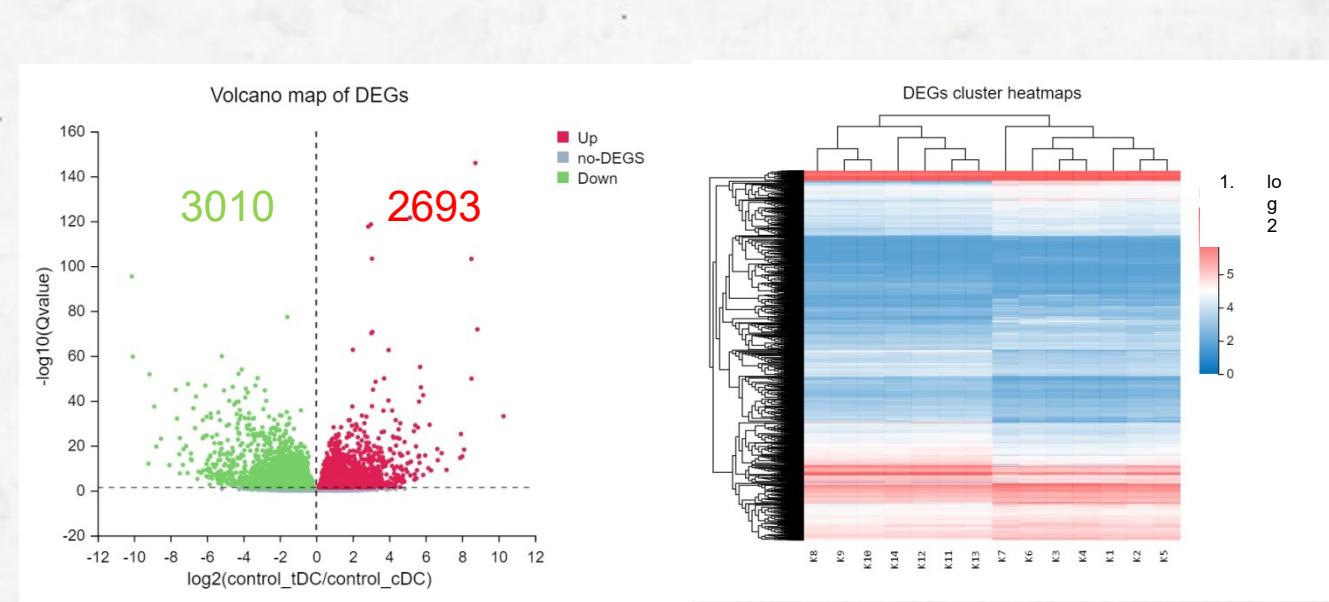
1. Cytokine production – tDCs produce more anti-inflammatory IL-10 and less pro-inflammatory TNF α



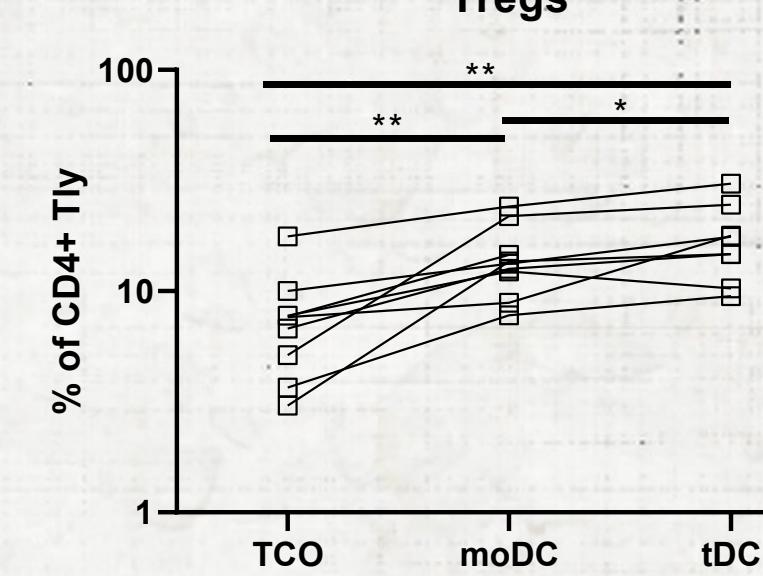
2. Phenotype – tDCs express more inhibitory markers

3. Treg induction – tDCs are capable to induce Tregs

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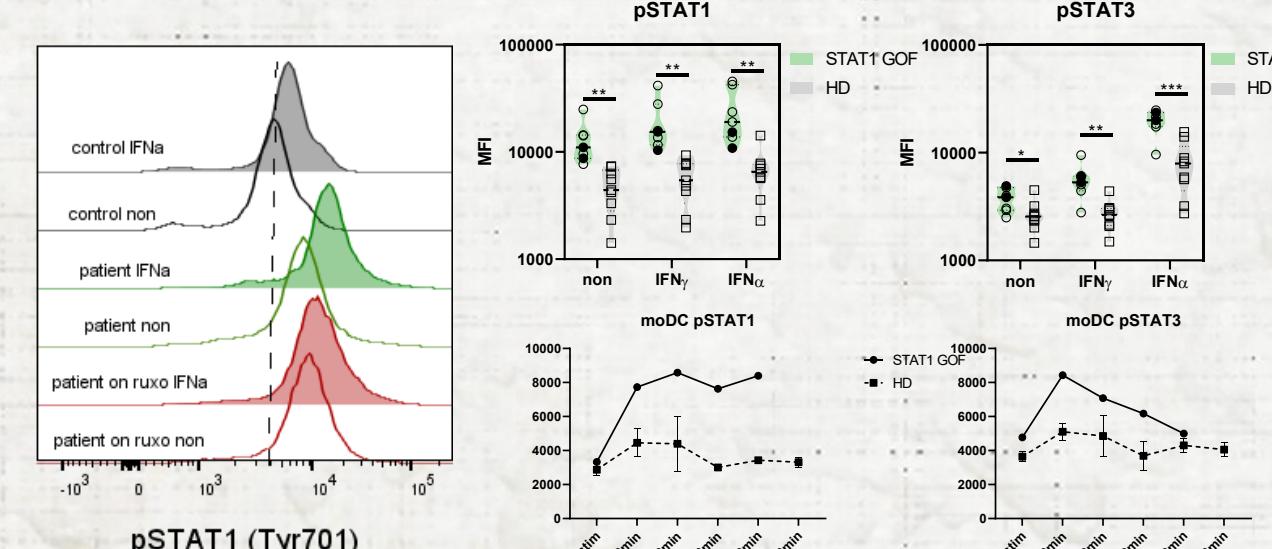


4. Transcriptomic analysis - more than 5500 differentially expressed genes (DEGs) distinguish tDCs from moDCs

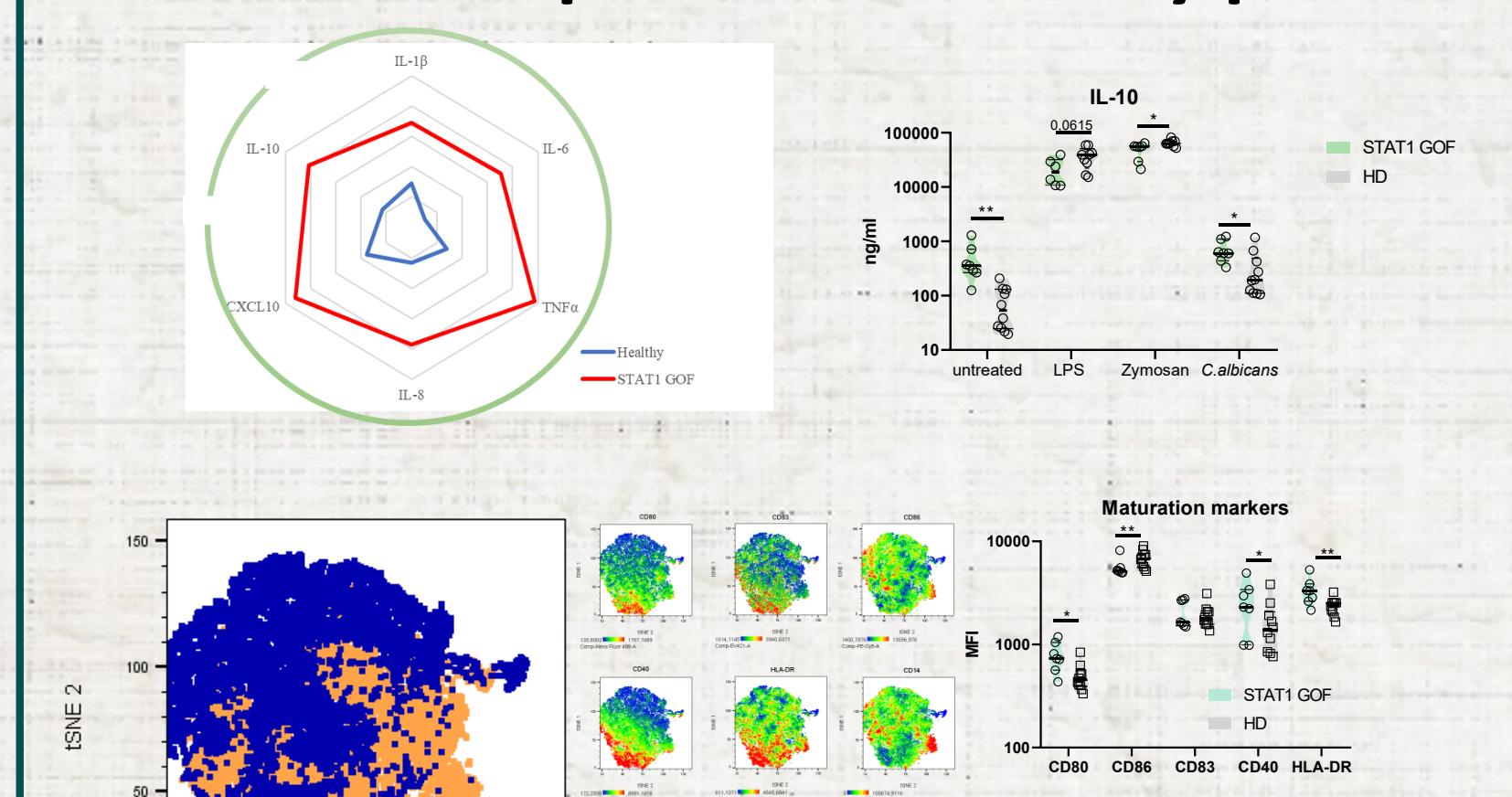


STAT1 GOF tDCs characteristics

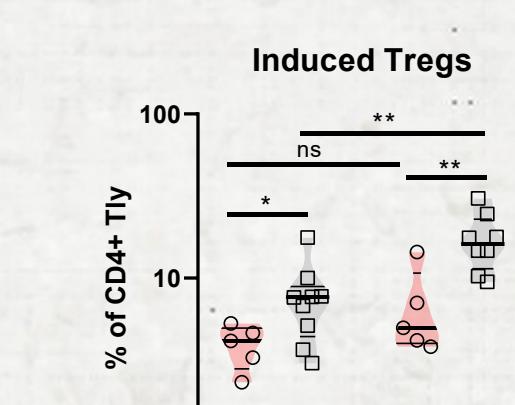
Increased STAT1 phosphorylation



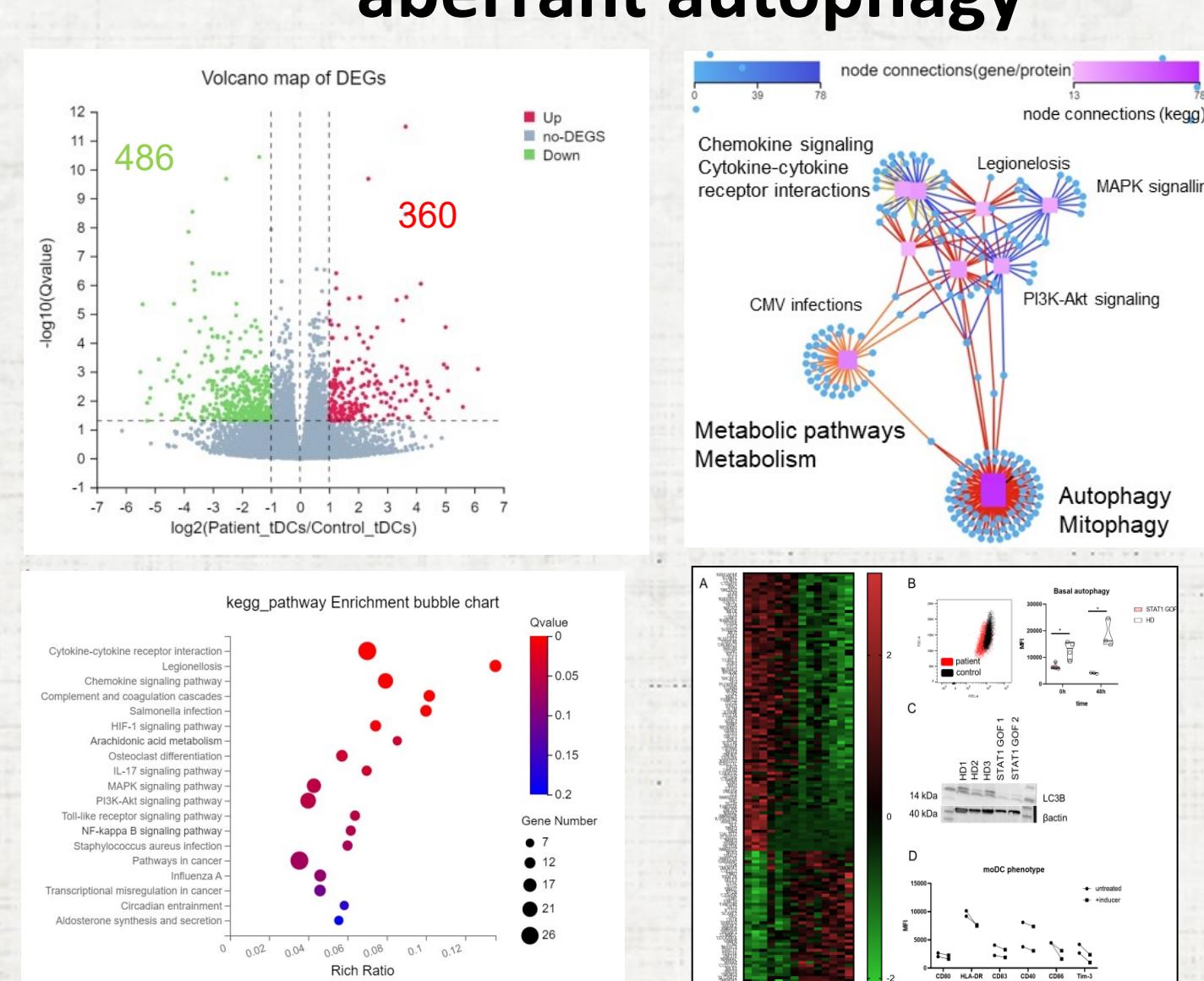
Profound pro-inflammatory profile



Inability to induce Tregs



Altered transcriptomics profile and aberrant autophagy



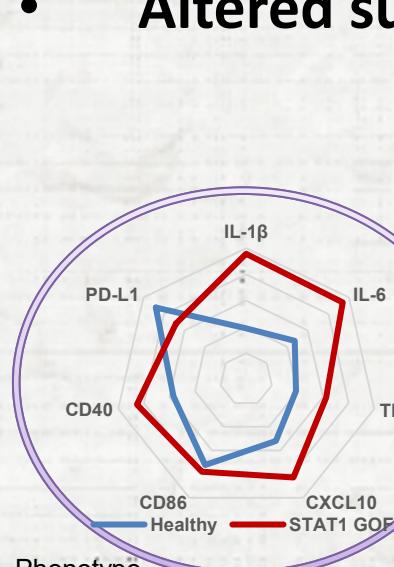
... not trusting the models?

STAT1 GOF patient monocytes and DCs

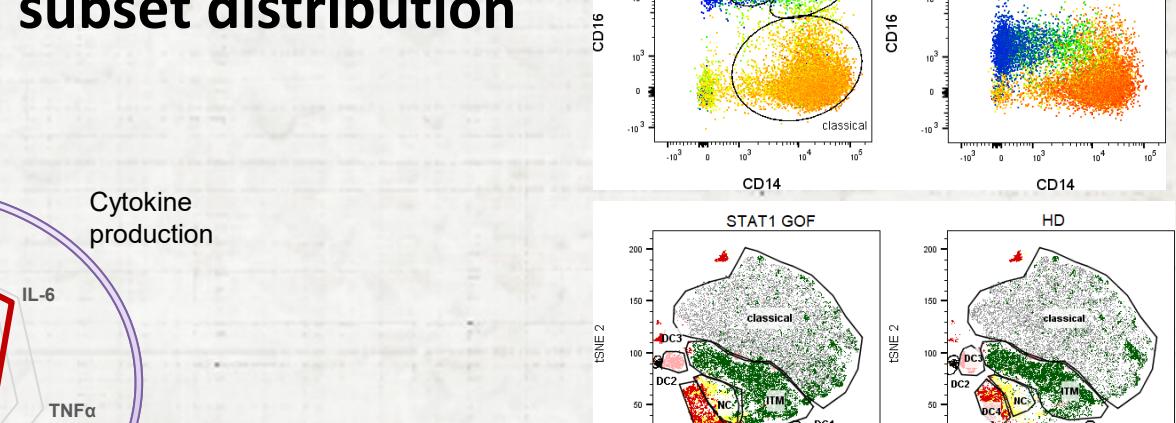
Increased STAT1 phosphorylation



Altered subset distribution

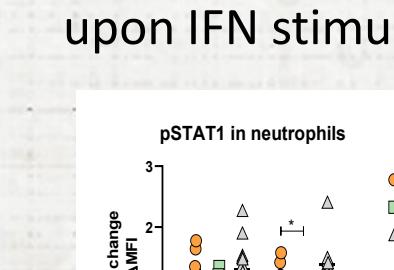


Pro-inflammatory character



STAT1 GOF neutrophils – expect the unexpected?

NO STAT1 hyper phosphorylation upon IFN stimulation



Signs of interferonopathy?

Enhanced activities towards *C. albicans*?

