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

Zuzana Parackova, Irena Zentsova, Petra Vrabcova, Anna Sediva, Marketa Bloomfield
Dpt. of Immunology, Faculty Hospital in Motol, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic

**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 mucosas via Th1-mediated immune failure
  - also underlies a variety of autoimmune features with 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

**Patient cohort:**

- 3 males, 7 females; CMC of various severity, three had clinically manifest autoimmunity and six had autoantibodies against organ-nonspecific antigens
- increased IFNs- and/or IFNγ-induced STAT1 signaling 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**

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

2. **Phenotype** – tDCs express more inhibitory markers

3. **Treg induction** – tDCs are capable to induce Tregs

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

**STAT1 GOF tDCs characteristics**

- Increased STAT1 phosphorylation
- Inability to induce Tregs
- Profound pro-inflammatory profile
- Altered transcriptomics profile and aberrant autophagy

**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?
- But also?
  - degranulated
  - activated

**SUMMARY**

This work identifies tDCs as important drivers of the STAT1 GOF-associated autoimmune manifestations. STAT1 GOF tDCs are characterized by loss of their tolerogenic properties, evidenced by profoundly altered phenotype and functions.