T helper cell phenotypic differences between Disseminated Coccidioidomycosis and Uncomplicated Valley Fever

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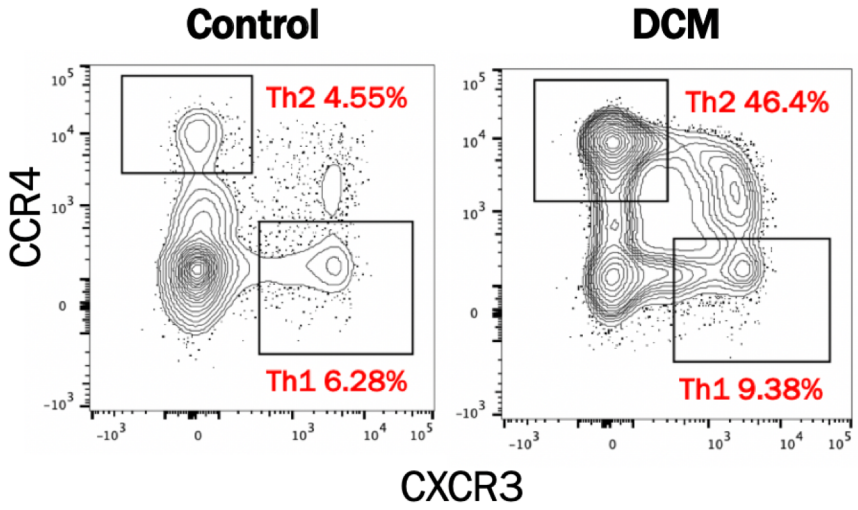
Introduction

- Infections with coccidioides fungi are endemic to the Southwestern United States with 1-2% progressing to severe, disseminated coccidioidomycosis (DCM), defined as spread beyond the lungs, often including the central nervous system, skin and/or musculoskeletal systems.
- Robust type 1 immunity, mediated by interferon-gamma (IFN-ɣ), plays a critical role in resolution of disseminated disease.
- It has been previously reported that an imbalance in type 1 versus type 2 immunity may confer susceptibility to severe DCM.
- Here, we sought to identify how generalizable these findings are by analyzing the T-helper cell phenotypes of patients with DCM compared to those with uncomplicated Valley Fever (UVF) and healthy controls.

Methods

- Blood samples from 38 donors at Valley Fever Institute (7 UVF, 31 DCM) and 11 healthy controls at UCLA were collected with informed consent according to IRB-approved protocols.
- T cells were analyzed by flow cytometry via staining for Th1 (CCR6-CCR4-CXCR3+), Th2 (CCR6-CCR4+CXCR3-) and Th17 (CCR6+CCR4+CXCR3-) markers (Figure 1) and for their production of intracellular cytokines upon stimulation.

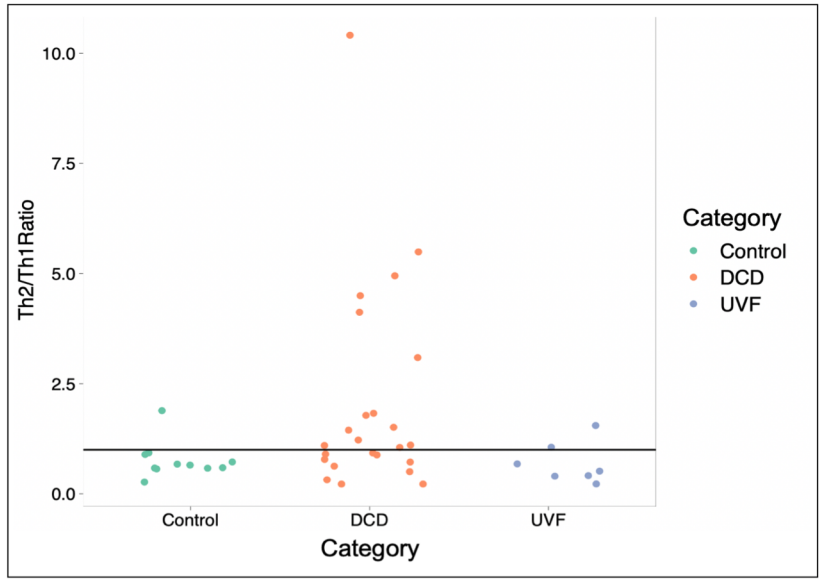
Figure 1. Flow cytometry plots demonstrate significant Th2 skewing in a patient with DCM as compared to control.



Results

- We identified a subset of patients with abnormal T helper cell phenotypes. We found that 30-40% of subjects with DCM demonstrated an excess in Th2 cells as compared to those with history of UVF (Figure 2).

Figure 2. A subset of patients with DCM demonstrate abnormal T-helper cell phenotypes with Th2/Th1 imbalance.



Conclusion

- These findings show that T helper cell dysfunction compromises immunity in a large subset of subjects with DCM.
- Excessive Th2 activity, or deficient Th1 activity, are potentially therapeutically actionable as has been previously published.
- The underlying causes for these skewed T cell responses is not yet clear and is the subject of ongoing genomic and transcriptomic analyses.