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CASE STUDY

AUTOIMMUNITY

High-throughput T cell receptor sequencing identifies clonally expanded CD8+ T cell populations in alopecia areata

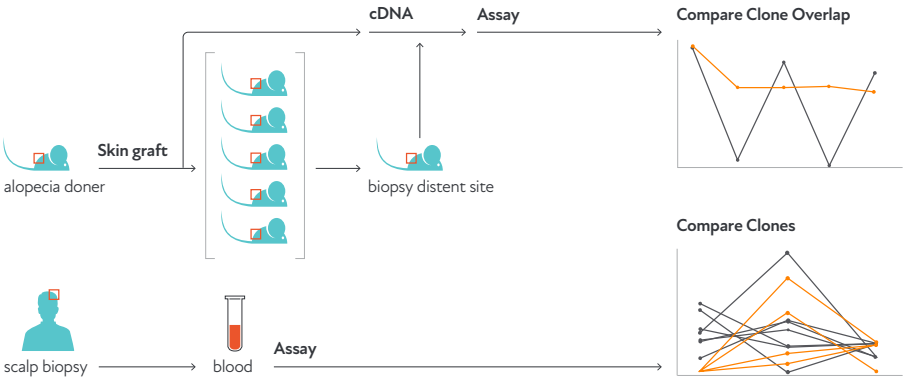
de Jong A., *et al.* (2018) *JCI Insight* 3(19): e121949

Background

Alopecia areata (AA) is an autoimmune disease characterized by non-scarring hair loss. Adoptive transfer of T cells from affected individuals can induce disease in mice, indicating T cells are the main pathogenic driver. However, the underlying causes of disease remain poorly understood. T-cell receptor (TCR) sequencing was used to analyze TCR diversity and dynamics of effector T-cell populations and to monitor pathogenic T cells during AA onset and during treatment.

Aims

- Determine whether AA is driven by specific auto-antigen recognition.
- Monitor pathogenic T-cell populations during disease onset and treatment with Tofacitinib to better understand disease progression and response to therapy.



Methods

1. Skin grafts were collected from adult mice with spontaneous AA and grafted onto 7-10 week old C3H/HeJ female recipient mice to induce AA
2. Lesional punch biopsies and peripheral blood samples were collected from human AA patients being treated with tofacitinib, a pan-JAK inhibitor
3. Snap frozen mouse skin tissue and human scalp biopsies → RNA extraction → cDNA → **immunoSEQ mmTCRß Assay**

WHY IMMUNOSEQ?

- The immunoSEQ Assay can be used to track T-cell clones and repertoire changes across different tissues and over time
- Flexible sample requirements allow for the use of cDNA
- Mouse and human TCRß assays support translational research

CASE STUDY: High-throughput T cell receptor sequencing identifies clonally expanded CD8⁺ T cell populations in alopecia areata —*de Jong A., et al. (2018) JCI Insight 3(19): e121949.*

Results

- Novel T-cell clonal expansion occurs in graft recipient mice coinciding with hair loss and displaying convergent clone selection (Figure 1).
- Human AA patients had significantly higher T-cell clonality in lesional scalp samples than scalp samples from healthy controls (data not shown).
- In a clinical trial for treatment of AA with Tofacitinib, 7 of 8 patients displayed decreased clinical severity of disease at 24 weeks and decreased abundances of the majority of expanded clones in the lesional scalp (Figure 2).

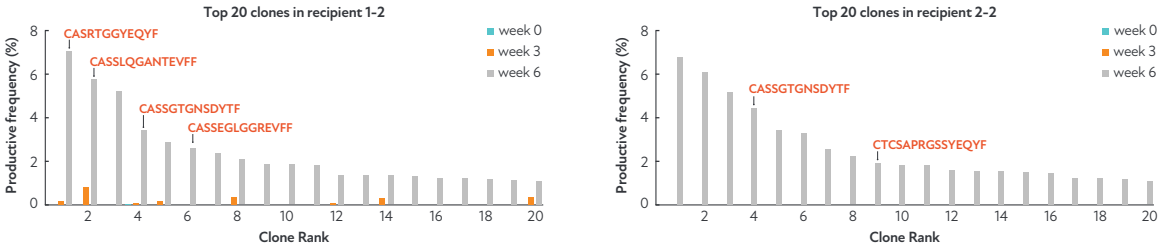


Figure 1. The 20 most abundant clones in the lesional skin of two C3H/HeJ graft recipient mice at 6 weeks post-transplant are plotted, and their respective abundance in the skin at baseline and at 3 weeks post-transplant. Among ten recipients, 6 commonly shared CDR3 sequences were detected. Five of those sequences are shown in red on the plots.

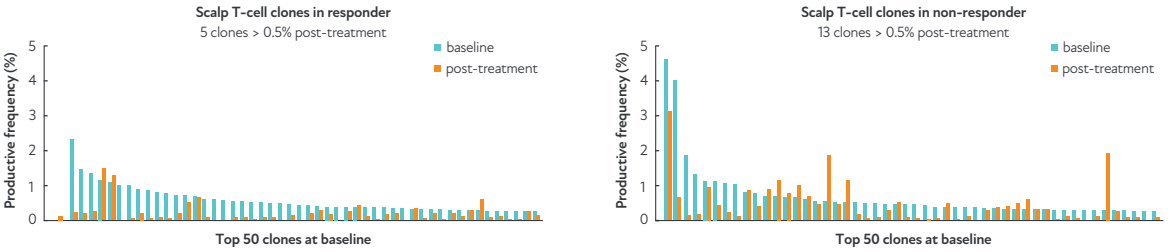


Figure 2. The 50 most abundant clones detected at baseline in patients receiving tofacitinib, and the abundances of those clones after 24 weeks of therapy. The left plot is representative of clonal dynamics observed in the 7 treatment responders.

Conclusions

- Commonly shared T-cell clones in the lesional skin repertoires of graft-recipient mice strongly supports the hypothesis that AA (Alopecia Aerata) is driven by antigen-specific responses.
- Although shared clones were not detected in human AA patients, the increased clonality of lesional repertoires is indicative of specific antigen-driven disease.
- Lesional scalp T-cell clones do not entirely disappear during tofacitinib treatment. The disease recurs when treatment is stopped, possibly due to incomplete reduction in pathogenic clones.

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