Circulating T follicular helper cells as emerging biomarkers in pediatric Evans syndrome

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Evans syndrome (ES) remains one of the most challenging diagnoses in pediatric hematology. It is a rare pediatric autoimmune condition with a widely variable clinical course in terms of severity, symptoms, duration of disease, and response to therapies. Pediatric ES also carries significant morbidity due to bleeding and infection. Despite its seemingly simple definition, two contemporaneous or serial immune cytopenias, pediatric ES is challenging to diagnose. There is no straightforward clinical test for pediatric ES, and distinguishing two immune cytopenias is impeded by significant limitations in serological testing for both autoimmune thrombocytopenia and neutropenia.[1,2] Given its diagnostic ambiguity there is a need for reliable biomarkers in pediatric ES to aid in diagnosis and guide clinical management. In this issue of *Haematologica*, Harris *et al*.[3] characterize circulating CD4$^+$ T follicular helper (cTfh) cells in a large cohort of children with autoimmune cytopenias, shedding new light on disease biology and presenting a new diagnostic biomarker for pediatric ES.

cTfh cells are the blood counterpart of Tfh cells in the lymphoid tissues. Both cTfh and Tfh cells share expression of CXC-chemokine receptor 5 (CXCR5), ICOS (inducible T-cell costimulatory), and programmed cell death protein 1 (PD-1).[4] cTfh cells support B-cell activation, facilitate the formation of the germinal center, and drive high affinity antibody production.[4] Beyond promoting normal protective antibody development, cTfh cells may also contribute to pathological antibody formation. Consistent with this, expansion of cTfh populations has been described in multiple autoimmune conditions including systemic lupus erythematosus, Sjögren syndrome, multiple sclerosis and rheumatoid arthritis, among others.[5,6]

Smaller studies in pediatric ES have previously demonstrated that cTfh cells are increased over those in chronic immune thrombocytopenia (ITP).[7,8] Harris *et al*. corroborate these findings in a large cohort of 153 children with autoimmune cytopenias including 42 with ES, 85 with ITP and 26 with warm autoimmune hemolytic anemia (AIHA). Harris *et al*. pose that cTfh quantification has clinical utility and can be used to diagnose pediatric ES. They report median cTfh percentages of 13% in those with ES as compared to 4.82%, 6.11% and 5.16% in ITP, warm AIHA and controls, respectively. Furthermore, cTfh percentages >9.5% can be used to distinguish pediatric ES from ITP or warm IHA with excellent sensitivity (76%) and specificity (86%). Bolstering the clinical relevance of cTfh quantity, cell percentages declined with both treatment and reduced disease activity in pediatric ES. Comparatively, for individuals with isolated ITP or warm AIHA, serial cTfh percentages remained stable within the normal ranges seen in healthy individuals.

Increasingly, hematologists have recognized that pediatric ES can arise from an ever growing list of monogenic inborn errors of immunity, some of which have targeted therapies and require specific screening for comorbidities.[9,10] It is even estimated that up to 65% of cases of pediatric ES are genetically determined.[9] Though rarely performed in adult ES patients, genetic testing is even being incorporated into the upfront diagnostic evaluation of pediatric ES.[11] However, the value of genetic testing is less clear when it comes to single lineage cytopenias. Harris *et al*. extend the relevance of cTfh percentages beyond distinguishing pediatric ES itself and demonstrate that cTfh percentages correlate to disease phenotype with higher quantities being linked to co-existing immune disorders and extra-hematologic autoimmune manifestations. Increased cTfh percentages were observed in both ITP and ES patients with associated immune disorders and in ITP patients with co-existing autoimmune features. These findings suggest that cTfh quantification could pinpoint which patients, including those with single lineage cytopenias, would benefit from genetic testing and more comprehensive evaluation for immune disorders.

Beyond quantification alone, the authors demonstrated that the transcriptional signature of cTfh cells differed

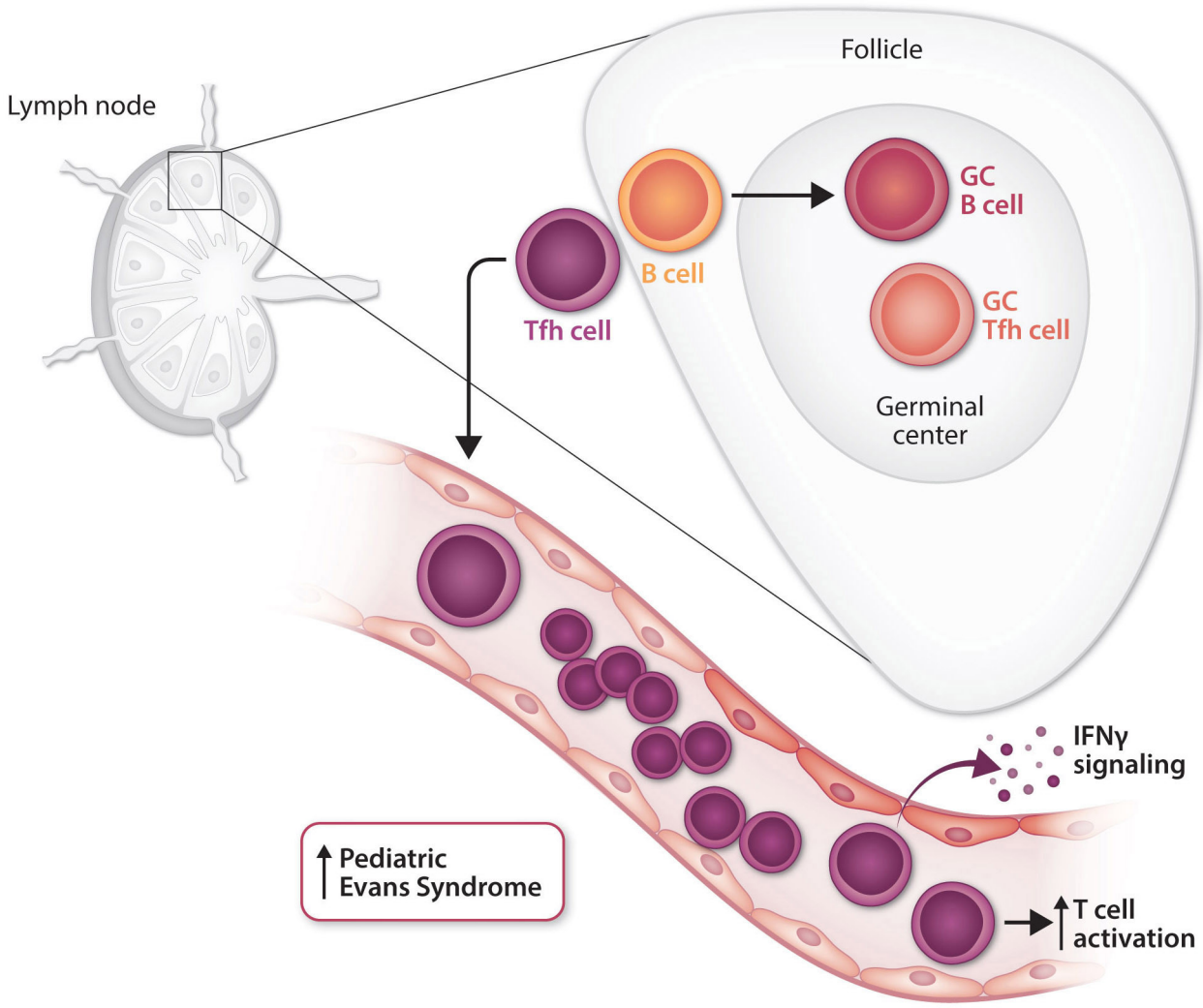


Figure 1. Schematic model to understand elevated circulating CD4⁺ T follicular helper cells in pediatric Evans syndrome. Circulating CD4⁺ T follicular helper cells (cTfh) are the blood counterpart of Tfh cells in the lymphoid tissues. Both cTfh and Tfh cells share expression of CXC-chemokine receptor 5, inducible T-cell costimulatory, and programmed cell death protein 1. While not typically quantified in standard clinical panels, cTfh cells would be identified as CD4⁺CXCR5⁺ cells by flow cytometric testing. These cells support B-cell activation, facilitate the formation of lymph node germinal centers, and drive high affinity antibody production. Beyond promoting normal protective antibody development, cTfh also contribute to pathological antibody formation. Harris *et al.* pose that cTfh cells may be released into the circulation from lymph nodes causing their increased numbers and elevated plasma interferon-gamma signatures leading to autoreactive T-cell activation. They propose that peripheral blood quantification of cTfh cells has clinical utility and can be used to diagnose pediatric Evans syndrome. GC: germinal center; IFN-γ: interferon-gamma.

markedly between those with active ES, ITP, and warm AIHA. Single-cell RNA-sequencing of cTfh cells revealed that patients with active, untreated pediatric ES exhibited increased T-cell activation and a prominent type II interferon (IFN-γ) signature (Figure 1). Consistent with this, plasma cytokine profiling revealed increased CXCL9, a cytokine downstream of IFN-γ signaling, in pediatric ES patients compared with controls. In pediatric ES, these type II interferon and T-cell activation signals diminish with treatment. In contrast, patients with warm AIHA, regardless of disease activity, despite not having increased cTfh percentages, displayed increased type I interferon (IFN-α/β) signatures and on hierarchical clustering grouped more closely to those with active ES. In contrast, ITP patients lacked strong interferon-driven activation signatures and exhibited reduced evidence of T-cell activation. Collectively, the observations of Harris *et al*. not only point to cTfh transcriptional profiles as a tool for distinguishing ES, warm AIHA and ITP, but importantly highlight type I and II interferon pathways as promising therapeutic targets in ES and warm AIHA.

While continued validation work on cTfh percentages and immune signatures in pediatric immune cytopenias is needed, the paper by Harris *et al*. offers a compelling step towards bringing diagnostic clarity to a disorder long marked by unknowns and advances our understanding of the pathogenesis of pediatric ES.

Disclosures

TOK receives honoraria from Sobi. JWS has no conflicts of interest to disclose.

Contributions

TOK wrote the first draft of this Editorial and drew the figure. JWS edited the draft and modified the figure.

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