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Recurrent Tonsillitis Tfh Cells Acquire a Killer Identity

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Abstract

Group A *Streptococcus* (GAS) infection causes recurrent tonsillitis (RT) in some individuals. A recent study (Dan *et al. Sci. Transl. Med.* 2019;11:eaau3776) demonstrates that RT is associated with an impaired antibody response against a key streptococcal virulence factor. This factor, SpeA, can induce abnormal T follicular helper (Tfh) cells that are able to kill B cells.

Group A streptococcus (GAS) infection is a common infection that causes ‘strep throat’. Patients present with throat swelling and pain, as well as swelling of the tonsils and cervical lymph nodes. GAS is commonly treated with antibiotics to quickly resolve the infection and prevent GAS-associated rheumatic fever and/or other associated pathologies; however, some pediatric patients suffer from RT caused by multiple episodes of GAS re-infection [1]. Why some patients suffer from reinfection and RT whereas others do not is not well understood.

T follicular helper (Tfh) cells are a specialized subset of CD4⁺ T cells that provide help for the germinal center (GC) reaction. In the GC reaction during an immune response to infection or vaccination, Tfh cells are crucial for providing help to B cells to undergo affinity maturation of antibodies, and they also promote the differentiation of long-lived memory B cells and plasma cells [2]. Consequently, Tfh cells are essential for productive and long-lived protective antibody responses. Studies of T cells isolated from human tonsils following tonsillectomy were among the first to specifically describe and characterize Tfh cells as a unique subset of helper T cells that localize to GCs and have specific functions and homing properties [3, 4].

In a recently published study by Dan *et al.* [5], Crotty and colleagues investigated whether inadequate immunity could explain GAS-driven RT. Tonsils were analyzed following tonsillectomy from pediatric patients with GAS-associated RT as well as from tonsils of age-matched sleep apnea patients as controls (non-RT group). GC Tfh responses in tonsils from GAS RT patients were significantly reduced relative to controls, and this coincided with a significant decrease in serum antibodies against streptococcal pyrogenic exotoxin A (SpeA) – an important GAS virulence factor and superantigen (Figure 1) [5].

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Given that some patients have recurrent GAS infection and RT, the authors asked whether RT might be associated with specific human leukocyte antigen (HLA) alleles. HLA DQB1*06:02 has previously been associated with protection against rheumatic heart disease [6], a known complication of strep throat infections. Samples from cohorts of RT, non-RT, and healthy adults from the general population were HLA-typed. HLA DQB1*06:02 was significantly less frequent in the RT group compared with the general population, suggesting that it might be protective against RT. In addition, within the RT group, those with the lowest frequency of both GC Tfh and GC B cells had significantly higher frequencies of the HLA alleles DRB1*01:01 and DRB1*07:01 than either the general population or the non-RT group, suggesting that these alleles might constitute risk factors for recurrent GAS infections [5].

Comparison of SpeA-specific GC Tfh cells following restimulation with their specific antigen revealed intriguing differences between cells from GAS RT versus non-RT control tonsils. Specifically, the *GZMB* gene was highly expressed in antigen-restimulated GAS RT GC Tfh cells, as determined by RNA sequencing. Analysis of these GC Tfh cells revealed a small but clear subset of restimulated GC Tfh cells that express granzyme B and perforin proteins, a subset that is not found in non-RT tonsils (Figure 1) [5]. Granzyme B and perforin are molecules used by cytotoxic T cells and natural killer (NK) cells to kill infected or transformed cells [7]. Indeed, GC Tfh cells from RT tonsils exhibited SpeA-specific killing of target B cells [5]. Previous studies in mice have shown that unlike T helper type 1 cells that can express granzyme B, Tfh cells do not express granzyme B [8] and even maintain repressive DNA methylation epigenetic programming at the *Gzmb* locus [9]. These findings indicate that repression of cytolytic molecule expression and killer T cell functions might be crucially important for Tfh cells in promoting the survival and selection of GC B cells [9]; however, the biological importance of this concept has not been experimentally demonstrated. Crotty and colleagues now propose that this small subset of killer Tfh cells that is observed in RT might sabotage the selective environment within the GC by killing GC B cells [5], which are already highly susceptible to cell death [10]. Moreover, irrespective of whether the Tfh cells originated from RT or non-RT patients, stimulation of these cells with SpeA induced granzyme B expression, suggesting that SpeA itself might be a crucial factor that drives the aberrant killer functions of this Tfh cell subset [5]. This proposed mechanism of immune evasion by GAS through the SpeA superantigen is particularly interesting because it provides a way to disrupt protective antibody responses: SpeA can turn Tfh cells – that otherwise normally provide survival signals for GAS-specific B cells – into killers. The potential result is that high-affinity SpeA-specific GC B cells, instead of being selected for survival in the GC, will be targeted and destroyed by killer Tfh cells, resulting in the loss of GAS-specific antibodies that would otherwise protect against reinfection. Furthermore, these findings have thus identified SpeA as a compelling target for potential GAS vaccine designs [5].

Together, the findings by Dan *et al.* provide novel insights into understanding why some patients experience GAS-associated RT. Their study identifies RT as an immunosusceptibility disease, in which specific HLA class II alleles are associated with either protection against, or susceptibility to, recurrent GAS infection/RT. Furthermore, such susceptibility was linked to a proposed immune evasion mechanism wherein SpeA induces

abnormal Tfh cell-mediated cytotoxicity of B cells [5]. As a result, reduced GC B cells and impaired anti-SpeA antibody responses were noted in RT patients relative to controls; this would counter the scenario where normal GC B cell responses would be expected to generate protective antibodies against future GAS reinfection and RT (Figure 1) [5]. These findings lead to many important questions for future investigation, including – what are the mechanisms by which SpeA can interact with HLA class II molecules? How do variations in these interactions based on the nature of the HLA polymorphisms drive conventional GC Tfh (protective) versus aberrant cytolytic GC Tfh cell responses? Further mechanistic studies may provide additional insights into the immunology and pathogenesis of RT. Ideally, these insights might help to identify candidate targets for the development of therapeutics and/or vaccination strategies aiming to prevent the cycle of RT.

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Figure 1. SpeA Induces Killer Germinal Center (GC) T follicular helper (Tfh) Cells that Can Impair Antibody-Mediated Immunity in Recurrent Tonsillitis (RT).

Patients with RT exhibit reduced frequencies of tonsil GC Tfh cells and anti-SpeA IgG antibodies compared with those with non-RT that mount protective GC responses against Group A streptococcus (GAS) infection. GAS SpeA, (a superantigen and virulence factor) was shown to alter the functionality of GC Tfh cells, inducing a subset of these cells to express granzyme B and perforin, killing target B cells. The mechanisms by which granzyme B⁺ GC Tfh cells are induced are unclear, but may involve interactions of SpeA with different HLA class II molecules (polymorphisms). These rare granzyme B⁺ killer GC Tfh cells have been proposed to kill SpeA-reactive B cells, resulting in impaired anti-SpeA antibody responses, thus leading to heightened susceptibility to recurrent GAS infections and RT [5]. Abbreviation: B_{GC}, germinal center B cell.