Ectopic B-helper CD4+ T cells

Pathogenic CD4+ T cells regulating B-cell differentiation in autoimmunity: not exactly Tfh cells

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Immunology and Cell Biology advance online publication, 18 April 2017; doi:10.1038/icb.2017.20

T follicular helper (Tfh) cells are typically defined by the expression of CXCR5, PD-1 and BCL-6, and their ability to promote the differentiation of B cells into antibody (Ab)-producing plasma cells.1,2 In a recent article in Nature, Brenner and colleagues described a putative pathogenic population of B-helper CD4+ T cells in tissues from patients with rheumatoid arthritis (RA).3 Curiously, while these cells expressed high levels of PD-1 and promoted B-cell differentiation, they lacked CXCR5 and BCL-6, suggesting they represent a novel subset of effector CD4+ T cells.

A fundamental function of B cells is to produce Abs that recognize and bind specific antigens on microbes, resulting in the neutralization and/or eradication of infectious pathogens.4 B cells usually require inputs from various cell types to ensure they produce the most appropriate class of Abs. The key cell type involved in this process is the Tfh cell, a subset of CD4+ T cells specialized to provide 'help' to B cells.1,2 Cardinal features of Tfh cells include expression of the B-cell zone homing chemokine receptor CXCR5, the transcriptional repressor BCL-6, the cytokine interleukin (IL)-21, the chemokine CXCL13 and a suite of surface molecules—CD40L, ICOS, SLAM receptors, PD-1—involved in T-cell/B-cell interactions.1,2 Critically, Tfh cells localize with B cells in follicles and germinal centers in secondary lymphoid tissues and promote the differentiation of activated B cells into memory cells and Ab-secreting plasma cells.1,2 It is this ability of B cells to generate memory and plasma cells that underlies long-lived serological memory following pathogen infection, and the success of most currently available vaccines that protect the host against infection for extended periods of time, and in some instances a lifetime.4

However, not all Abs produced by B cells are good—in fact, in the setting of autoimmunity, autoreactive B cells are pathogenic, producing Abs that result in severe tissue damage and ultimately organ failure.5 Akin to responses against non-self antigens, the production of autoAbs by B cells can be driven by Tfh cells.6 Indeed, many studies have reported increased proportions of circulating Tfh-like cells (usually defined as CXCR5hiPD-1hi or CXCR5hiICOShi CD4+ T cells) in the peripheral blood of patients with a broad range of autoimmune diseases often associated with production of autoAbs, such as systemic lupus erythematosus (SLE), Sjogren’s syndrome, RA and diabetes.2,5-8 Remarkably, the proportions of circulating Tfh-like cells in these immunopathologies often correlates with levels of autoAbs or other readouts of disease, and therapeutic interventions that alleviate disease severity also reduced Tfh-like cells.2,5-8 Collectively, these studies have defined Tfh cells—along with their partner B cells—as being drivers of autoimmunity in humans, and thus represent targets for potential therapies.

A limitation of many studies performed to date that have investigated the potential role of Tfh cells in human autoimmunity is that analysis has largely been performed on blood cells—when clearly the ‘action’ in these conditions occurs in affected tissues. Thus, a strength of the study by Rao et al.3 is their access to inflamed tissues and peripheral blood from individuals with RA, coupled with the multidimensional analysis of cells in these sites. Synovial fluid and synovial tissue from patients with seropositive, but not seronegative, RA were found to be enriched for a population of memory CD4+ T cells expressing high levels of PD-1, MHC class II and ICOS. Transcriptional assessment of these PD-1hi CD4+ T cells revealed them to contain higher levels of messenger RNA encoding IL-21, CXCL13, MAF, SAP, BATF, OX2 (CD200) and BTLA than PD-1-i CD4+ T cells present in the same sites.3 Importantly, the synovial PD-1hi CD4+ T cells from RA patient tissues were more efficacious at inducing B-cell differentiation, with respect to generating Ab-secreting plasmablasts in vitro, than PD-1− or PD-1intermediate CD4+ T cells present in the same sites. This process required interactions involving the surface receptor SLAMF6 (CD84) and IL-21,3 as reported previously for murine and human Tfh cells1,2 (Figure 1).

These phenotypic, molecular and functional features, as well as mechanisms of action, of synovial PD-1hi CD4+ T cells are signatures of Tfh cells detected in human lymphoid tissues.8,10 However, in contrast to classic Tfh cells, synovial PD-1hi CD4+ T cells from RA patients lacked expression of CXCR5 and BCL-6; they also expressed elevated levels of interferon gamma (IFNγ).5 Interestingly, BLIMP-1, which is regulated by a balance between BCL-6 and BLIMP-1 inasmuch that Tfh cells are BCL-6hi BLIMP-1lo (refs 1, 10) was also increased in synovial PD-1hi CD4+ T cells (Figure 1). Thus, despite sharing many features with Tfh cells, PD-1hi CD4+ T cells clearly do not belong to the Tfh compartment of effector CD4+ T cells—rather they represent a distinct subset of B-helper CD4+ T cells enriched at inflamed sites, the crucible for the production of pathogenic autoAbs.

The lack of CXCR5 on these effector cells perhaps is not surprising. The first detailed description of pathogenic B-helper CD4+
CXCR5—a shift in expression from homeostatic by B-helper CD4+ T cells in cases of autoimmunity. 12

Inflammation and tissue damage, it was found that lung infiltrating CXCR5 Bcl-6 CD4+ T cells could promote B-cell differentiation. 12 These cells were also enriched for IFNγ production.12 Thus, CXCR5 is not a prerequisite for functionality of B-helper CD4+ T cells. Rather, CXCR5 is required for localization of Thf cells to B-cell zones of conventional lymphoid tissues, while in the setting of autoimmunity, alternative guidance cues are utilized to recruit effector cells to sites of inflammation. Indeed, synovial PD-1hi CD4+ T cells expressed high levels of chemokine receptors including CCR2, CX3CR1 and CCR5 (Figure 1), which are typically associated with trafficking to inflammatory sites. Thus, there is a clear shift in expression from homeostatic—CXCR5—to inflammatory chemokine receptors by B-helper CD4+ T cells in cases of autoimmunity.

Some interesting questions regarding PD-1hi CD4+ T cells in the synovium of RA patients remain unanswered. The transcriptional network underpinning pathogenic PD-1hi CD4+ T cells in RA is enigmatic. The absence of BCL-6 implies roles for additional molecular regulators—it would be important to determine whether ASCL2, which is upstream of BCL-6 in murine Thf cells, is expressed by these cells. Alternatively, BCL-6 expression may be downregulated in PD-1hi CD4+ T cells as they migrate to ectopic non-immunological sites.1,2,5 Expression of BLIMP-1 is also striking; BLIMP-1 can restrain Thf formation via IL-2/STAT5 signaling.1 However, PD-1hi CD4+ T cells exhibit reduced production of IL-2.3 Thus, elucidating the mechanism inducing and maintaining BLIMP-1 expression in PD-1hi CD4+ T cells in RA will inform our understanding of the molecular circuitry of these pathogenic cells. Another interesting observation was that there are distinct CCR2 and CCR2+ subsets of synovial PD-1hi CD4+ T cells, and the CCR2+ subset could give rise to CCR2+ cells in vivo.3 But it is unclear whether these cells represent a precursor/progeny relationship in vivo and if one subset is more pathogenic than the other. These questions notwithstanding, the identification by Rao et al.3 of potent B-helper cells in the reactive sites in human autoimmunity is an important advance, and further analysis of these cells may identify approaches of targeting them to reduce their pathogenicity and improve outcomes for individuals affected by autoimmunity.

CONFLICT OF INTEREST
The author declares no conflict of interest.

1 Crotty ST. Follicular helper cell differentiation, function, and roles in disease. Immunity 2014; 41: 529–542.


