Follicular helper T cells: a new marker of type 1 diabetes risk?

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The incidence of type 1 diabetes is increasing at an alarming rate, particularly in young children, and a better understanding of the immune response that triggers this condition is urgently required. A consistent immune feature in many individuals is the appearance of autoantibodies against pancreatic islet antigens, and this can precede the onset of diabetes by many years. Monitoring the autoantibody response is of considerable predictive value, with seroconversion to multiple islet autoantibodies incurring a high risk of future T1D development (1), particularly if the autoantibodies are of high affinity (2). Islet autoantibodies are produced by B cells in a manner that generally requires the help of specialised CD4+ T cells. Exciting recent progress in immunology has generated a new molecular definition of the T cells that provide this help, now called follicular helper T cells (Tfh)(reviewed in (3)) (**Fig 1A**). Importantly, it has been established that Tfh can give rise to a memory population that circulates in peripheral blood and can be identified on the basis of particular surface markers including CXCR5 (the chemokine receptor that attracts T cells to B cell follicles), ICOS and PD-1 (4). This has changed the landscape for immune monitoring in diseases characterized by autoantibody production, and elevations in Tfh have been reported in a number of autoimmune conditions including systemic lupus erythematosus, rheumatoid arthritis and autoimmune thyroid disease (reviewed in (3)). It has recently been shown that T cells with a Tfh phenotype are overrepresented in the peripheral blood of individuals with established T1D (5, 6). In this issue of *Diabetes*, Viisanen and colleagues (7) test whether increases in Tfh cells can be detected early after T1D onset and crucially, even before the diagnosis of overt disease. The latter is a key question since there is currently a dearth of reliable T cell biomarkers in the at-risk setting.

Using a strict pairwise comparison with age-matched healthy controls, the authors found that CXCR5+PD-1+ICOS+ activated circulating Tfh cells were significantly elevated in children who had been diagnosed with T1D within the last 7 days [ref]. The observation was specific to the CXCR5+ T cell compartment, since the frequency of CXCR5-PD-1+ICOS+ cells did not differ between the two groups. Remarkably, analysis of autoantibody positive at-risk children revealed that elevations in activated Tfh could be detected even prior to onset of diabetes (**Fig 1B**). Of note, the presence of increased activated Tfh appeared to identify children at the late stages of preclinical T1D, exhibiting multiple autoantibody positivity and impaired glucose tolerance. So are elevations in Tfh numbers linked to progression to overt disease? As a first step to exploring this, the authors performed a limited longitudinal analysis on 11 autoantibody positive at-risk children, 6 of whom progressed to diabetes during the study period. In 4 out of the 6 progressors, the frequency of activated Tfh increased around the time of clinical manifestation of T1D. In contrast, the 5 non-progressors maintained relatively stable frequencies of Tfh over time. Whilst clearly the small group size precludes firm conclusions, these data provide a strong imperative for future exploration of circulating Tfh in individuals at risk of diabetes development.

Alterations in peripheral blood B cell subsets were not observed in the current study, in either the newly diagnosed or autoantibody-positive at-risk children [ref]. This is consistent with another recent report (8) and fits with the notion that germinal center B cells, the key recipients of Tfh help, are not found in peripheral blood. Interestingly, it has previously been shown that IL-21, the signature cytokine made by Tfh, is overproduced in people with T1D (reviewed in (9)). In addition to acting on B cells (10), IL-21 can impair immune regulation (11, 12) potentially promoting autoimmune

outcomes. Indeed, the authors observed a tendency towards a higher frequency of IL-21 producing cells within the CXCR5+ T cells in children with T1D, although this did not reach statistical significance.

The work by Viisanen and colleagues is timely given our emerging understanding of T cell/B cell interactions in the setting of T1D. Recent work has revealed that diabetes is associated with loss of anergy in insulin-binding B cells (13) and skewing B cell specificity towards islet antigens can promote diabetes in mouse models (14, 15). Although it is not believed that B cells or autoantibodies directly trigger beta-cell destruction, recent evidence suggests that a high relative frequency of B cells within inflamed islets is associated with more aggressive and earlier onset T1D (16). In light of the findings by Viisanen et al [ref] and others (5, 6), is tempting to speculate that Tfh cells might contribute to aggressive islet lesions since they produce CXCL13 (17), which is a B cell-attracting factor, as well as IL-21 which can promote expansion of CD8 T cells. Tfh and B cells exhibit a highly symbiotic relationship, with Tfh promoting B cell homeostasis and B cells in turn being required for the full differentiation and/or maintenance of Tfh (17). In this regard it is interesting that depletion of B cells in newly diagnosed T1D patients appears to reduce Tfh cell numbers (18) while partially preserving beta-cell function (19).

The present demonstration that elevations in activated Tfh can be detected prior to T1D onset represents an important advance since it excludes the possibility that the phenomenon is due to insulin therapy or emerges late as a secondary consequence of disease. Instead it supports the idea that Tfh may play a role in T1D pathogenesis. Stratifying T1D patients on the basis of immune parameters (20) may be useful in

selecting immunotherapies that are most likely to be beneficial. In this regard, targeting Tfh products (such as IL-21) and B cells may be particularly appropriate in individuals with multiple autoantibody positivity and elevated numbers of activated Tfh. If borne out by larger studies, Tfh analysis could conceivably feed into multi-parameter algorithms for predicting onset of disease in individuals at risk of T1D development (21).

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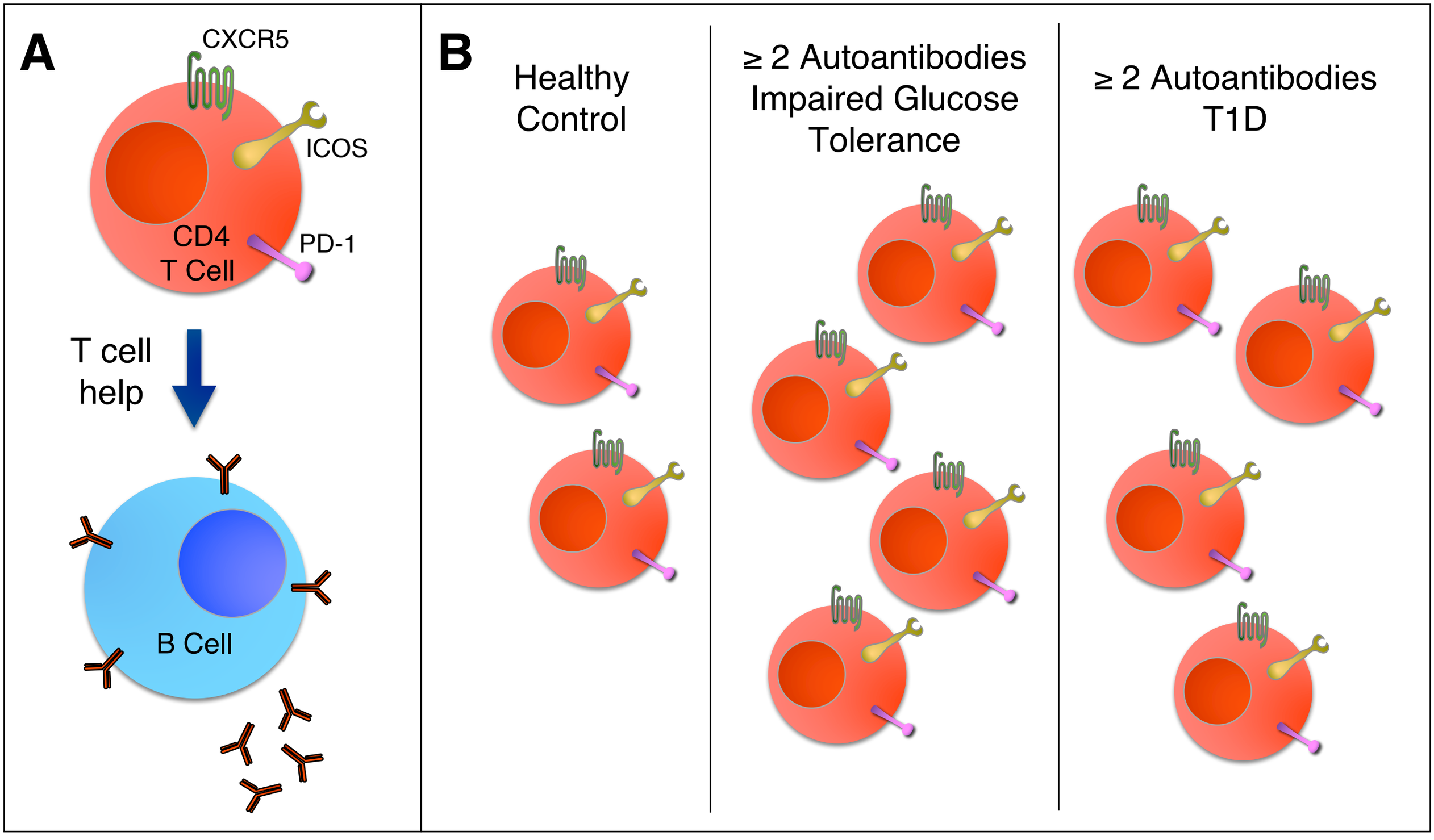
Figure Legend

Figure 1: CD4 T cells act as gatekeepers to the autoantibody response. In order to produce high affinity antibodies, B cells require help from CD4+ T cells with a CXCR5+PD-1+ICOS+ phenotype (follicular helper T cells, Tfh) (**A**). The proportion of activated circulating Tfh cells is increased in individuals at risk of developing T1D who have 2 or more autoantibodies and impaired glucose tolerance (central panel) as well as individuals with T1D (right panel) (**B**).

Figure 1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