Although autoantibodies (auto-Abs) against β-cell antigens helped in defining type 1 diabetes as an autoimmune disease and are invaluable biomarkers, their pathogenic role is unclear. Studies in nonobese diabetic (NOD) mice devoid of B cells (IgMnull or treated with anti-μ Abs) suggest that B cells are necessary for the disease to develop (1,2). The critical role of B cells in this process is thought to be linked to their antigen-presenting function through major histocompatibility class II molecules, as NOD mice harboring I-Ag7-deficient B cells are also protected from diabetes (3). The capacity of B cells to efficiently uptake β-cell antigens through surface Ig is critical to this function, as inhibiting this Ig-mediated uptake abolishes the β-cell antigen-presenting function of B cells in vitro (4), while transgenic manipulation of the Ig specificity in NOD mice impacts on diabetes incidence (5). Thus, autoreactive B cells may be exquisitely efficient in capturing and presenting self antigens, leading to autoimmune T-cell activation. In a therapeutic perspective, treatment with depleting anti-CD20 Abs delays and reduces diabetes onset in NOD mice and is even capable of reversing established disease (6). These findings have been successfully translated into human clinical trials (7).

In this scenario, the role of B cell–secreted auto-Abs has been controversial. On one hand, NOD embryos implanted into nonautoimmune foster mothers are diabetes-protected compared with embryos implanted into NOD females, suggesting that maternally transmitted factors (but not necessarily Abs) play a role (8). Moreover, passive transfer of Abs against islet-expressed ovalbumin enhances activation of ovalbumin-reactive CD8+ T cells and breaks tolerance (9). On the other hand, Ig infusion from sera of diabetic NOD mice does not restore diabetes susceptibility in IgMnull NOD recipients (10). Moreover, NOD transgenic mice in which B cells express membrane but not secreted IgM display an increased diabetes incidence compared with nontransgenic littermates that lacked B cells altogether, further suggesting that secreted Abs are not required to induce disease (11). Importantly, none of these reports examined the influence of auto-Abs on islet-reactive CD4+ T cells.

A new piece is now added to the puzzle by the study by Silva et al. (12). To address the effect of auto-Abs on islet-reactive CD4+ T cells, these authors used a T-cell receptor (TCR) transgenic mouse harboring high frequencies of CD4+ T cells recognizing the hen egg lysozyme (HEL) “autoantigen” transgenically expressed in β-cells (TCR+HEL+ mice). In a first set of experiments, a mutated Roquin transgene (Roquin	sub>on) was introduced in these mice, causing accumulation of follicular helper T cells and germinal center B cells (13), leading to increased secretion of anti-HEL IgG Abs. These mice rapidly and uniformly developed diabetes, accompanied by accumulation of HEL-specific CD4+ T cells. However, diabetes susceptibility was reduced not only in the absence of B cells (cd79ab transgene), but also in the absence of IgG (IgM>IgG transgene), and passive serum transfer from Roquin	sub>on mice was sufficient to confer diabetes susceptibility.

In a second set of experiments, TCR+HEL+ females crossed with nontransgenic males gave rise to diabetes-prone TCR+HEL+ offspring, whereas TCR+HEL+ litters were diabetes-protected when TCR+HEL+ males were crossed with nontransgenic females. The same observation was repeated by crossing TCR+HEL+ fathers with HEL-immunized nontransgenic mothers, in which case diabetes developed in the TCR+HEL+ but not in the TCR−HEL+ offspring, ruling out a direct cytotoxic effect of Abs on HEL-expressing β-cells. TCR+HEL+ neonates receiving anti-HEL IgG also developed diabetes, strongly suggesting that maternally transmitted anti-HEL Abs were at play.

Anti-HEL Abs acted by increasing survival of proliferating islet-reactive CD4+ T cells, and Fcy receptor (FcγR) blockade delayed and reduced diabetes incidence. Since CD4+ T cells do not express these receptors, the observed activation of T cells is probably achieved through FcγR-bearing antigen-presenting cells. The critical role of FcγRs has been previously proposed (9,14), making them attractive therapeutic targets. Importantly, Harbers et al. (9) further showed some involvement of the complement system in these Ab-mediated mechanisms. Silva et al. conclude that B cells can promote type 1 diabetes by secreting Abs that act in an FcγR-mediated manner to enhance the expansion of islet HEL-reactive CD4+ T cells, thus adding another facet to the multiple roles of B cells in β-cell autoimmunity (Fig. 1).

These data are difficult to reconcile with multiple observations. A case report of type 1 diabetes development in a patient suffering from X-linked agammaglobulinemia indicates that B cells are dispensable in disease pathogenesis (15). In line with this interpretation, another B cell–deficient NOD mouse line still developed diabetes in 29% of animals (16). It is possible that the role of auto-Abs in igniting autoreactive T cells may be a facilitating rather than an essential one, as suggested by in vitro human studies (17). However, human type 1 diabetes occurs in children of a type 1 diabetic father twice as frequently as...
in children of type 1 diabetic mothers (18). These difference may be linked to a protective role of auto-Ab transmission from type 1 diabetic mothers, as auto-Ab mothers confer a higher type 1 diabetes risk to their progeny compared with auto-Ab mothers (19). Thus, vertical auto-Ab transmission seems to be protective rather than harmful in humans.

As learned through many years of clinical trials (20,21), animal models may not suffice to deconvolute the complexity of human type 1 diabetes. Although critical to precisely dissect disease mechanisms as is elegantly done by Silva et al., reductionist transgenic models may further fall short of explanations when confronted by the outbred human species freely wandering in a specific pathogen-rich environment. Although the genetic heterogeneity of human type 1 diabetes casts a first level of complexity, the additional layers of epigenetic (e.g., genomic imprinting) and metagenetic (e.g., microbial colonization) factors are only starting to be dissected both in human and mouse. Comprehensive digging of these multiple layers may offer new solutions to this intriguing conundrum.

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