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Common variable immunodeficiency: two mutations are better than one

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B cells from common variable immunodeficiency (CVID) patients who have one mutant copy of the gene encoding the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) often display dysfunctional antibody production. Interestingly, some individuals with mutations in both TACI alleles do not present with CVID, suggesting that TACI mutations influence CVID pathogenesis via dominant interference or haploinsufficiency. In this issue of the JCI, Romberg and colleagues report how TACI mutations impact B cell activation, removal of autoreactive B cells, and the development of autoimmune disease in CVID.

CVID, TACI, and B cells

Common variable immune deficiency (CVID) is a primary immunodeficiency characterized by hypogammaglobulinemia and the inability to mount effective, specific antibody responses. The disease symptoms in CVID can be highly heterogeneous among patients because the perturbed antigen-dependent B cell response that typifies the disease may occur at different stages of the B cell differentiation process. As a consequence, CVID complications can range from bacterial infection to autoimmune or malignant disorders (1).

Approximately 7%–10% of CVID patients carry mutations in the gene encoding the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) (2), a member of the TNF receptor family that is predominantly expressed on peripheral B cells. TACI is upregulated following B cell stimulation and interacts with the B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), which are ligands expressed by numerous cell types including dendritic cells, macrophages, and neutrophils (3). The activation of TACI upon BAFF and APRIL binding leads to intracellular recruitment of TNF receptor-associated factors (TRAFs) and subsequent activation of NF- κ B and other transcription factors involved in immune responses, such as the nuclear factor of activated T cells (NFAT) (4). Additionally, antibody diversification can occur follow-

ing TACI-dependent activation of NF- κ B through the myeloid differentiation primary response 88-dependent (MyD88-dependent) TLR pathway (5). In this context, the interactions between TLRs and TACI have synergistic effects for antibody production in human B cells (6) — an aspect that could be relevant to the pathogenesis of CVID. Also, both TLR9- and TLR7-mediated responses are altered in most CVID patients, along with abnormalities in B cell receptor-mediated (BCR-mediated) responses (7), suggesting an involvement of those pathways in CVID pathogenesis.

In the physiopathology of the immune response, TACI plays a key role in regulating T cell-independent B cell antibody responses, isotype switching, and B cell homeostasis, and loss of TACI function is associated with a deficiency of B cell responses. To date, more than 20 TACI mutations have been identified in CVID patients (8).

Interestingly, CVID patients are typically heterozygous for TACI mutations, and the presence of two mutated alleles appears to protect against aberrant B cell production of antibodies and the development of autoimmunity (9). Furthermore, CVID-associated mutations are found in healthy subjects (about 1% of the general population), suggesting the possibility of linked susceptibility genes or an incomplete penetrance of TACI in CVID (9).

In response to the puzzling observations described above, it has generally been hypothesized that a mutated TACI allele exerts a dominant-negative effect on the normal allele and/or that the impairment of TACI function is due to haploinsufficiency (10, 11).

Are two mutations better than one?

In the current issue of the *JCI*, Romberg and colleagues present data suggesting that a single mutated TACI allele facilitates CVID through residual B cell responsiveness, whereas mutations in both TACI alleles repress B cell activation and thus prevent autoimmunity (12). This interpretation fulfills both the apparent paradox of a preferential association of CVID with heterozygous rather than homozygous TACI mutations and the relatively high frequency of TACI mutations in carriers without CVID manifestations.

The authors cloned and expressed *in vitro* recombinant antibodies from single new emigrant/transitional B cells from both CVID patients and control donors carrying one or two mutated TACI alleles. It was found that the frequency of polyclonal reactive clones was increased in new emigrant/transitional B cells from all individuals with TACI mutations (both healthy donors and CVID patients) compared with controls. This finding suggests that the presence of TACI mutations impairs the removal of autoreactive B cells during the establishment of central B cell tolerance. Since the phenomenon occurred in both CVID and healthy carriers with TACI mutations, the findings also indicate that mutations of TACI per se are not solely responsible for the CVID phenotype. The authors also found that the inefficient removal of autoreactive B cells that associated with TACI mutations could be partly ascribed to dose-dependent effects of mutated TACI on BCR, TLR7, and TLR9 signaling, regardless of CVID status. In other words, a mutated form of TACI cannot properly activate B cells and/or promote productive interactions with the mature forms of TLR7 and TLR9.

After evaluating the influence of TACI mutations on central B cell tolerance, the authors investigated the effects of TACI mutations on peripheral B cell tolerance. They cloned peripheral mature naive B cells from CVID patients and from controls carrying one or two TACI mutations

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and assessed the reactivity of the antibodies produced by these cells on HEP-2 cell lysates. The authors identified defects in peripheral B cell tolerance in all the CVID patients, which correlated with elevated BAFF plasma levels and reduced Treg cell frequency. These features were not associated with the presence of *TACI* mutations, yet could likely be relevant to CVID pathogenesis, since both elevated BAFF and reduced Treg cell function have been described to facilitate autoreactive B cell expansion and survival (13).

Overall, the set of studies on the peripheral B cell repertoire nicely complements the authors' analysis of defective central B cell tolerance due to the presence of *TACI* mutations. In this part of the study, the authors demonstrated that peripheral B cell tolerance, which was independent of *TACI*, effectively counteracts the central B cell defects in healthy individuals but not in CVID patients. Together, these data provide an explanation of why only CVID patients display a pathogenic phenotype in the presence of *TACI* mutations.

Finally, the authors found that the breach in immune tolerance observed in CVID patients with one mutated *TACI* allele was associated with an increased incidence of autoimmunity, as suggested by the presence of antinuclear antibodies (ANAs) and an increase in circulating T follicular helper (Tfh) cells. This increase in Tfh cells could likely be responsible for the stimulation of ANA-producing B cells in CVID patients with one *TACI* mutation. In contrast, CVID patients with two *TACI* mutations had no detectable ANAs or autoimmunity, and low numbers of Tfh cells. It remains unknown whether the abundance of Tfh cells observed in CVID relates to the reduced number/function of Treg cells observed in those patients, since some Treg cells can control the number of Tfh cells in the germinal centers (14, 15), or whether these two phenomena could concur independently in promoting autoimmunity in CVID patients. In any case, the above findings contribute to explain why CVID patients with a single mutated *TACI* allele are prone to develop autoimmune diseases, whereas CVID patients with two mutated copies of *TACI* are not (9). This discrepancy became even more puzzling after the finding that subjects with two mutated *TACI* alleles had increased frequency of autoreactive naive B cells compared with CVID patients with only a single *TACI* mutation. A plausible explanation provided by the current study

is that in the complete absence of functional *TACI* (i.e., when the mutations occur in both alleles), autoreactive B cells are unable to fully activate, whereas in the presence of partially preserved *TACI* function (one mutant allele), autoantibody production can occur and allow the development of autoimmunity (likely in concert with contributing factors such as an increase in Tfh cells and a reduction in Treg cells).

Future directions

This study provides convincing answers to several questions on CVID pathogenesis. *TACI* mutation-associated impairment in the central removal of developing autoreactive B cells is not influenced by the mutation itself or by CVID status. This negative impact of *TACI* mutations on central B cell tolerance could be explained by negative dominance and/or haploinsufficiency, with a CVID-promoting role for mutant forms of *TACI* due to alterations of B cell activation following BCR, TLR7, and TLR9 stimulation. The subsequent accumulation of autoreactive B cells in the periphery would then increase the risk of autoimmunity only when the mechanisms of peripheral B cell tolerance are inefficient. Whether any additional genetic or environmental factors would also be required for the development of CVID remains an open question. Notwithstanding these considerations, this study reasonably explains why many people carrying *TACI* mutations are healthy and do not develop CVID and why subjects with single *TACI* mutations have defects in B cell activation and impaired removal of autoreactive B cells that predispose them to autoimmunity.

Since CVID associates with an increased risk of autoimmunity, the results of this study are relevant to understanding the link between *TACI* mutations and the development of B cell autoimmunity. Autoreactive B cells may not fully express their autoimmune potential in the absence of at least one functional *TACI* molecule, due to the key role of this protein in B cell activation. In other words, subjects with mutations in both *TACI* alleles would have impaired *TACI*-mediated activation of autoreactive B cells that would protect them from autoimmunity. In contrast, a single *TACI* mutation in CVID patients would allow their autoreactive B cells to maintain responsiveness to self-antigen stimulation (also facilitated by increased numbers of Tfh cells, elevated BAFF, and reduced num-

bers of Treg cells). Though highly speculative, this aspect implicitly suggests that blockade of the residual *TACI* function in subjects with a single *TACI* mutation would provide clinical and prognostic benefits in CVID patients, although additional work is needed to further explore this possibility.

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