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SUPPLEMENTARY MATERIALS

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Materials and Methods

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AUTOIMMUNE DISEASE

Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy

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Mutations in the *LRBA* gene (encoding the lipopolysaccharide-responsive and beige-like anchor protein) cause a syndrome of autoimmunity, lymphoproliferation, and humoral immune deficiency. The biological role of *LRBA* in immunologic disease is unknown. We found that patients with *LRBA* deficiency manifested a dramatic and sustained improvement in response to abatacept, a CTLA4 (cytotoxic T lymphocyte antigen-4)–immunoglobulin fusion drug. Clinical responses and homology of *LRBA* to proteins controlling intracellular trafficking led us to hypothesize that it regulates CTLA4, a potent inhibitory immune receptor. We found that *LRBA* colocalized with CTLA4 in endosomal vesicles and that *LRBA* deficiency or knockdown increased CTLA4 turnover, which resulted in reduced levels of CTLA4 protein in FoxP3⁺ regulatory and activated conventional T cells. In *LRBA*-deficient cells, inhibition of lysosome degradation with chloroquine prevented CTLA4 loss. These findings elucidate a mechanism for CTLA4 trafficking and control of immune responses and suggest therapies for diseases involving the CTLA4 pathway.

Common variable immune deficiency (CVID) is a heterogeneous primary immunodeficiency characterized by antibody deficiency, infections, autoimmunity, and lymphoproliferation (1, 2). Lymphocytic interstitial lung disease (ILD) causes substantial morbidity and mortality in CVID, and there is no effective treatment (3–6). CVID can be caused by “lipopolysaccharide (LPS)–responsive vesicle trafficking, beach- and anchor-containing” (*LRBA*) gene defects (7). The *LRBA* protein has domains homologous to vesicle trafficking proteins, but its function and relation to disease pathogenesis are unknown (8, 9).

Cytotoxic T lymphocyte–associated protein 4 (CTLA4) is an inhibitory checkpoint protein, expressed on activated T cells and FoxP3⁺ regulatory T cells (T_{regs}) (10). CTLA4 inhibits immune responses by negative signaling, by competition with the costimulatory molecule CD28 for the ligands CD80 and CD86, or by removing these ligands from antigen-presenting cells by transendocytosis (11, 12). CTLA4 resides in endocytic vesicles that are released to the cell surface after

T cell receptor (TCR) stimulation (13). The clinical effectiveness and adverse effects of CTLA4 modulation are revealed by three approved drugs that mimic or target CTLA4: abatacept for rheumatoid arthritis, belatacept for prevention of rejection after renal transplantation, and ipilimumab for the immunotherapy of melanoma (14–16).

We identified nine patients with immune deficiency and/or autoimmunity from eight unrelated kindreds with biallelic loss-of-function mutations in *LRBA* that have not been previously reported (Fig. 1A). All mutations decreased or abolished *LRBA* protein expression as assessed by immunoblotting and flow cytometry (Fig. 1, B and C, and fig. S1).

The clinical features of these patients are described in detail in the supplementary text and table S1. Most patients were diagnosed in early childhood with CVID, and all patients experienced substantial inflammatory and/or autoimmune complications. Notably, *LRBA* deficiency was associated with interesting phenotypic characteristics in several patients, including type 1 diabetes mellitus (patients 1 and 2), Burkitt’s lym-

phoma (patient 6), and exocrine pancreatic insufficiency (patient 1). Patients 1 to 3 experienced severe ILD—consisting of dense, predominantly T cell interstitial infiltrates—which was refractory to multiple medications and led to progressive impairment of lung function (Fig. 1D). Note that, when patients were treated with abatacept [a CTLA4-immunoglobulin (CTLA4-Ig) fusion protein that inhibits T cell responses by competing for costimulatory ligands], their overall clinical status, computed tomography (CT) scans, and pulmonary function showed rapid and dramatic improvement (Fig. 2). Treatment also halted ongoing inflammatory and/or autoimmune conditions (Fig. 2A); decreased levels of soluble CD25 (sCD25, a biomarker of T cell–mediated inflammation) (17); increased naive:effector (CD45RA:RO) T cell ratios (fig. S2); and improved functional antibody responses to polysaccharide vaccine antigens in patient 2. In the three patients treated initially, the improvements in lung disease were maintained when abatacept was continued for 5 to 8 years. This treatment had minimal infectious or autoimmune complications. Patients 1 and 3 acquired norovirus infection (see supplementary text), which can cause chronic enteritis

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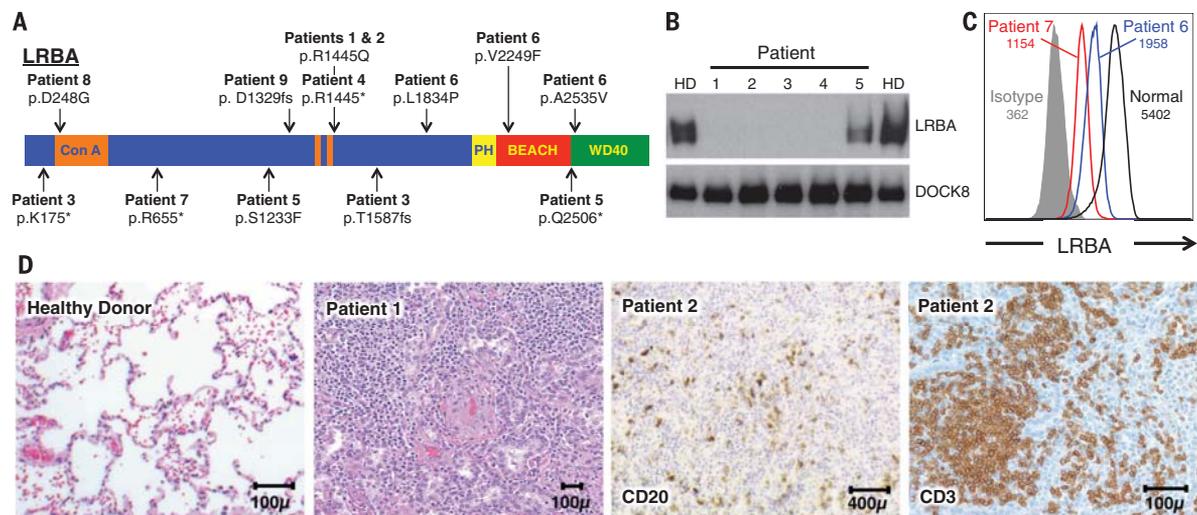


Fig. 1. LRBA deficiency and interstitial lung disease. (A) Shown are the novel biallelic *LRBA* mutations of nine patients from eight unrelated kindreds mapped onto a schematic representation of *LRBA* illustrating the protein domains. Amino acid changes are referred to by their single letter code. Asterisk (*) indicates a premature stop codon. Orange thin double bars indicate the A-kinase-anchoring protein (AKAP) motif. Con A, Con A-like lectin domain. Patients 3 and 5 are compound heterozygous for the two mutations indicated. Patient 6 is compound heterozygous for p.V2249F mutation from father and

p.A2535V and p.L1834P mutations from mother. Patient 8 is compound heterozygous for the mutation indicated and an intronic mutation c.8502-1G>C, which is predicted to affect mRNA splicing. (B) Immunoblotting for patients 1 to 5 and (C) flow cytometry for patients 6 and 7 show loss of *LRBA* compared with a healthy donor (HD). *DOCK8* is included as a loading control. Mean fluorescence intensity for *LRBA* is indicated in histogram. (D) Hematoxylin and eosin staining of healthy donor lung and lung from patient 1. Also shown are immunostains for CD20 (B cells) and CD3 (T cells) on lung from patient 2. Scale bars are indicated in microns.

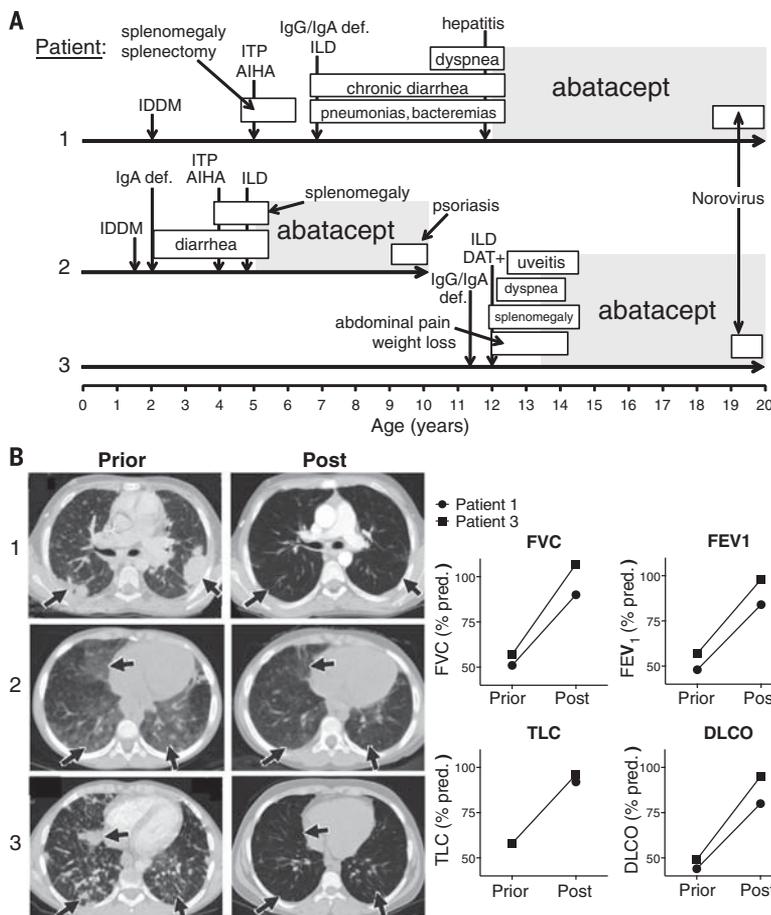


Fig. 2. Sustained response to abatacept in three *LRBA*-deficient patients. (A) Timeline showing multiple clinical features and therapy with abatacept in patients 1 to 3. Gray shading indicates time of therapy with abatacept with dosing initially 20 mg/kg of body weight intravenously (i.v.) every 2 weeks for patients 1 and 3, and 20 mg/kg i.v. every 4 weeks in patient 2. "Norovirus" indicates onset of intermittent abdominal symptoms associated with acquisition of chronic norovirus infection. (B) High-resolution CT scans (patients 1 to 3) and pulmonary function tests (patients 1 and 3) before and after abatacept. Arrows highlight examples of lung disease improvement before and after abatacept. FVC, forced vital capacity; FEV1, forced expiratory volume; TLC, total lung capacity; DLCO, diffusing capacity of the lungs for carbon monoxide.

in patients with CVID (18). Patient 1 also developed *Legionella pneumophila* pneumonia, and patient 2 developed psoriasis. Patients 4, 8, and 9 were started on abatacept within the last 6 months for the treatment of intractable enteritis and other features of autoimmunity and have begun to show improvement (see supplementary text).

Given the dramatic clinical improvement of *LRBA*-deficient patients with a CTLA4 immunomodulator, we hypothesized that LRBA might control the expression, function, or trafficking of CTLA4. In healthy donors, CTLA4 is mainly in intracellular vesicles of T_{regs} (19). CTLA4 can be mobilized to the cell surface by TCR stimulation (fig. S3A). We found that the abundance of total (intracellular) and mobilized (cell surface) CTLA4 was substantially depressed in T_{regs} from *LRBA*-deficient patients (Fig. 3A and fig S3, A to C). Note that *CTLA4* mRNA levels were normal in these patients, which suggested that *LRBA* posttranslationally regulates CTLA4 protein (fig. S3C). After stimulation with CD3-specific antibody and interleukin 2 (IL-2), conventional (FoxP3⁻) T cells express CTLA4, but this response was also deficient in patient cells (fig. S3D). Patients 5 and 6, who have residual LRBA protein (Fig. 1, B and C), had the highest residual CTLA4 levels in FoxP3⁺ T cells (Fig. 3A, triangles), which suggests an LRBA dose-dependent effect on CTLA4 expression. Even so, patient samples showed normal mobilization of other endosomal proteins, including CD154 and CD107 (20), which indicated that LRBA-deficient T cells were not globally defective in vesicle trafficking (fig. S4). We also found that CTLA4-dependent cellular functions were impaired in patient cells: CD4⁺ and CD8⁺ T cells were hyperproliferative in vitro; patient T_{regs} showed impaired trans-endocytosis of CD80 and had decreased suppressive function in a CTLA4-dependent assay (fig. S5). Consistent with these functional defects and the reported phenotypes of CTLA4-haploinsufficient patients and the original description of *LRBA*-deficient patient T_{regs} by Charbonnier and colleagues (21, 22), we found that patient T_{regs} expressed lower levels of CD25 and Foxp3 along with CTLA4 (fig. S6).

To verify that *LRBA* deficiency was sufficient to impair CTLA4 expression, we performed small interfering RNA (siRNA)-mediated knockdown of *LRBA* in normal donor T cells. This treatment lowered the abundance of CTLA4 protein to levels comparable to those in patient samples but had no effect on *CTLA4* mRNA (Fig. 3B and fig. S7B). Further, when protein synthesis was inhibited with cycloheximide (CHX), CTLA4 protein was rapidly lost in *LRBA* knockdown cells, which indicated accelerated degradation (Fig. 3C). Thus, decreased LRBA protein caused an apparent post-translational loss of CTLA4 protein in T cells. CTLA4 trafficking to the cell surface was apparently not impaired by LRBA deficiency, because the amount of CTLA4 that mobilized to the cell surface was proportional to the total intracellular levels of CTLA4 (Fig. 3, A and B). We also found that CTLA4 endocytosis was normal after *LRBA* knockdown using previously described

techniques. The majority of CTLA4 was internalized whether or not *LRBA* was knocked down (fig. S8).

These results, especially the rapid loss of CTLA4 after CHX treatment, led us to hypothesize that LRBA regulates the lysosomal degradation of

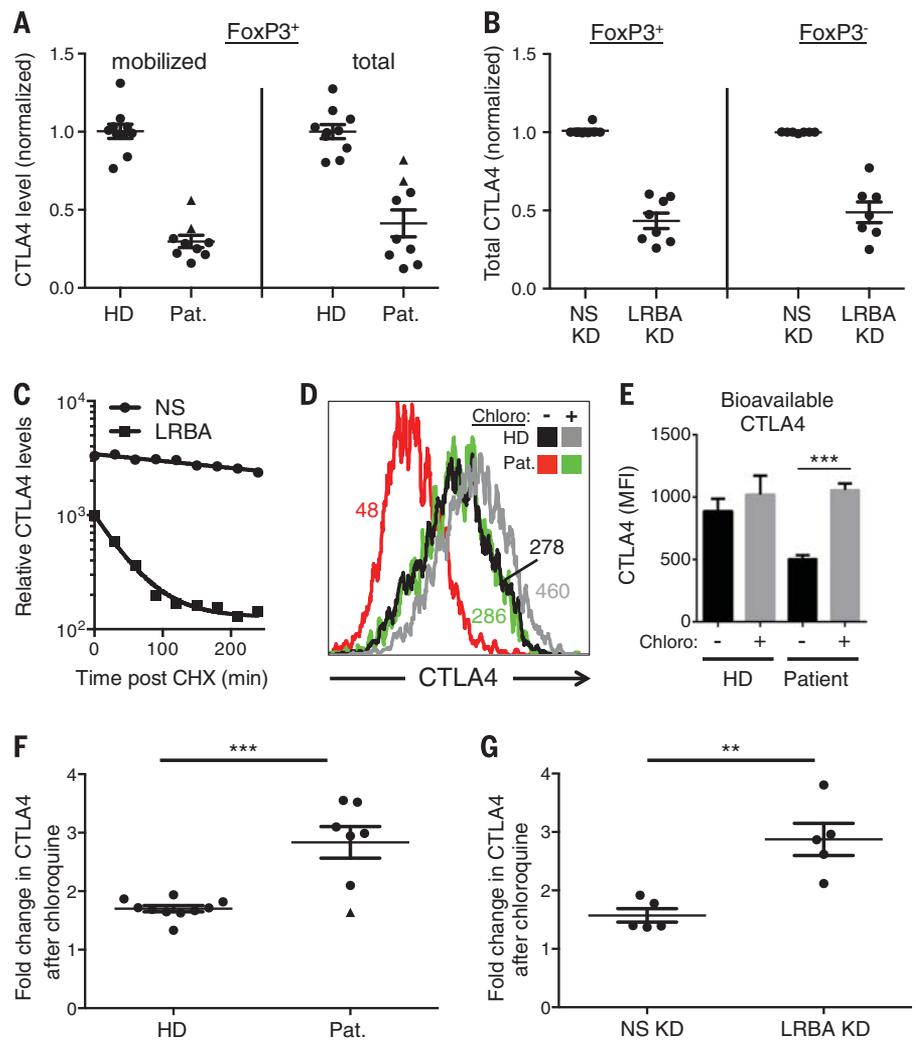


Fig. 3. LRBA regulates CTLA4 protein turnover. (A) The quantification of total and surface mobilized CTLA4 in FoxP3⁺ T cells from healthy donors (HD) and *LRBA*-deficient patients (Pat.). FoxP3⁺ cells were assessed fresh or after overnight culture in medium alone. Triangles represent the two patients (5 and 6) with residual LRBA protein expression. Data are normalized as described in Materials and Methods and represented as means \pm SEM. $P < 0.001$, for all displayed comparisons of healthy donors and patients (unpaired t test). (B) siRNA-mediated KD of *LRBA* in T cells from healthy donors suppressed CTLA4 levels in FoxP3⁺ and FoxP3⁻ T cells compared with nonspecific (NS) siRNA-transfected cells. $P < 0.001$, for comparisons of NS and *LRBA* knockdown (unpaired t test). (C) CTLA4 turnover kinetics were evaluated. NS or *LRBA* KD cells from normal donors were cultured for varying amounts of time with cycloheximide (CHX) to block protein synthesis, then total amounts of CTLA4 protein were assessed by flow cytometry. Relative CTLA4 levels were calculated as the geometric mean fluorescence of CTLA4 staining minus that of the isotype control. Data are representative of three or more independent experiments. (D and F) Healthy donor and patient-derived T cells were cultured overnight with or without chloroquine, and total CTLA4 levels were assessed by flow cytometry. Mean fluorescence intensities of CTLA4 staining are indicated on histogram. Fold change in CTLA4 levels after chloroquine exposure for the individual control and patient samples is shown. Means \pm SEM are shown. $***P < 0.001$ (unpaired t test). Triangular point represents patient 5 (with residual LRBA expression). (E) T cells from HD and patients were cultured with or without chloroquine and CTLA4 staining within CD4⁺Foxp3⁺ cells was assessed by mean fluorescence intensity (MFI). "Bioavailable CTLA4" refers to signal not associated with Golgi (58k), lysosomes (CD107a), or autophagosomes (LC3) and, hence, includes CTLA4 available for mobilization to the cell surface. $***P < 0.01$, as determined by t test (unpaired, two-tailed) (G) NS or *LRBA* KD cells from normal donors were cultured with or without chloroquine, and total CTLA4 was assessed by flow cytometry. $**P = 0.003$ (unpaired t test).

CTLA4. Indeed, when we examined the subcellular localization of CTLA4 using a flow microscopy technique (ImageStream), we found that more CTLA4 localized to CD107⁺ lysosomes in patient T cells than in T cells from healthy donors (fig. S9). Furthermore, when we treated T cells from patients and healthy donors with chloroquine to inhibit lysosomal degradation, we found that CTLA4 protein levels rose sharply in patient T cells but only modestly in healthy donor (HD) T cells (Fig. 3, D to F, and fig. S10). We also observed rescue of CTLA4 in *LRBA* knockdown cells with chloroquine and other agents that

inhibit lysosomal acidification, fusion, or protein degradation, including brefeldin A, monensin, NH₄Cl, and a cocktail of protease inhibitors (Fig. 3G and figs. S10 and S11).

Although the function of LRBA has been unclear, related BEACH domain-containing proteins regulate trafficking of intracellular vesicles (8, 23). Consistent with our hypothesis that LRBA controls CTLA4-containing vesicles, we observed that CTLA4 and LRBA colocalized within recycling endosomes and the trans-Golgi network in normal T cells indicated by their coincidence with the Rab11 and Syntaxin 6 (STX6) markers,

respectively (Fig. 4, A and B). It is interesting that the transferrin receptor (CD71), which traffics through recycling endosomes, was also reduced in *LRBA* knockdown cells, which suggests that LRBA may specifically regulate recycling endosomes (fig. S12 and S13). CD28 family members and molecules known to traffic through other vesicles, including CD28, ICOS, PD-1, and CD154 were unaffected in *LRBA* knockdown cells (fig. S12). Consistent with their cellular colocalization, we found that CTLA4 and LRBA coimmunoprecipitate (Fig. 4C) and that this interaction required the concanavalin A (Con A)-like lectin

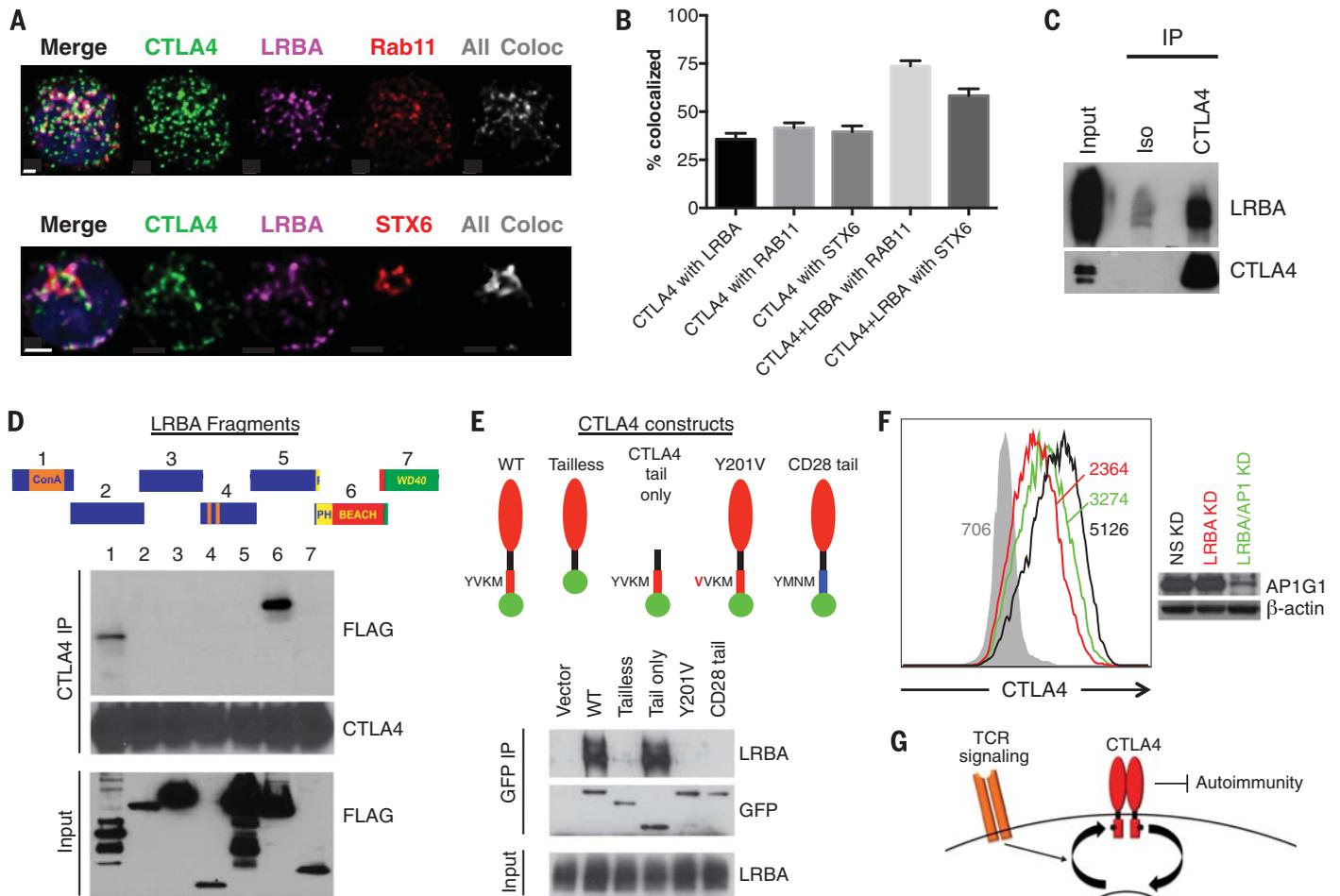


Fig. 4. LRBA and CTLA4 coimmunoprecipitate and colocalize predominantly within recycling endosomes.

(A) Confocal microscopy shows that LRBA and CTLA4 colocalize with Rab11 (recycling endosome marker) and Syntaxin-6 (STX6, trans-Golgi network marker) in activated T cells. Hoechst staining in blue. All Coloc, Colocalization of LRBA and CTLA4 with Rab11 (top) or STX6 (bottom). Scale bar, 1 μ m. (B) Quantification of the colocalization. Percent colocalized indicates percentage of fluorescent signal (volume) overlap of the indicated molecules. Data are represented as means \pm SEM pooled from three independent experiments with 40 and 32 images total, respectively, for Rab11 and STX6 analyses. (C) LRBA and CTLA4 immunoblots of CTLA4-specific antibody or isotype control (iso) immunoprecipitates from lysates of activated T cells. (D) Human embryonic kidney (HEK) 293T cells were transfected with DNA encoding wild-type (WT) CTLA4 and FLAG-tagged fragments 1 to 7 of LRBA as indicated. CTLA4 immunoprecipitates from the transfected cells were immunoblotted with antibodies against FLAG and CTLA4. (E) HEK 293T cells were transfected with constructs of green fluorescent protein (GFP) fused to WT CTLA4, tailless CTLA4, YVKM mutant CTLA4 (Y201V), CTLA4 tail only, and CTLA4 with CD28 tail. GFP immunoprecipitates from the transfected cells were immunoblotted with antibodies against LRBA and GFP. CTLA4 extracellular domain as a red oval; transmembrane domain, black bar; cytoplasmic tail, red (CTLA4) or blue (CD28) rectangle; GFP, green circle. (F) CTLA4 intracellular staining of NS KD, LRBA KD, or LRBA and AP1G1 (subunit of AP-1) double-KD T cells. Mean fluorescence intensities of CTLA4 staining are indicated on graph. Shaded gray histogram is isotype control. Data are representative of at least three independent experiments. Immunoblot on right shows AP1G1 KD efficiency. (G) Model depicting the regulation of CTLA4 vesicle trafficking by LRBA.

domain and the pleckstrin homology (PH)-like BEACH domain of LRBA and the cytoplasmic tail of CTLA4 (Fig. 4, D and E). CTLA4 with its cytoplasmic tail substituted with the corresponding CD28 tail could not bind LRBA (Fig. 4E). Note that we found that mutating the conserved tyrosine residue in the Tyr-Val-Lys-Met (YVKM) motif present in the tail of CTLA4 led to loss of binding (Fig. 4E). These experiments established that the CTLA4 tail—and the YVKM motif specifically—are necessary for LRBA association. We next investigated whether the tail of CTLA4 is sufficient for the LRBA interaction. If so, this would be consistent with the topology of CTLA4 (tail facing the cytoplasm) and would allow LRBA to use the tail as a handle to guide the movement of CTLA4-bearing recycling endosomes. We found that addition of the CTLA4 tail to GFP could coimmunoprecipitate LRBA, which confirmed that the CTLA4 tail is necessary and sufficient to mediate the interaction (Fig. 4E).

Finally, to further understand how the loss of LRBA leads to CTLA4 degradation, we assessed the role of AP-1, the clathrin-associated adaptor protein complex previously implicated in the shuttling of CTLA4 to lysosomes (24). Knockdown of AP-1, but not AP-2 nor AP-3 (other trafficking adaptors), could partially rescue the loss of CTLA4 and CD71 in *LRBA* knockdown cells (Fig. 4F and fig. S13). Note that the YVKM motif of CTLA4, which is critical for the interaction with LRBA, is also known to bind to AP-1, which suggests that LRBA may block CTLA4 trafficking to lysosomes by competing with AP-1 for binding to this motif. Taken together, these data indicate that LRBA plays a major immunoregulatory role by protecting CTLA4 from being sorted to and degraded within lysosomes.

In summary, therapy targeting CTLA4 was highly effective in reversing life-threatening infiltrative and autoimmune disease in *LRBA*-deficient patients. Molecular investigation of this effect revealed LRBA as an important control point for the lysosomal turnover of CTLA4 protein in T lymphocytes. LRBA is a 300-kD protein, one of the largest intracellular proteins, with a structure suggesting an adaptor function (8, 9). It harbors a BEACH domain that has been implicated in intracellular vesicle regulation. A previous investigation suggested that lysosomal processes involving autophagy were defective in *LRBA*-deficient cells (7). By contrast, our data indicate that, at least for CTLA4, lysosomal degradation is enhanced when LRBA is absent. Thus,

LRBA helps maintain intracellular stores of CTLA4, which allows the protein to mobilize rapidly to the cell surface where it can perform its inhibitory function in T_{regs} and memory T cells. This post-translational mechanism for regulating CTLA4 expression in human T cells is depicted schematically in Fig. 4G.

Early investigations of CTLA4 deficiency in mice revealed fatal lymphoproliferative and autoimmune disease (25–27). Also, CTLA4 haploinsufficiency with autoimmune infiltration (CHAI) disease due to genetic haploinsufficiency of CTLA4 has been described (21, 28). Patients with CHAI disease exhibit a clinical phenotype similar to that of people with *LRBA* deficiency, which underscores the disease connection between CTLA4 and LRBA (7, 29, 30). Our findings provide a clear rationale for the prospective study of CTLA4-targeted therapies for *LRBA* deficiency and other disorders that lead to reduced CTLA4 levels. Recent reports have confirmed the long-term safety and efficacy of abatacept in patients with rheumatoid arthritis, although treatment is associated with increased infections (31, 32). Because abatacept will reinforce the immune checkpoint on T cells, it could hypothetically blunt antitumor responses, and this will need to be monitored with long-term use. Our studies also suggest that chloroquine or hydroxychloroquine, relatively inexpensive drugs that inhibit lysosomal degradation, may merit investigation as therapies for diseases with *LRBA* or CTLA4 deficiency. Note that hydroxychloroquine has shown therapeutic efficacy in systemic lupus erythematosus (33), which we now postulate might stem from an enhancement of CTLA4.

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Figs. S1 to S14
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Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy

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Editor's Summary

Trafficking from bedside to bench

Typically in translational research, a discovery in cell or molecular biology is later exploited to improve patient care. Occasionally, information flows in the opposite direction. Lo *et al.* found that patients with an autoimmune disorder caused by deficiency of a protein called LRBA responded dramatically to the drug abatacept (see the Perspective by Sansom). Abatacept contains a segment of a potent inhibitory immune receptor, CTLA4. Experiments prompted by this observation revealed the relationship between the two proteins: LRBA controls the intracellular trafficking and degradation of CTLA4. This information may further improve patient care, because other clinically approved drugs have the desired mechanism of action with potentially fewer side effects.

Science, this issue p. 436; see also p. 377

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