**Invited Review**

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# Structure and Function of the LRBA Protein

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**Abstract**

Beige and Chediak (BEACH) domain-containing protein (BDCP) family proteins are large cytoplasmic adaptor proteins associated with endosomal and lysosomal recycling and degradation pathways. These proteins have C-terminal PH, Beach and WD40 domains, whose structures are solved or can be predicted using recently developed algorithms such as Alphafold. Family members such as LRBA, LYST and NBEAL2 are implicated in human disease. LRBA was shown to be responsible for the re-shuttling of the T-cell co-inhibitory receptor CTLA4 back to the plasma membrane after internalization and lack or mutation of LRBA results in surface deficiency of CTLA4 in regulatory and activated T lymphocytes. The large molecular size of these proteins indicates that they may have pleiotropic functions in the immune system and beyond. Sequence and domain structure similarities between the proteins suggest that a level of redundancy may be present, which could potentially result in new therapeutic avenues.

**Keywords:** LRBA, LYST, CTLA4, immune dysregulation, common variable immunodeficiency, Chédiak Higashi syndrome

## Beige and Chediak (BEACH) Domain-containing Protein (BDCP) Family Proteins

LRBA, the main focus of this review article, is a large 319 kDa protein with pleiotropic function. Patients with LRBA deficiency present with common variable immunodeficiency with a predominant regulatory T-cell defect (1,2). The phenotypes of this disease are very similar to CTLA4 deficiency and point to the fact that LRBA is responsible for CTLA4 surface expression on regulatory T lymphocytes (3-5). LRBA knockout mice also display very similar phenotypes to patients, although LRBA dependent CTLA4 deficiency does not proceed to full-blown immune dysregulation in this case (6).

LRBA belongs to a family of 9 proteins, all containing a Beach domain, encoded by the human genome with similar domain structures (Figure 1) (7). An alignment of the amino acid sequences of the family members demonstrates a high level of conservation in key residues (Figure 2). Several of these PH-Beach proteins were implicated in human disease. LYST (lysosomal trafficking regulator) is mutated in Chédiak-Higashi syndrome (CHS), an autosomal recessive disease that has a lysosomal phenotype and results in hypopigmentation, abnormal bleeding and increased susceptibility to infection with defects in the nervous system (8). Mutations in the murine *Lyst* gene cause coat color phenotypes consistent with the human disease and in the lysosomal trafficking role for this protein (9,10). In fact, CHS patients' T-cells, similar to LRBA deficiency, do not express appropriate levels of CTLA4, indicating that some redundancy may be at play among LRBA, LYST and also NBEAL2 (11). NBEAL2 (Neurobeachin-like protein 2) mutations cause Gray Platelet syndrome (GPS), with abnormalities in the biogenesis of thrombocytes and their secretory α-granules (12). Reduced Neurobeachin (Nbea/Lyst2) expression, a neuronal membrane trafficking protein controlling neuronal feeding circuits, was associated with obesity in mice and humans (13). All of these phenotypes point to the lysosomal functions of this family of proteins.

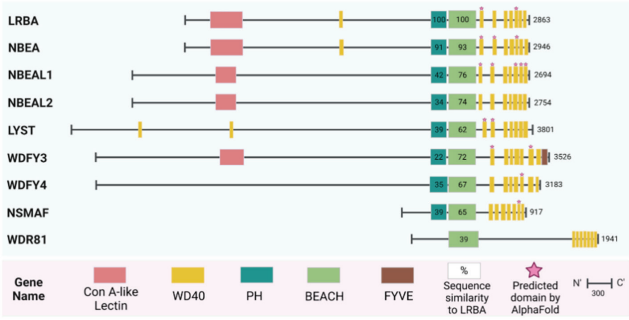


**Figure 1.** Domain structure of the Beige and Chediak (BEACH) domain-containing (BDCP) family of proteins. Each domain is indicated in color, predicted by Uniprot and Supfam (63,64). The percentage of similarity of the family members, compared to the LRBA protein are indicated in each of the PH and Beach domains by numerals. Similarity scores were generated using pairwise alignment by Needle using Blosum62 (65). The size of the proteins in amino acids is indicated on the C-terminus. In some cases, the number of predicted WD40 motifs varies between Uniprot and structural predictions by AlphaFold, which predicts 7 C-terminal motifs for each protein. Protein sequences were aligned using Omega Clustal (default settings) (65). The figure was created by Biorender software.

### The PH-Beach Domain

BDCP family proteins are typically large, suggesting a potential structural or scaffolding role in the cell. These proteins contain various domains, among which the best characterized ones are the ConA-like, PH, Beach and WD40 domains. The structures of the PH-Beach and WD40 domains for the human LRBA protein can be predicted by Alphafold software (Figure 3a, 3b). The crystal structures of the PH-Beach domains of LRBA (PDB ID: 1T77) and Neurobeachin (Nbea/Lyst2) (PDB ID: 1MI1) were solved (14,15). While the crystal structures do not contain any information about the WD40 motifs, the Alphafold predictions have high confidence scores and are very similar to the crystal structures (root mean square deviation-RMSD of 0.709 Angstroms between the PH-Beach domains of the crystal structure and model). These structures indicate that the PH and Beach domains have a Pac-Man or clam-like structure connected by a positively charged, flexible linker region. A potential mode of regulation of the linker structure can be deduced by the (cAMP)-dependent protein kinase (PKA) mediated phosphorylation of serine 2189 in the RRIS motif in the linker (16). When expressed and purified individually, the PH and Beach domains have a high affinity towards each other *in vitro,* even without the linker (14). The flexibility of the linker indicates that these domains could be opening and closing on top of a ligand with which the protein associates. This possibility can be visualized by looking into the interface of the two sub-domains that face each other. This analysis indicates that there are potential grooves that are formed when the two domains close on top of each other, potentially accommodating a peptide from a ligand (Figure 3c).

### The WD40 Domain

BDCP family proteins contain a C-terminal WD40 domain composed of multiple beta-sheet containing propellers. The WD40 domain was named for the two amino acids that could be found before each blade of the propeller, tryptophan (W) and aspartic acid (D) (17). These propeller structures can function as a protein-protein interaction surface, a DNA binding domain or as an epigenetic reader (18). Most propellers contain seven blades but can vary from five to eight in different proteins. Each blade is composed of 44-60 amino acids, folding into a four stranded antiparallel beta sheet that points towards a central pore. This structure resembles a funnel shape and the central pore is large enough to accommodate a peptide (19).

The LRBA WD40 domain is composed of seven WD40 blades that immediately follow the PH-Beach domain at the extreme C-terminus and a single blade that is in the middle of the protein. Examples of single blades being inserted into WD40 propellers exist in other proteins (20). This finding has made us hypothesize that the central blade of LRBA may fold back and complete the WD40 propeller for function. In fact, other PH-Beach family members also contain central single blades, which may indicate a conserved mechanism (7). Alternatively, the blades of one protein may complement the propeller of another protein, resulting in hetero association.

A mutagenesis screen in mice found a LYST missense mutant in the WD40 domain with a predominantly neurodegenerative phenotype and did not display phenotypes similar to CHS (21). This mutation that changes a small hydrophobic isoleucine residue to a hydrophilic arginine may block an interaction with a neuronal specific partner protein or may result in a structural change in the WD40 domain without affecting the functions of the other domains important for immunological functions. Similarly, the Ile2657Ser mutation in the WD40 domain of LRBA results in decreased protein levels, likely by interfering with stabilizing interactions. The WD40 domain of LRBA was shown to be not necessary for binding to the tail of CTLA4, discussed in detail below (4). Other studies identified WD40 domains with varying number of propellers from numerous proteins to function as ubiquitin binding domains (22). Whether the interaction between LRBA and CTLA4 is dependent on ubiquitination or some other post-translational modification like phosphorylation or SUMOylation is not known. As there is X-ray crystallographic structural information for only the PH-Beach domain of the LRBA protein, we created Alphafold models of the region of the protein containing the PH-Beach and WD40 domains. These models indicate that the WD40 domain can associate with the PH-Beach


**Figure 2.** Sequence alignment of the PH and Beach domains of BDCP family of proteins. Protein sequences were aligned using Omega Clustal (default settings). Amino acid sequences are indicated in single letter code, where X denotes lack of conservation. Numbering is relative to the LRBA Uniprot sequence (P50851) starting at 2073 for the PH domain and 2200 for the Beach domain. For PH (blue) and Beach (green) domains the color grading indicates conservation scores, where darker colors are more conserved. A consensus score and sequence for each position is annotated at the bottom of the alignment. Visualization was generated by the Python package, pyMSAviz.

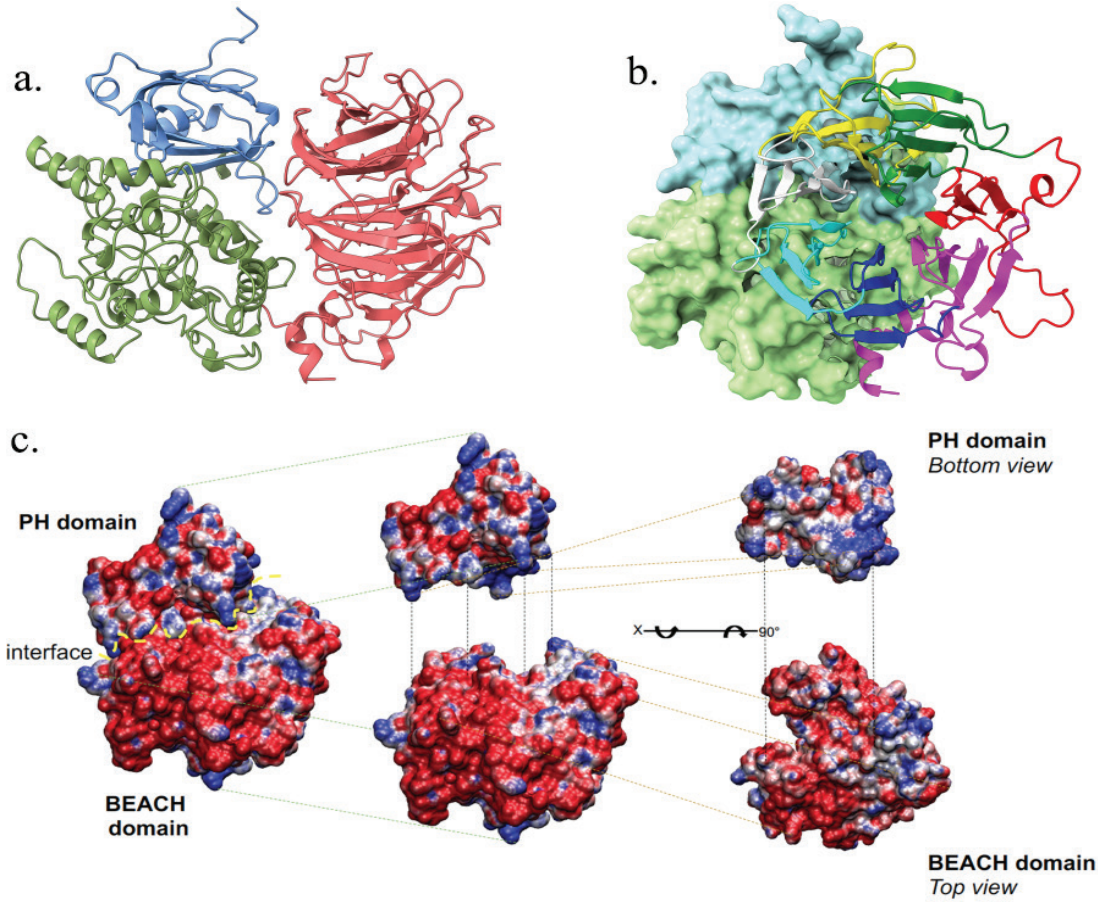


**Figure 3.** The prediction of the structure of the LRBA protein by Alphafold2 viewed from the front (a) and side (b). a. ColabFold (v. 1.5.2) was used to predict the LRBA structure. The PH (amino acids 2073-2181), BEACH (amino acids 2200-2489) and WD40 (amino acids 2591- 2858) domains are color coded in Blue, Green and Pink respectively. b. Side view of the structure shown in cartoon representation looking into the WD40 propeller structure where each blade is highlighted in different colors. c. Front view of the X-ray structure of the PH-Beach domain showing surface electrostatic potentials where positivity is indicated by blue and negativity by red. The interface between the PH (top) and Beach (bottom) domains are shown where each domain is separated and rotated 90 degrees.

domains (Figure 3). The structural model indicates that if indeed the WD40 propeller central hole accepts a peptide from a protein interactor, for example the C-terminal cytoplasmic tail of the CTLA4 receptor, it could in fact be fed into the groove formed by the clamshell of the PH and Beach domains, which is known to stably bind this tail (4). We imagine a scenario where the funnel of the WD40 domain docks onto the cytoplasmic tail of CTLA4 in a recycling endosome and feeds this tail into the PH-Beach clam structure that clamps on top of the tail with higher specificity.

### Association with Protein Kinase A

LRBA was originally identified as a cyclic adenosine monophosphate (cAMP)-dependent protein kinase (PKA) scaffold (AKAP) protein. N-terminal to the PH-Beach domain, LRBA, contains two repeats responsible for docking onto PKA (23). Many roles for PKA have been shown in immune system cells. This kinase is a holoenzyme formed by catalytic and regulatory subunits, the latter of which binds to AKAPs (24). In fact, LRBA binds to and colocalizes with the regulatory subunit RIIb in cytoplasmic vesicles in B lymphocytes (25). Other BDCP family proteins have also been shown to function as AKAPs. Among these are the Drosophila AKAP, dAKAP550, identified as an orthologue of LRBA and/or Neurobeachin, a neuronal transport protein (26,27). The Drosophila *rugose (rg)* gene locus encodes the dAKAP550 protein, mutations of which cause eye phenotypes (28). Another AKAP function of LRBA was discovered in renal cells, where it promotes the phosphorylation of aquaporin receptors (AQP2) by PKA (29). Activation of PKA resulted in the phosphorylation of LRBA in PKA target RRXS motifs. The spatial resolution between these RRXS motifs (residues 1296, 1607 and 2189) and PKA regulatory subunit RII binding alpha helices (residues 1350-1420) indicate that PKA can dock onto LRBA and phosphorylate it (16). LRBA bound PKA also phosphorylates AQP2. PKA is known to be a basophilic kinase, phosphorylating sites that fit the consensus (R/K)(R/K)X(S/T) (30). In addition

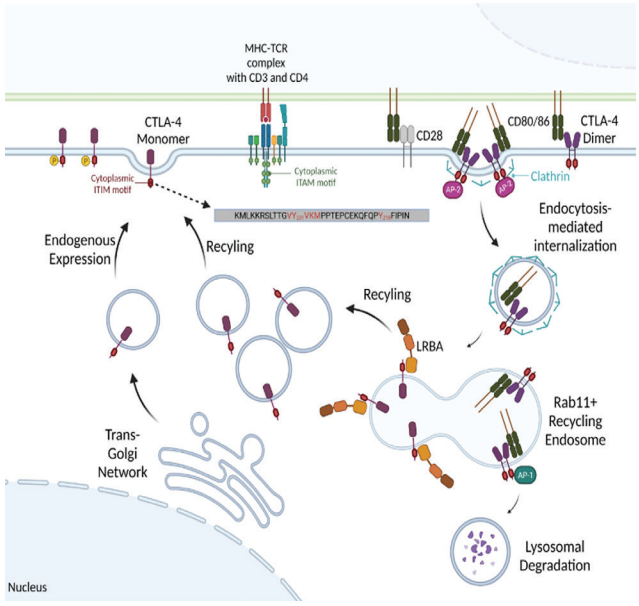


**Figure 4.** A model showing how LRBA controls the trafficking of CTLA4 in T lymphocytes. Nascent CTLA4 is exported to the plasma membrane where it is phosphorylated in its cytoplasmic ITIM motif. The interaction of peptide MHC-II on antigen presenting cells and a clonotypic T-cell receptor complex with the CD4 co-receptor initiates TCR signaling. This signal is helped by the CD28 co-stimulatory receptor which is antagonized by surface CTLA4, which has a higher affinity for the same ligand (CD80/CD86) on the APC. CTLA4 that binds CD80/CD86 is internalized by endocytosis in Clathrin coated pits and strips this ligand from the APC surface by transendocytosis. The CTLA4-CD80/86 complex is transported to Rab11+ recycling endosomes where cytoplasmic LRBA binds the cytoplasmic tail of CTLA4 and rescues it from lysosomal degradation and re-shuttles it back to the plasma membrane. In the absence of LRBA, CTLA4 is degraded in the lysosome.

to the three sites mentioned above, another potential target site exists at position 1213 (KKAT) in the human protein, but like the site at 1296, there is no indication that it can get phosphorylated by PKA.

## Roles in the Immune System and Associated Disorders

In 2012, Lopez-Herrera et al. (3) discovered human autosomal recessive LRBA deficiency in five patients from four families. This disorder manifests with recurrent sinopulmonary infections, hypogammaglobulinemia, lymphoproliferation, and autoimmunity. Further patient descriptions revealed heterogeneous presentation as a common variable immune deficiency, autoimmune lymphoproliferative syndrome, or Immune dysregulation polyendocrinopathy-X linked-like disease (31). The patients usually demonstrated various autoimmunities encompassing hemolytic anemia, thrombocytopenia, enteropathy, arthritis, type 1 diabetes, vitiligo, alopecia, uveitis, and optic neuritis (32,33). The autoimmunity has been partly explained by reduced CTLA4 expression in regulatory T lymphocytes, usually accompanied by a reduction of this cell population (Figure 4). The defective Treg-mediated immunosuppression was also attributed to impaired immunosurveillance, leading to malignant transformation (lymphoma and gastric adenocarcinoma) (34). Our current cohort includes 60 LRBA-deficient patients with various clinical phenotypes depicted in Figure 5a (35).

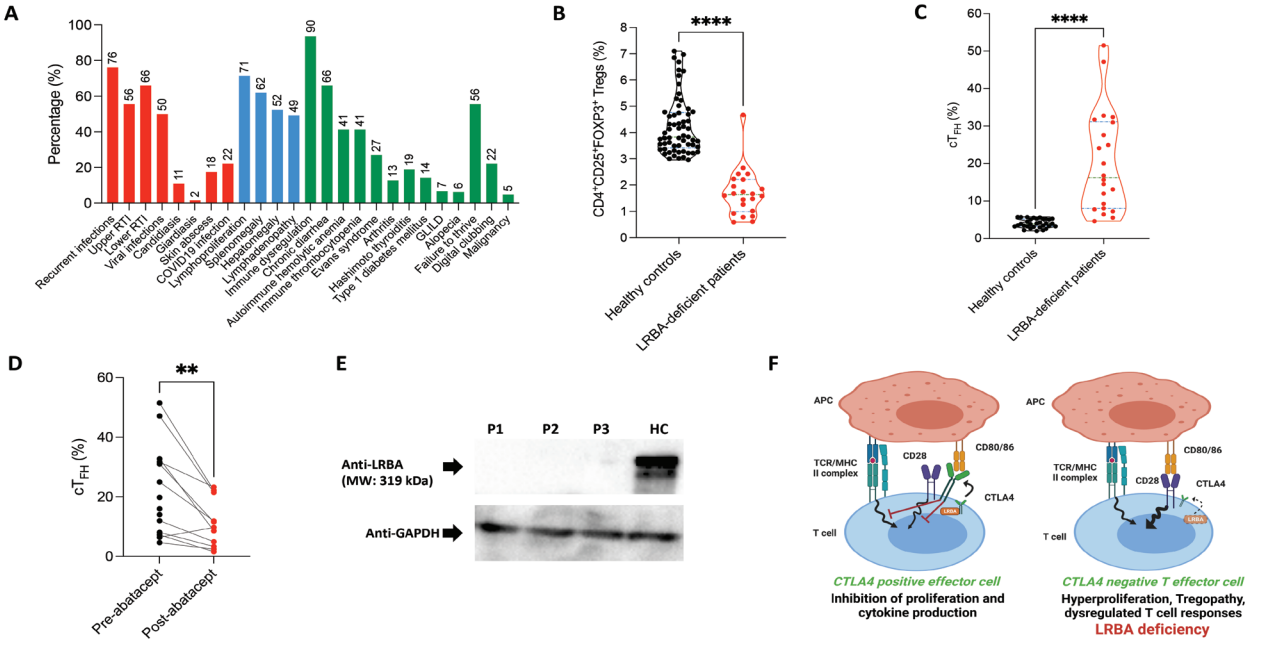


**Figure 5.** Clinical and immunological features of LRBA deficiency. (A) Clinical manifestations are presented as percentages. The disease symptom clusters are shown with different colors. Red bars demonstrate infections, blue bars denote Lymphoproliferation, and green bars display immune dysregulation. GLILD: Granulomatous lymphocytic interstitial lung disease. (B) Treg cell percentages in LRBA deficient patients compared to healthy controls. (C) Frequency of cTfh cells in LRBA deficiency. (D) The percentages of cTfh in LRBA-deficient patients pre- and post-abatacept. (E) western blot analysis in 3 LRBA-deficient patients compared to healthy control (HC). (F) The human LRBA deficiency disease model demonstrates dysfunctional T-cells compared with normal T-cells. The data are presented with a median (green line) and 25$^{th}$-75$^{th}$ interquartile range (blue) in panels B, C, and D.

LRBA-deficient patients generally showed hypogammaglobulinemia and reduced vaccine responses (33). Lymphocyte subset analyses exhibited diminished $CD3^+$T-cells with a memory phenotype, increased double-negative T-cells, and reduced total B-cells accompanied by increased naive ($CD27^-IgD^+$) and reduced class-switched memory ($CD27^+IgD^-$) cells, as well as increased activated B-cells ($CD21^{low}CD38^{low}$) in some patients (36). The percentage of Treg cells is low when compared to healthy controls (Figure 5b). Due to the insufficient CTLA4-mediated Treg suppression, increased numbers of circulating follicular helper T-cells (cTfh, $CD4^+PD1^+CXCR5^+$) were also discovered in this disease (Figure 5c), contributing to enhanced B-cell responses with abnormal autoantibody production (37). As reported previously, the reduced CTLA4 expression can be recovered with brief T-cell stimulation. This recovery helps differentiate LRBA deficiency from CTLA4 insufficiency, which shows permanent low CTLA4 levels even after stimulation (5,38).

Studies regarding clinical manifestations and treatment modalities were reported for both disorders by defining the efficacy of the conventional (immunoglobulin replacement therapy, antimicrobial prophylaxis, and classical immunosuppressants, targeted therapies (abatacept; a CTLA4-Ig fusion protein, sirolimus; an mTOR inhibitor), and hematopoietic stem cell transplantation (HSCT) (36,39). Abatacept showed very well-controlled disease activity in most patients, especially for lymphoproliferation, immune cytopenia, and chronic diarrhea in LRBA deficiency. Combining abatacept with sirolimus has also effectively mitigated symptoms in severe patients (39). On the other hand, HSCT is reported in small cohorts with end-organ damages, and success rates of symptom control were 17/24 (70.8%) (39,40). Post-HSCT complications have determined both disorders' outcomes, including graft versus host disease (GvHD), graft rejection, multiorgan failure, autoimmunity, and cytomegalovirus reactivation.

More recently, we reported a prospective study showing the long-term effect of abatacept in 22 LRBA-deficient patients (36). The most common clinical features of patients were recurrent infections (86.4%), immune dysregulation (72.7%), and lymphoproliferation (72.7%). The median duration of abatacept therapy was 12.5 months (range: 5-33 months). Abatacept showed the best complete remission for lymphoproliferation, followed by chronic diarrhea and immune dysregulation symptoms. Interestingly, from the autoimmune perspective, more favorable responses were achieved for hematological autoimmunities (hemolytic anemia and thrombocytopenia), while type 1 diabetes mellitus was not controlled well with abatacept. The study also demonstrated the efficacy of dosing intervals used for patients. Receiving abatacept at one-week or two-week intervals exhibited more disease control than a 4-week regimen. Using the cTfh cells as a biomarker for disease control over time revealed a good correlation with the disease activity, showing a reduction with treatment (Figure 5d). No serious side effects related to abatacept were reported, showing the safety of the treatment.

Mutational analysis in LRBA deficiency revealed different homozygous or compound heterozygous mutations throughout the gene, mainly characterized by frameshift or nonsense mutations, leading to premature protein production, followed by missense, splice site mutations and deletions. The reported mutations usually lead to abolished or low LRBA expression, while normal protein expression can be observed in some patients with missense mutations (Figure 5e). Analyzing the reported mutations regarding causative genetic variants, classified as missense, nonsense and frameshift, did not show a strong genotype-phenotype relationship that could predict the manifestations or outcomes of the disease even though it presents full penetrance like other autosomal recessive disorders (41). The human LRBA deficiency disease model depicting the dysfunctional T-cells is provided in Figure 5f.

**Functions in T lymphocytes and Natural Killer Cells**

CTLA4 is a critical T lymphocyte co-inhibitory receptor that negatively regulates T-cell receptor (TCR) signaling. Phenotypes of CTLA4 deficiency and the success of checkpoint inhibition approaches targeting CTLA4 function indicate the centrality of this molecule in TCR signaling (42-44). The T lymphocyte surface levels of CTLA4 are tightly regulated and this regulation is mediated by the motifs in the cytoplasmic tail of this molecule (45). Tyrosine phosphorylation and dephosphorylation of the tail allow the docking of adaptor proteins that regulate the internalization of plasma membrane CTLA4 and the transport of CTLA4 bearing cytoplasmic vesicles back to the plasma membrane or to the lysosome for degradation (46,47). As evident from the phenotypes of mutations of the human *LRBA* gene, one of the roles of this protein is to regulate the surface levels of the CTLA4 co-inhibitory receptor expressed on Treg and activated T lymphocytes (Figure 4). The LRBA protein binds to the YVKM motif of the cytosolic tail of CTLA4 using its Concanavalin A and Ph-BEACH domains and controls vesicular trafficking of CTLA4 (4). A critical role for LRBA was the delivery of CTLA4 into Rab11 positive recycling endosomes, preventing its lysosomal degradation and allowing the recycling of CTLA4 molecules to the cell surface (48).

After recycling to the plasma membrane, CTLA4 can compete with the co-stimulatory receptor, CD28, to bind the CD80 (B7-1) and CD86 (B7-2) ligands expressed on antigen-presenting cells. The interaction between CTLA4 and CD80/CD86 was shown to strip CD80/CD86 molecules by transendocytosis, which contributes to T-cell inhibition by diminishing the levels of co-stimulatory ligands on APCs (49,50). The interaction between CTLA4 and CD80 and the

resulting transendocytosis was recently shown to release PDL1 from binding to CD80 and elevate its expression levels on the surface of APCs (51). Transendocytosis is similar to the well-known process of trogocytosis, whereby mainly T lymphocytes but also other immune system cell types exchange cell membrane fractions with target cells (52). Trogocytosis requires actin filament reorganization and the formation of an immunological synapse.

The autoinflammatory disease in ctla4$^{-/-}$ mice was shown to require an Lck binding motif in the cytoplasmic tail of CD28, which is necessary for *in vivo* co-stimulation (53). LRBA knockout mice also display similar CTLA4 deficiency without advancing to full-blown immune dysregulation (6). As LRBA was shown to be a pleiotropic protein, it is possible that other compensatory pathways contribute to the phenotype observed in lrba$^{-/-}$ mice. It would be interesting to test the importance of the CD28 tail in these mice.

LRBA knockout mice were shown to have defects in rejecting allogenic, xenogenic and missing-self bone marrow transplants (54). These findings are in line with LRBA's role in activating receptor signaling and natural killer cell cytotoxicity. Deficiency of family member LYST in NK cells of CHS patients shows a much more dramatic phenotype in which NK cytotoxicity is reduced because of a failure of vesicular-membrane fusion (55).

**Functional Similarities of PH-BEACH Domain Proteins**

The domain similarities among the Beige and Chediak (BEACH) domain-containing protein (BDCP) family described in Figure 1 indicate that they may have similar and possibly redundant functions. A recent study has shown that NBEAL2 controls CTLA4 levels in conventional T lymphocytes but not in Treg cells (56). NBEAL2 and LRBA function in a redundant fashion in conventional T-cells, while in Treg cells, which do not express NBEAL2, LRBA seems to be solely responsible for regulating CTLA4 recycling. On the other hand, in activated T lymphocytes, both LRBA and NBEAL2 seem to interact with CTLA4. It is unclear why LRBA, which binds to the tail of CTLA4 and rescues it from lysosomal degradation in Treg cells, cannot do so in conventional activated T-cells lacking NBEAL2, even though it is expressed in this subset and interacts with CTLA4. Whether the interaction between LRBA and NBEAL2 was direct or not was not addressed in this study. It is formally possible that both cytoplasmic proteins are associated with endosome/lysosome compartments containing CTLA4 and that the interaction is indirect. However, this seems to be unlikely as earlier studies on Treg cells and in heterologous systems showed that the PH-BEACH domain of LRBA was necessary and sufficient to interact with the cytoplasmic tail of CTLA4 (4). It is also unknown if these and perhaps other BDCP family proteins interact with each other and are in multi-protein complexes.

**Functions in B Lymphocytes**

B-lymphocytes from LRBA-deficient patients demonstrate defective autophagy and increased apoptosis, resulting in reduced plasmablast survival and contributing to poor humoral responses (3). Recently, the impact of LRBA at the early and late stages of the autophagy process has been shown by its physical interaction with PIK3R4 (phosphoinositide 3-kinase regulatory subunit 4) and FYCO1 (FYVE And Coiled-Coil Domain Autophagy Adaptor 1) (57). In fact, other BDCP family proteins have been implicated in autophagy, which is a highly specialized lysosomal degradation pathway. Prime among these proteins is ALFY/ WDFY3, which was shown to play a role in the autophagic degradation of ubiquitinated proteins (58). ALFY/WDFY3 contains a FYVE domain at the extreme C-terminus after the WD40 domain that was shown to bind to PI3P (58). LRBA was also recently shown to interact with the phosphoinositide 3-kinase regulatory subunit 4 (PIK3R4), which was in turn shown to facilitate the production of phosphatidylinositol-3 phosphate (PI(3)P) required for autophagosome formation (57). The LRBA-PIK3R4 interaction is thought to be mediated by the WD40 domains of the two proteins. Unlike ALFY/WDFY3, LRBA does not contain a FVWE domain, but it interacts with FYCO1 (FYVE And Coiled-Coil Domain Autophagy Adaptor 1), using its PH-Beach domain, possibly mediating similar scaffolding functions to ALFY/WDFY3.

**Non-immune System Functions of LRBA**

LRBA was recently shown to regulate the expression of G proteins in olfactory neuron cilia (59). LRBA expression is upregulated in cancer cells, promoting proliferation and preventing apoptosis (60). The connection between EGFR signaling and LRBA is conserved as Drosophila *rugose*/dAKAP550 has also been shown to genetically interact with EGFR. In addition, *rugose*, expressed in the Golgi network, affects synaptic architecture, brain morphology and associative learning (61).

**Regulation of the *LRBA* Gene**

The murine *LRBA* gene (then named *lba*) was cloned by retroviral gene trapping, where it was found to be upregulated four-fold upon Lipopolysaccharide (LPS) induction in macrophages and B-cells (23). The human gene is located on chromosome 4q31.3, spanning more than 750.000bp over 58 exons. (60). Various innate immune stimulators classified as pathogen-associated motifs were shown to upregulate LRBA protein expression (62). TCR co-stimulation (anti-CD3/anti-CD28) also activates robust expression of the LRBA protein. These findings indicate that the gene is likely under the control of transcription factors such as NF-kB, NF-AT, AP-1. An analysis of the promoter region revealed the presence of an NF-kB site directly upstream of the start codon of the gene (60). The

promoter also contains numerous p53 binding sequences and p53 was shown to inhibit *LRBA* gene expression (60).

## Conclusion

LRBA and the other Beige and Chediak (BEACH) domain-containing protein family are large, multidomain proteins. While many of the domains in these proteins were identified by sequence homology, the functional significance of these domains still needs to be completely identified. While many proteins are ubiquitously expressed, tissue and cell-type specific functions have been reported. These functions span from cell surface protein trafficking in T lymphocytes to neuronal synapse formation. A compounding effect on these observed phenotypes is the presence of consanguinity in LRBA deficient patients, which brings unknown modifier alleles in other homozygotic gene loci. The domain similarity among the protein family members indicates that, when co-expressed, family members may perform redundant functions. There are also indications that proteins of this family may associate with each other, but whether this is direct protein-protein interaction and if it is functionally significant are yet to be addressed. In summary, the BEACH domain-containing protein family has unique cytoplasmic and membrane-associated functions and may have pleiotropic functions yet to be discovered.

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### Authorship Contributions

Concept: E.E., M.C.Ç., F.B.Ç., S.P., P.Z., E.Ü., S.B., B.E., Design: E.E., M.C.Ç., F.B.Ç., S.P., P.Z., E.Ü., S.B., B.E., Data Collection or Processing: E.E., M.C.Ç., F.B.Ç., S.P., P.Z., E.Ü., S.B., B.E., Literature Search: E.E., M.C.Ç., F.B.Ç., S.P., P.Z., E.Ü., S.B., B.E., Writing: E.E., M.C.Ç., F.B.Ç., S.P., P.Z., E.Ü., S.B., B.E.

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